“Analyzing the underlying symptom-dimensions of Gilles de la Tourette Syndrome”

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Abstract:

Aim: Gilles de la Tourette syndrome (GTS) is a complex and heterogeneous disorder which might best be viewed as part of a spectrum of tics and comorbidities. There has been little research on GTS and its co-morbid disorders on a symptom dimension level. The hypothesis is that the model of symptom dimensions across tic symptoms and symptoms of OCD and ADHD will provide a good fit, will better represent the heterogeneity of the disorder and comorbid symptoms between disorders will partly correlate.

Method: The total study sample included 225 patients and 371 family members, summing up to a total of 596 participants. Using Mplus 5.21, a Confirmatory Factor Analysis (CFA) was conducted on a total of 10 symptom dimensions, covering GTS and comorbid OCD and ADHD.

Results: The symptom dimension model fit the data best ($\Delta\chi 2 > 0.948$, $p < 0.001$) and presented the lowest AIC ($\Delta AIC = -224$). The OC dimensions Taboo (0.773) and Rituals (0.657) correlate highest with the tic symptom dimensions ($p = < 0.05$). Of the GTS dimensions the body tics dimension correlates lowest with OC symptom dimensions (0.731, $p < 0.05$). Surprisingly, the ADHD dimensions showed no correlations with the other symptom dimensions.

Conclusion: In line with previous research (Mathews et al. 2009, Cath et al. 2004) the data suggest that overall 10 symptom dimension model (Katerberg, 2010; de Haan, 2010; (American Psychiatric Association [*DSM-IV-TR*], 2000) is superior to the 1 factor model. The OC symptom dimension Taboo showed the highest correlation with GTS. The symptom dimension body tics showed the lowest correlation with OCD. The findings complement earlier findings that the symptom dimensions of GTS and comorbid OCD can best be viewed as belonging to a spectrum of disorders, probably with shared underlying etiology. In contrast with the literature, ADHD seems to be independent from tic and OCD symptom dimensions. We do not have an adequate explanation for this finding.

Introduction

Background

Gilles de la Tourette syndrome (GTS) is a chronic neuropsychiatric tic-disorder characterized by the presence of both motor tics and vocal tics with a childhood onset (American Psychiatric Association [*DSM-IV-TR*], 2000 & ICD-10, 1992).

Tic symptoms are considerably variable within persons, especially during childhood, and may change in type, frequency and intensity; they increase and decrease over time within and across individuals. In addition to heterogeneity in tic presentation, GTS also varies across individuals with regard to comorbid neuropsychiatric symptoms, most frequently including obsessive-compulsive symptoms, attentional problems, and hyperactivity/impulsivity (Cath et al., 2001b).

In clinical samples, tics, obsessive-compulsive disorder (OCD), attention-deficit /hyperactivity disorder (ADHD) and autism often co-occur (Leckman et al., 2001). Their overlap in clinical settings has supported the idea that the conditions may share a common pathophysiology (Cath et al. 2004; Pauls et al.,1986). Robertson et al. (2008) reported that coprolalia and echophenomena were related to obsessional symptoms and increased tic severity. Although available epidemiological studies inconsistently document associations among tics, OCD, and ADHD (Douglass et al., 1995; Flament et al., 1988), a longitudinal study by Peterson et al. (2001) reports significant associations between tics, OCD and ADHD. The findings of an important study by Robertson et al. (2008), in which 5 different tic factors were found, -adds to the growing body of evidence that GTS is not a unitary condition and might be seen as an entity in a spectrum of disorders.

Comorbidity

As mentioned earlier, GTS is known to be highly co-morbid with obsessive compulsive disorder (OCD) and OC related symptoms (OCS). Fifty percent of all GTS patients suffer from OCD (Cath et al., 2004). OCD is diagnosed as an anxiety disorder according to DSM-IV criteria (American Psychiatric Association, 2000). Patients suffer from intrusive thoughts and compulsive behaviors and rituals. Symptoms may include repetitive hand washing;

extensive hoarding; preoccupation with sexual or aggressive impulses, or with particular religious beliefs; aversion to odd numbers; and nervous habits, such as opening a door and closing it a certain number of times before one enters or leaves a room. In GTS patients the most common obsessive compulsive symptoms include sexual, religious or aggressive obsessions, checking compulsions, need for symmetry and ordering behavior (Cath et al., 2001; Leckman, 2003).

Attention Deficit Hyperactivity Disorder (ADHD) is just as common in GTS patients as is OCD (Sheppard, 1999). This disorder is characterized by lack of concentration (most prominent in girls), impulsivity and hyperactivity (most prominent in boys). This disorder is unjustly seen as a childhood disorder. Its onset is in childhood, but the symptoms (especially symptoms of inattention) persist in to adulthood and often stay present throughout the patients lives.

Furthermore, autism is seen in 12% of all GTS patients (Cath et al., unpublished data). Cath et al. (2001b) Cath et al. (2001b) and Eapen et al. (2004) found a high occurrence of depression, along with the anxiety and obsessions that other research already had shown (Eapen et al., 1997; George at al., 1993; Leckman et al., 1995).

Symptom Dimensions of GTS

Different studies on GTS symptom dimensions have portrayed different results. Mathews et al. (2007) performed a cluster analysis and distinguished only two dimensions; simple and complex tics. Robertson et al. (2008) performed a principle components analysis on a large cohort of GTS patients and found 5 factors; socially inappropriate behaviors and other complex vocal tics, complex motor tics, compulsive behaviors, simple tics, touching self. Katerberg et al. (2010) performed an item-level factor analysis in 290 GTS patients and found 6 factors to explain most of the tic variance; complex and self-injurious motor tics, compulsions, simple tics, complex vocal tics, common complex tics and miscellaneous tics. Heritability analysis suggests that the predominantly the simple facial motor tics and complex tics are heritable (de Haan, 2010).

Symptom Dimensions of OCD

To reduce the phenomenological heterogeneity of OCD, several factor analyses have been performed (Leckman et al. 1997; Feinstein et al. 2003; Stewart et al. 2007; Wu et al. 2007; Katerberg et al., 2010). The majority of these studies identified three or four main symptom dimensions based on factor analyses of symptom categories -not individual items. A recent

meta-analysis found four OC symptom dimensions: (1) symmetry obsessions; counting, ordering and arranging compulsions; (2) obsessions and checking (aggressive, sexual, religious and somatic obsessions; and related checking compulsions); (3) contamination/cleaning, and (4) hoarding (Bloch et al. 2008).

Katerberg et al. (2010) however, suggests in the to date largest item-level factor-analytic and heritability study conducted for OC symptoms that a five factor model offers the best fit: (1) taboo (religious, sexual, and aggressive obsessions) symptoms, (2) contamination and cleaning symptoms, (3) doubts (fears of harming self or others, doubting and checking symptoms), (4) superstitions and rituals, and (5) hoarding and symmetry symptoms (including perfectionism).

Symptom Dimensions of Autism

The general assumption is that autism and Asperger Syndrome lie on a continuum of social-communication disability (Baron-Cohen, 1995). The continuum view moves away from categorical diagnosis and towards a quantitative approach; autism is seen in this view as part of a spectrum of which tic disorders and OCD are part.Baron –Cohen (2001) identify five dimensions: social skill, attention switching, attention to detail, communication and imagination.

Symptom Dimensions of ADHD

According to the DSM IV -TR, ADHD is divided in three subtypes: The inattentive subtype, the hyperactive subtype and the combined hyperactive –inattentive subtype (American Psychiatric Association [*DSM-IV-TR*], 2000). There is a broad consensus regarding the validity of the inattentive symptoms and hyperactive symptoms model (Milich, Ballentine & Lynam, 2001).

Hypothesis and aim:

The aim of this study is to identify the underlying structure of GTS and its co -morbid symptomatology, illustrated in Figure 1. Data from different questionnaires are used to asses the symptom dimensions of tic, OC and ADHD symptoms in a large group of GTS patients and non-clinical family members.

Figure 1. Hypothesis Model

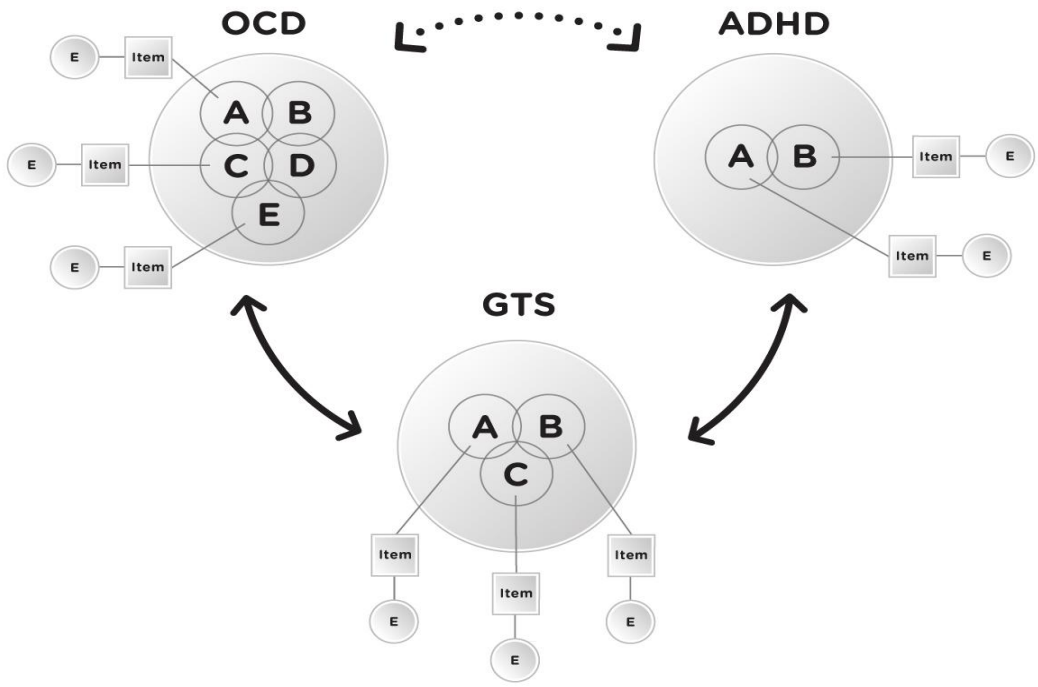

Figure 1. Hypothesis Model. The three spheres represent the disorders OCD, ADHD and GTS. In each disorder the given symptom dimensions are represented by an alphabetic letter. OCD: Taboo, Contamination /cleaning, Doubts, Rituals /superstition and Hoarding /symmetry. ADHD: inattentive and hyperactive symptoms. GTS: Vocal tics & obscene behavior, Body tics and Simple head/neck tics. Each symptom dimension is referred to by an Item box indicating these have been measured by a specific set of items. The "E -box" represents the error; given that the observed score is a true score plus an error.

Hypothesis 1)

GTS model 3 (de Haan, 2010) will provide the best fit.

Hypothesis 2)

The model of symptom dimensions across tic symptoms and symptoms of OCD will provide a good fit, will better represent the heterogeneity of the disorder and comorbid symptoms between disorders will partly correlate.

Hypothesis 3)

The model of symptom dimensions across tic symptoms and symptoms of ADHD will provide a good fit, will better represent the heterogeneity of the disorder and comorbid symptoms between disorders will partly correlate.

Identification of such structures can lead to advances in future genetic as well as treatment studies of GTS.

Methods:

Subjects:

The total study sample included 225 patients and 371 patients family members, making a total of 596 participants. Participants for this study were recruited at outpatient clinics in the Netherlands (GGZ Ingeest, Amsterdam) and from the Dutch Tourette's Syndrome Association. The controls were recruited via the snowball method and also constituted family members of Myoclonus-Dystonia (M-D) patients, recruited in a family study conducted by the department of neurology at the AMC Amsterdam (dr. de Koning-Tijssen).This study was approved by the Medical Ethical Review Board of the VUmc and informed consent was obtained from all participants.

The subjects' frequencies are presented in table 1. The mean age of the patients was 30.12 years (SD =15.27). Most patients (N=145) were male; 95.1% was diagnosed with GTS (the residue being CMT CVT or Tics NAO); Tic severity was estimated at 19.39 (SD =10.19) with a range of 0 to 50. Co -morbid disorders were also assessed: 31.1% of the patients were diagnosed with an Obsessive Compulsive Disorder and 23.9% had Obsessive Compulsive Symptoms, with a mean YBOCS score of 9.12 (SD= 8.85), a score of ≥ 16 defined as fulfilling a clinical diagnosis of OCD and a score of <16 as Sub –threshold OCD.

With the aid of CAARS (Conners et al., 1999) was ADHD assessed: A total of 15% of the patients were diagnosed with ADHD Inattentive type (6 or more inattentive symptoms) , 12% with ADHD Hyperactive type (6 or more hyperactive symptoms) and 5.3% with ADHD Combined type (5 or more inattentive symptoms in combination with 5 or more hyperactive symptoms).

The mean age of the patients' relatives was 41.43 years (SD =19.20). Participants' gender distribution was even ; 13.7% of the relatives was GTS diagnosed; Tic severity in relatives was estimated at 2.55 (SD =5.45)) with a range of 0 to 50.

Co -morbid disorders were also assessed: 4.3% of the patients relatives was diagnosed with an Obsessive Compulsive Disorder and 16.7% had Obsessive Compulsive Symptoms, with a mean YBOCS score of 1.67 (SD= 4.57). A total of 5.1% was diagnosed with ADHD Inattentive type, 4.3% with ADHD Hyperactive type and 2.0% with ADHD Combined type.

Table 1. Subjects Frequencies

	Age (SE)	GTS	YGTSS (SE)	OCD	OCS	YBOCS (SE)	ADHD Inatt.	ADHD Hyper	ADHD Comb.
Male Patient (N=145)	29,75 (15,27)	95.9%	19.39 (10.19)	30.3%	25.5%	7.79 (8.87)	14 %	12%	5.3%
Female Patient (N=80)	30.79 (15.27)	93.8%	17.92 (8.38)	32.5%	21.3%	10.72 (9.04)	16%	12%	5.8%
Mother (N=115)	49,80 (10.49)	10.7%	1.94 (4.90)	4.9%	18.0%	1.84 (4.57)	4%	6.1%	2.6%
Father (N=104)	52,84 (11,80)	3.9%	2,15 (5,25)	1.0%	11.8%	0,63 (2,82)	0.8%	0%	0%
Brother (N = 28)	21.7 (14.7)	14.3%	3,96(6,26)	0%	17.8%	1,83 (4,73)	11%	3.6%	0%
Sister (N = 35)	25.4 (17.9)	34.3%	8,50 (11,62)	14.3%	31.4%	4,13 (7,44)	2.8%	0%	0%
Half-brother (N=3)	14.7 (4.0)	33.3%	3,50 (4,95)	0%	100%	2,00 (3,46)	0%	0%	0%
Halfsister (N=1)	14.0 (-)	0%	0,00	0%	100%	1,00	0%	0%	0%
Son (N = 22)	16.3 (6.8)	40.9%	5,83 (7,80)	4.5%	31.8	3,31 (5,78)	13.6	9%	4.5%
Daughter (N=13)	17.2 (9.5)	30.8%	6,64 (7,20)	23.1%	23.1%	4,92 (8,36)	0%	15.4%	0%
Male Partner (N = 5)	48.6 (10.1)	0%	2,67 (4,62)	0%	80%	0,20 (0,45)	0%	0%	0%
Female Partner (N = 10)	46.7 (12.6)	0%	0,00	0%	20%	1,10 (3,48)	0%	0%	0%
Other Family (N=38)	44,63 (21,11)	5.3%	1.00 (2.66)	0%	18.4%	0.50 (1.99)	0%	0%	0%

Table 1. Subjects Frequencies. Age (Standard Error), Gilles de la Tourette Syndrome, Yale Global Tic Severity Scale (Standard Error) , Obsessive Compulsive Disorder, Obsessive Compulsive Symptoms , the Yale-Brown Obsessive Compulsive Scale Total Score (Standard Error), ADHD Inattentive symptoms, Hyperactive symptoms and ADHD combined type.

Measures:

GTS

The Yale Global Tic Severity Scale (YGTSS) is a clinical rating instrument that was designed for use in studies of Tourette's syndrome and other tic disorders (Leckman et al., 1989). The YGTSS provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms. The Yale Tic Scale was used to asses Tourette's symptoms.

The items in this study were chosen from selected items corresponding with the factors found in a large Tourette study by de Haan et al. (2010); vocal tics & obscene behavior, Body tics; and Head and neck tics. Items with > .40 factor loadings were included, making a total of 26 items.

Due to relativity small amounts of variation in positive responses all Tourrette -data was dichotomized from the original item responses "never", "in the past" and "in the present". The two latter were combined to obtain a lifetime tic score. For the distribution of tic symptoms: see Figure 2 below. An example of an item from the questionnaire reads as follows: "Occurrence of eye blinking, eye squeezing".

Figure 2. Number of Subjects versus Tic Diagnoses

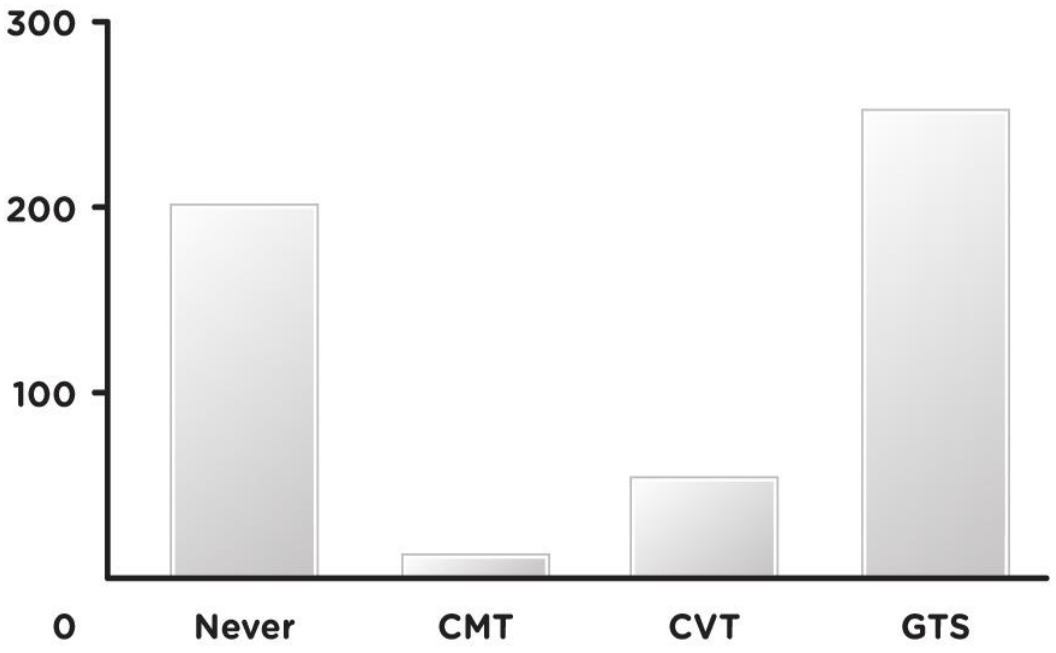

Figure 1. Number of Subjects versus Tic Diagnoses in the total sample. Vertical axis = Number of subjects. Horizonal axis = "Never" indicates no diagnosis, "CMT" indicates Cronic Multiple Tics, "CVT" indicates Cronic Vocal Tics and GTS indicates Gilles de la Tourette.

With the final 26 GTS items selected and dichotomized, this data was further prepped for analysis by cueing all items by symptom dimension in Statistical Package for the Social Sciences (SPSS, 2007). This resulted in the following items per symptom dimension:

Vocal Tics:
TICV01 (Throat clearing), TICV02 (Coughing, sniffing), TICV04 (Animal noises), TICV04 (Animal noises), TICV06 (Syllables), TICV07 (Words), TICV08, (Echolalia), TICV09 (Palilalia) and TICV12 (Obscene Language).

Simple head and Neck Tics::
TICM01 (Eye blinking), TICM02 (Looking surprised), TICM03 (Lift nose, bite tongue), TICM04 (Widen nostrils, smile), TICM05 (Lift chin) and TICM06 (Throw head backwards).

Body Tics:
TICM07 (Single shoulder movements), TICM08 (Complex shoulder movements), TICM09 (Single movements with arm or hand),TICM10 (Complex movements with arm), TICM11 (Single movements with leg), TICM12 (Complex movements with leg), TICM13 (Single Movements stomach), TICM17 (Rude /obscene gestures), TICM18 (Unusual positions), TICM19 (Bend or rotate) and TICM20 (Turn or stretch).

OCD

Also, every participant filled out the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) which does not only allow information about presence of Obsessive Compulsive symptoms, but also about symptom severity (Rosario -Campos et al., 2006). Containing over 80 original items, 48 items were included in this study to assess OCD symptom dimensions. Inclusion of items was based on a recent and extensive Item -level Factor Analysis study of the questionnaire by Katerberg (2010), drawn from a international cohort. In this study five factors were found; Taboo, Contamination /cleaning, Doubts, Rituals /superstition and Hoarding /symmetry.

Items were included with factor loadings >.40. OCD. All OCD data was dichotomized due to small variations in positive responses. This is most likely because to the variance of Y-BOCS severity scores in the total population, as illustrated in Figure 3 below. From the options “never”, “in the past” and “in the present” the life time occurrence was computed. An example of an item from the questionnaire reads as follows: “Fear of acting impulsively”.

Figure 3. OCD Y-BOCS Severity: Patients versus Relatives

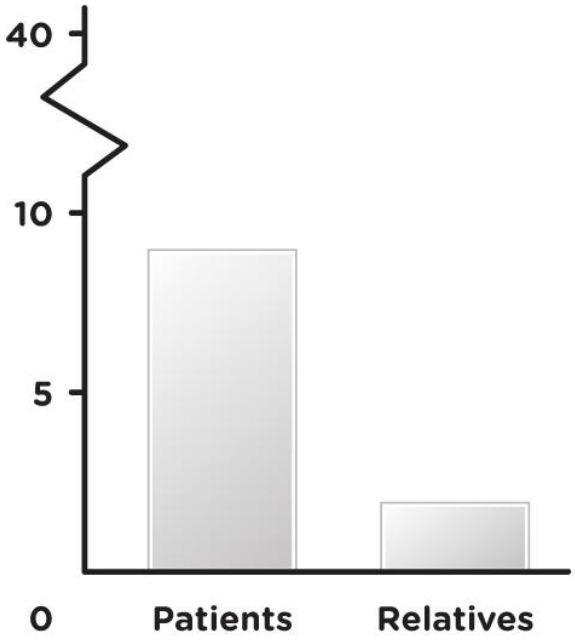

Figure 2. OCD Y-BOCS Severity: Patients versus Relatives. Vertical axis = Y-BOCS Sererity score. Horizonal axis = Patients and Relatives.

With the final 48 OCD items selected and dichotomized, this data was further prepped for analysis by cueing all items by symptom dimension in SPSS. This resulted in the following items per symptom dimension:

Taboo:
YBTA37 (Afraid of hurting myself), YBTA38 (Hurting others), YBTA39 (Violent images), YBTA40 (Blurring out obscenities), YBTA41 (Acting inappropriate), YBTA42 (Acting impulsively), YBTA43 (To steal), YBTA57 (Sexual thoughts), YBTA59 (Blasphemy) and YBTA60 (Moral).

Doubt:
YBDO06 (Check hurting others), YBDO07 (Check hurting myself), YBDO08 (Check catastrophe), YBDO09 (Check for error), YBDO10 (Check machinery), YBDO44 (Fear hurting others) and YBDO45 (Fear responsible disaster).

Rituals /superstition:
YBDO06 (Check hurting others), YBDO07 (Check hurting myself), YBDO08 (Check catastrophe), YBDO09 (Check for error), YBDO10 (Check machinery), YBDO44 (Fear hurting others) and YBDO45 (Fear responsible disaster).

Contamination /cleaning:
YBCL01 (Showering),YBCL04 (Cleaning House), YBCL05 (Prevent contamination), YBCL51 (Body secretions), YBCL52 (Dirt /bacteria's), YBCL53 (Fear of contamination), YBCL55 (Sticky substances) and YBCL56 (Worrying about contamination).

Hoarding /symmetry:
YBHO12 (Re –reading /writing), YBHO16 (Arrange things), YBHO17 (Applying symmetry), YBHO19 (Hoarding), YBHO58 (Collective obsessions), YBHO62 (Obsessions on symmetry), YBHO64 (Things in sequence), YBHO68 (Must remember things) and YBHO70 (Saying exactly wrong thing).

ADHD

The Conners' Adult ADHD Rating Scales–Observer: Long Version (CAARS–O:L) was used to asses participant's ADHD Inattentive and Hyperactive /Impulsive symptoms (Conners et al., 1999). The CAARS-O:L has symptom checklists with ratings of "not at all," "just a little," "pretty much," and "very much". An example of an item from the questionnaire reads as follows: "I give answers to questions before the questions have been completed". The 18 DSM-IV ADHD items can be extracted from the CAARS, which recently were used as the primary outcome measure in the largest medication trials in adult ADHD to date (Mighelson, 2003). These 18 items were included in the analysis:

Inattentive:
CARS02 (I lose things), CARS24 (Keeping attention focused), CARS29 (Forgetful in daily activities), CARS33 (Trouble listening), CARS42 (Trouble attention to detail), CARS48 (Don't like homework), CARS60 (Trouble finishing job tasks), CARS64 (Distracted) and CARS65 (Problems organizing tasks).

Hyperactive:
CARS09 (Talk too much), CARS14 (Trouble doing leisure activity quietly), CARS21 (I leave my seat unauthorized), CARS22 (Trouble waiting in line), CARS38 (Always on the go), CARS41 (I fidget), CARS50 (Restless or overactive), CARS58 (Give answers before completed) and CARS62 (I interrupt others).

Autism

Autism was also assessed in this study, by the Autism-Spectrum Quotient (AQ) (Baron-Cohen et al. 2001). However, this data was left out of the final analysis because of a poor fit of the model ($\Delta\chi 2 > 0.598$, $p < 0.001$).

Before starting the analysis we recoded the autism data. “Definitely agree” or “slightly agree” responses scored 1 point, on the following items: 1, 2, 4, 5, 6, 7, 9, 12, 13, 16, 18, 19, 20, 21, 22, 23, 26, 33, 35, 39, 41, 42, 43, 45, 46. “Definitely disagree” or “slightly disagree” responses scored 1 point, on the following items: 3, 8, 10, 11, 14, 15, 17, 24, 25, 27, 28, 29, 30, 31, 32, 34, 36, 37, 38, 40, 44, 47, 48, 49, 50. The former being recoded: all item responses “4” to “1”, “3” to “2”, “2” to “3” and “1” to “4”.

The applied model consisted five factors found by Baron -Cohen et al. (2001): *social skill* (items 1, 11, 13, 15, 22, 36, 44, 45, 47, 48); *attention switching* (items 2, 4, 10, 16, 25, 32, 34, 37, 43, 46); *attention to detail* (items 5, 6, 9, 12, 19, 23, 28, 29, 30, 49); *communication* (items 7, 17, 18, 26, 27, 31, 33, 35, 38, 39); *imagination* (items 3, 8, 14, 20, 21, 24, 40, 41, 42, 50).

Statistical Analyses

The Confirmatory Factor Analysis (CFA) was conducted using Mplus 5.21 (Muthén and Muthén, 2007). Statistical Package for the Social Sciences Version 17.0 (2007) was used for data preparation.

Goodness-of-fit was evaluated using the Comparative Fit Model (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean

Square Residual (SRMR). The Maximum Log Likelihood Estimator (MLE) was used as the estimator.

Although there is little consensus on the cut-off values for the most adequate fit (Lance et al., 2006), conventional guidelines were followed whereby fit is considered adequate if CFI and TLI values are >0.90, RMSEA is <0.08, and SRMR is <0.05. and Akaike Information Criterion (AIC) and Bayesian Method were used to compare the fit of the assessed models. AIC rewards a models goodness of fit. On the other hand, it gives a penalty for increasing the number of estimated parameters. In this way overfitting is discouraged.

In the subsequent section we want to present the consecutive results as follows: First, we want to use factor analytic strategies mentioned above to to reduce symptom heterogeneity per disorder.

We begin with GTS, fitting 4 models with an ascending number of factors. The First model consists of one factor, representing GTS as a single factor disorder. The second model is a 2 – factor model suggested by Mathews et al. (2007). They found the factors Simple motor and vocal tics versus Complex motor and vocal tics in a population of 254 patients with GTS.

The 3 factor model is based on the most recent GTS factor study on 494 GTS patients by de Haan et al. (2010). They're results yielded the factors Vocal tics & obscene behavior, Body tics and Simple head/neck tics.

Lastly, the GTS model with 4 factors is derived from a 2008 study on 410 patients with GTS (Robertson et al, 2008). They found a factor model consisting of: Socially inappropriate behaviors and other complex vocal tics, Complex motor tics, Simple tics, Compulsive behaviors; and Touching self.

For OCD, we will fit two different factor models. The first OCD model, like the first GTS model, will consist of one single factor representing the disorder. The second model contains 5 factors found in the factor study with by Katerberg (2010) as mentioned before. The factors found by 1224 subjects are Taboo, Contamination /cleaning, Doubts, Rituals /superstition and Hoarding /symmetry.

For ADHD, two models will be fitted as well. The first being a single factor model and the second a 2 factor model based on the DSM IV (American Psychiatric Association [*DSM-IV-TR*]) diagnoses ADHD inattentive and hyperactive.
When all disorder models are computed, the best model fits selected are selected.
These models will be used to build a consecutive model of 3 disorders, which will be tested for its fit in a final CFA.

Results

Table 2 shows the outcome of the GTS CFA on the total sample. Model 1 provided a good fit on the data ($\Delta\chi2 > 0.965$, $p < 0.001$). Model 2 did better then the perceived unitary model $\Delta AIC = -23$ and $\Delta\chi2 > 0.967$, $p < 0.001$. Model 3 fit the data best ($\Delta\chi2 > 0.969$, $p < 0.001$) and presented the lowest AIC ($\Delta AIC = -18$). Model 4 resulted in a poorer fit as the AIC increased ($\Delta AIC = 6$) Thus, model 3 was selected for the analysis in this paper. Factors include 1) Vocal tics & obsence behavior 2) Body tics and 3) Simple head and neck tics.

Table 2. GTS Model Fit Criteria

Model	AIC
1	8653
2	8630
3	8612
4	8618

Table 2 GTS Model Fit Criteria. AIC = Akaike information criterion.

The GTS correlations between it's symptom dimensions is shown in table 3 below. It presents a high correlation between the three symptom dimensions. In particular the body factor correlates highly with other factors (E> .938). Factors Vocal and Simple Head differentiate themselves in about the same degree. Standard errors and estimated errors display similar values between these two factors. Between the factors Simple Head and Body the error is slightly smaller.

Tabel 3. GTS Factor Correlations

	Vocal Tics	Body Tics	Simple Head Tics
Vocal Tics		E: 0.942 SE: 0.020 ESE: 46.006	E: 0.890 SE: 0.020 ESE: 44.259
Body Tics			E: 0.938 SE: 0.015 ESE: 62.365
Simple Head Tics			

Tabel 3. GTS factor Correlations.
E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.001

Table 4 shows the outcomes of the CFA we preformed on the OCD and ADHD data. Model 1 of OCD provided a good fit of ($\Delta\chi2$ >0.920, p <0.001) with an AIC of 9752. However, Model 2 was superior tot Model 1 given a better fit ($\Delta\chi2$ >0.931, p <0.001) and a lower AIC (ΔAIC = -3).

Table 4. CFA models OCD and ADHD

	OCD Model 2 (5 factors)	OCD Model 1(1 factor)	ADHD Model 2 (2 factors)	ADHD Model 1 (1 factor)
CFI	0.931	.920	0.925	0.846
TLI	0.948	.941	0.967	0.928
AIC	4931	5057	6494	6607

Table 4 CFA Models OCD and ADHD.
CFI = Comparative Fit Index
TLI = Tucker –Lewis Index
AIC = Akaike information criterion.

Table 5. OCD Factor Correlations

	Taboo	Clean	Doubt	Ritual	Hoarding
Taboo		E: 0.578 SE:0.091 ESE: 6.338	E:0.840 SE:0.068 ESE:12.343	E:0.738 SE:0.072 ESE: 10.248	E:0.681 SE:0.064 ESE:10.716
Clean			E:0.858 SE:0.051 ESE:16.681	E: 0.844 SE: 0.053 ESE:16.046	E: 0.818 SE:0.053 ESE:15.507
Doubt				E: 0.872 SE:0.042 ESE:20.986	E: 0.803 SE:0.039 ESE:20.547
Ritual					E:0.825 SE:0.042 ESE:19.465
Hoarding					

Table 5. OCD Factor Correlations.
E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.001

The correlations between the five OCD symptom dimensions are shown in table 5 above. The Taboo factor shows the lowest correlations with respect to other factors (E = < 0.58, 0.84, 0.74 and 0.68). This factor differentiates itself from other factors. The other factors have correlations equal to each other and vary between 0.80 and 0.87.

ADHD Inattentive and Hyperactive Symptoms have a correlation of 0.75, with a standard error of 0.04 and an estimated error of 17.98.

Table 6. Main model of Symptom dimensions GTS vs. OCD and ADHD

	OCD Taboo	OCD Clean	OCD Doubt	OCD Ritual	OCD Hoard	ADHD Inattent	ADHD Hyper
GTS Vocal	E: 0.760 S: 0.049 P: 0.001	E: 0.468 S: 0.091 P: 0.001	E: 0.596 S: 0.063 P: 0.001	E: 0.637 S: 0.065 P: 0.001	E: 0.543 S: 0.058 P: 0.001	E: 0.072 S: 0.106 P: 0.496	E -0.028 S: 0.094 P: 0.768
GTS Body	E: 0.731 S: 0.054 P: 0.001	E: 0.334 S: 0.107 P: 0.002	E: 0.397 S: 0.060 P: 0.001	E: 0.596 S: 0.070 P: 0.001	E: 0.540 S: 0.061 P: 0.001	E: 0.084 S: 0.095 P: 0.378	E -0.061 S: 0.089 P: 0.497
GTS Simple Head	E: 0.828 S: 0.041 P: 0.001	E: 0.531 S: 0.089 P: 0.001	E: 0.608 S: 0.060 P: 0.001	E: 0.738 S: 0.056 P: 0.001	E: 0.571 S: 0.064 P: 0.001	E: 0.075 S: 0.101 P: 0.459	E: 0.009 S: 0.089 P: 0.918

Table 6. Main model of Symptom dimensions GTS vs. OCD and ADHD.
E= Estimator.
SE= Standard Error.
P-Value's are all <.0.001

In table 6 we present the correlations between the GTS symptom dimensions and the OCD and ADHD dimensions. The dimensions that correlate highest with GTS are OCD Taboo with an average correlation of 0.77 and OCD Rituals 0.66. The other three OCD dimensions correlated with GTS on average as follows: Hoarding: 0.55, Doubt: 0.53, Cleaning: 0.44. All correlations were significant p = < 0.005.

GTS Vocal correlates with OCD on average with 0.60, GTS Body with 0.52 and GTS Simple Head with 0.67.

ADHD symptom dimensions do not correlate with any symptom dimensions above 0.084. Also, none of these correlations are significant (p = < 0.05).

Table 7. OCD, ADHD and GTS Model fits.

	Model 1 -1 Factor	Model 2 -3 Factors	Model 3 -10 factors
CFI	0.414	0.931	0.948
TLI	0.401	0.942	0.952
WRMR	1.830	1.991	1.824
AIC	14236	12823	12599

Table 7. OCD, ADHD and GTS Model fits.
CFI = Comparative Fit Index
TLI = Tucker Lewis Index
WRMR = Weighted Root Mean Residual
AIC = Akaike Information Criterion

Table 7 shows the outcome of the final CFA of all included disorders on the total sample. Model 1 provided a poor fit on the data ($\Delta\chi2 > 0.414$, $p < 0.001$). Model 2 did better than the perceived unitary model $\Delta AIC = -1413$ and $\Delta\chi2 > 0.931$, $p < 0.001$. Model 3 fit the data best ($\Delta\chi2 > 0.948$, $p < 0.001$) and presented the lowest AIC ($\Delta AIC = -224$).

*All item level analysis are provided in appendix.

Discussion

The aim of this study was to identify the underlying structure of GTS and its co -morbid symptomatology using a large sample of GTS patients and relatives. The hypothesis is that the model's fit between the populations will differ, indicating a spectrum of disorders. A large difference between this study and previous studies is that this is the first study to assess the co-morbid structure of GTS using Confirmatory Fator Analysis. First, we will discuss the single disorders followed by the final analysis.

Hypothesis 1)
GTS model 3 (de Haan, 2010) will provide the best fit.

Of the four GTS models assessed, model three provided the best fit and was selected for further analysis. This model is in line with the findings suggested by de Haan (2010) providing three symptom dimensions: 1) Vocal tics & obscene behavior 2) Body tics and 3) Simple head and neck tics. The GTS inter -correlations are relativity high. The three factor model presented here brings the notion of distinct subjects of tic formation and employs dichotomous specification based on international diagnostic criteria of TS (Alsobrook 2002). This model fills the gap between Mathew's two factor model and Robertson's five factor model. These findings suggest, in line with other research, there are certain clusters of tics that may occur together more often than expected by chance.

OCD

The five factor OCD model provided the best fit with relativity high correlations. This model is in line with the model proposed by Katerberg et al. (2010) with the factors: Taboo, Contamination /cleaning, Doubts, Rituals /superstition and Hoarding /symmetry.

The Taboo Factor which yields religious, sexual and aggressive obsession symptoms, stands out in the analysis with the lowest correlation. The Taboo and Doubts factors share a high correlation. In earlier bivariate analyses (Pauls, 2008, Katerberg et al., 2011), the taboo and doubts factors were found to share genetic influences. In the OCD Collaborative Genetics Study was also found that taboo thoughts are being the most strongly familial (Pinto et al. 2008).

It is also suggested that heritability for the one-factor OC symptom dimension model may be greater than any multiple symptom dimension model (Mathews et al., 2007, van Grootheest et al., 2008). However, the findings do not support the idea of a one-factor model for OCD .
The five symptoms dimension model reveals substantial overlap with the factor structures identified in previous item-level analyses (Feinstein et al., 2003; Pinto et al., 2008; Stein et al., 2007; Wu et al., 2007).

ADHD

The two factors model provided the best fit for ADHD. This was no surprise given the extent of research regarding this topic (Nikolas & Burt, 2010). The ADHD internal correlation turned out a bit lower compared to the correlations of respectively GTS and OCD. This is in line with the general finding that there are meaningful etiological differences between inattentive symptoms and hyperactive symptoms (Milich, Ballentine & Lynam, 2001).

Final Model

After all CFA's were preformed on a individual level per disorder and all symptom dimensions were established, we went on to preform the final CFA model: an assessment of the correlations between the given disorders. As in previous research (Mathews et al. 2009, Cath et al. 2004) the data suggest that the symptom dimension model is superior to the unitary model.

Figure 4 offers an schematic illustration of the final preformed CFA with all disorders. The solid arrows in between GTS and respectively ADHD and OCD indicate main model as shown in table 6.

Figure 4. Final CFA Model.

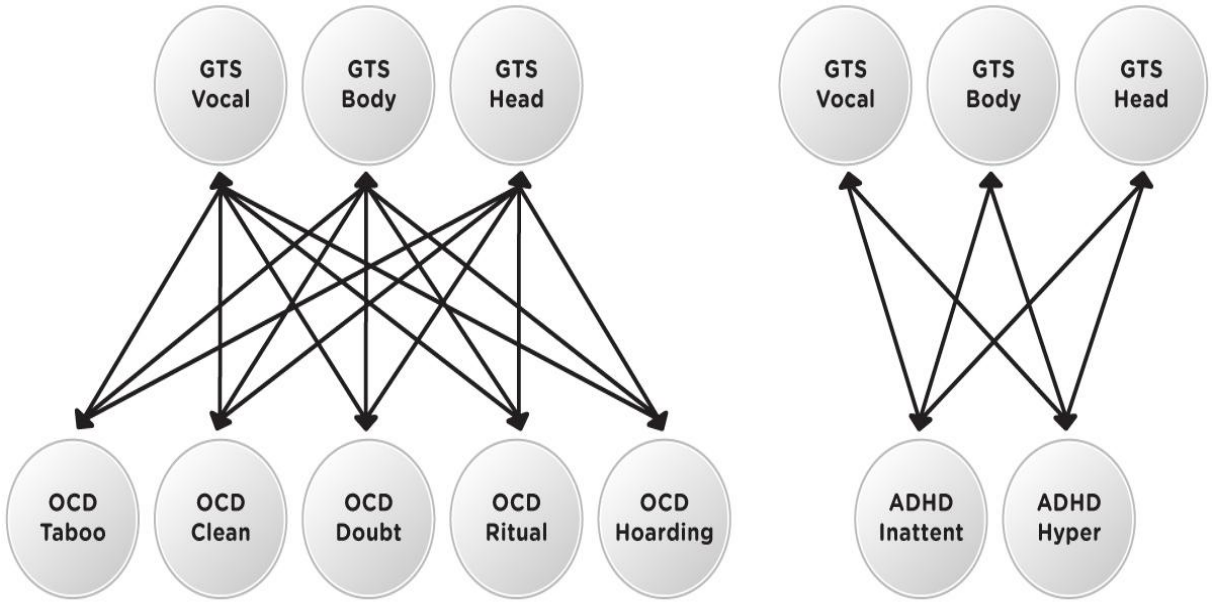

Figure 4. Final CFA Model. All tested correlations are shown.

Hypothesis 2)
The model of symptom dimensions across tic symptoms and symptoms of OCD will provide a good fit, will better represent the heterogeneity of the disorder and comorbid symptoms between disorders will partly correlate.

The hypothesis was confirmed. The findings are consistent with the conclusions from family-genetic studies that tics and OCD share a common underlying etiology (Swedo et al. 1993). Regarding all symptom dimensions, OCD Taboo showed the highest correlation with GTS, followed by OCD Rituals. The correlation with OCD Taboo is especially interesting given it's lowest internal OCD correlation. According to these measurements, the OCD symptom dimension Taboo shares more correlation with GTS than with OCD itself. Y -BOCS items of this OCD dimension include: forbidden impulses, fear of acting on unwanted impulses, fear of blurting out obscenities, fear of doing something embarrassing and aggressive obsessions. This corresponds with the finding of Cath et al. (2004) that aggressive obsessions are more regularly found in GTS -patients and tic -free OCD patients suffer more from cleaning symptoms. The latter is in line with the finding that the OCD Cleaning symptom dimension holds the lowest correlation with GTS.

Also, collaborative Genetics Study identified in four OCD factors the Taboo Factor as the most robustly familial (Hasler et al. 2007; Pinto et al. 2008). A proportion of the variance can be explained by the fact that the scores of this factor are in general a bit higher in males than in females (Katerberg, 2010).

The factor GTS Body has the lowest correlation with OCD. In combination with the observation that GTS Body has the highest inter -disorder correlation (table 3), these findings suggest that Body factor is indeed the most core dimension of OCD. The factors Vocal and Simple Head correlate the highest with OCD.

Hypothesis 3)
The model of symptom dimensions across tic symptoms and symptoms of ADHD will provide a good fit, will better represent the heterogeneity of the disorder and comorbid symptoms between disorders will partly correlate.

The hypothesis was not confirmed. In the analysis, there is a low correlation between ADHD and GTS. This can be accounted for in two ways. First, it is possible that there is a low correlation between ADHD and GTS in the general population. The frequent co-occurrence of tics and ADHD that has been noted in clinical samples was not observed in the sample. The findings are in line with Peterson's longitudinal study (2001) who suggested that the co-occurrence of tics and ADHD in clinic patients may result in part from a complex sharing across development of numerous psychopathological risk factors, including OCD, other anxiety disorders, conduct disturbances, and depression.

Second, there is the assumption that the ADHD data was not correctly integraded with the other disorder data. One argument in favor of this respect is the fact that the internal correlation of ADHD is high and the model fit is good. So the ADHD data by it's self seems to be in order. However, an argument against the assumption of an erroneous data integration is the fact that the overall model fit was good as well ($\Delta\chi 2 > 0.948$, $p < 0.001$) and an AIC ($\Delta AIC = -224$). Thus, at this point, no straight forward explaination can be given about the low corrlation between GTS and ADHD.

Strenghts of this study include a large number of subjects and a variety in fit models. Weaknesses are that the data was in part self-reported and its reliance on one sample with

different characteristics. Notwithstanding these considerations, the findings complement earlier findings that GTS and OCD can best be viewed as a spectrum of symptom dimensions (Cath et al. 2004; Robertson et al. 2008). At certain points the disorders seem to be entwined. The results of the current research and those of the previously published studies, although not identical, suggest that the symptom distribution of GTS is complex. Further identification its structure can lead to advances in future studies and ultimately in treatment of GTS.

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Appendix Item level Analysis

GTS

TABEL 1A. Standardized Factor loadings Vocal Tics

Vocal Tics			
	Estimate	Stand. Error	Est./S.E.
TICV01 (Throat clearing)	0.818	0.028	29.277
TICV02 (Coughing, sniffing)	0.890	0.026	34.689
TICV04 (Animal noises)	0.733	0.039	18.871
TICV06 (Syllables)	0.728	0.039	18.838
TICV07 (Words)	0.722	0.040	17.990
TICV08 (Echolalia)	0.756	0.032	23.367
TICV09 (Palilalia)	0.807	0.027	29.648
TICV12 (Obscene Language)	0.763	0.032	23.644

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 1B. Standardized Factor loadings Simple Head and Neck Tics

Simple Head and Neck Tics			
	Estimate	Stand. Error	Est./S.E.
TICM01 (Eye blinking)	0.698	0.038	18.276
TICM02 (Looking surprised)	0.931	0.022	43.065
TICM03 (Lift nose, bite tongue)	0.810	0.028	29.277
TICM04 (Widen nostrils, smile)	0.888	0.025	35.981
TICM05 (Lift chin)	0.836	0.025	32.971
TICM06 (Throw head backwards)	0.812	0.026	30.678

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 1C. Standardized Factor loadings Body Tics

Body Tics			
	Estimate	Stand. Error	Est./S.E.
TICM07 (Single shoulder movements)	0.796	0.029	27.456
TICM08 (Complex shoulder movements)	0.843	0.025	34.278
TICM09 (Single movements with arm or hand)	0.809	0.028	29.301
TICM10 (Complex movements with arm)	0.855	0.027	31.733
TICM11 (Single movements with leg)	0.811	0.028	29.144
TICM12 (Complex movements with leg)	0.884	0.022	40.872
TICM13 (Single Movements stomach)	0.739	0.041	18.253
TICM17 (Rude /obscene gestures)	0.852	0.023	37.109
TICM18 (Unusual positions)	0.654	0.045	14.394
TICM19 (Bend or rotate)	0.820	0.033	24.599
TICM20 (Turn or strech)	0.698	0.047	14.998

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 2A. Standardized Factor loadings ADHD Inattentive Symptoms

ADHD Inattentive			
	Estimate	Stand. Error	Est./S.E.
CARS02 (I lose things)	0.549	0.066	8.265
CARS24 (Keeping attention focused)	0.822	0.034	24.511
CARS29 (Forgetful in daily activities)	0.660	0.052	12.656
CARS33 (Trouble listening)	0.767	0.043	17.633
CARS42 (Trouble attention to detail)	0.716	0.049	14.463
CARS48 (Don't like homework)	0.688	0.051	13.498
CARS60 (Trouble finishing job tasks)	0.819	0.034	23.802
CARS64 (Distracted)	0.786	0.040	19.810
CARS65 (Problems organizing tasks)	0.744	0.045	16.397

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 2B. Standardized Factor loadings ADHD Hyperactive Symptoms

ADHD Hyperactive			
	Estimate	Stand. Error	Est./S.E.
CARS09 (Talk too much)	0.623	0.054	11.499
CARS14 (Trouble doing leisure activity quietly)	0.779	0.043	17.945
CARS21 (I leave my seat unauthorized)	0.872	0.043	20.461
CARS22 (Trouble waiting in line)	0.719	0.049	14.528
CARS38 (Always on the go)	0.541	0.060	8.988
CARS41 (I fidget	0.610	0.060	10.193
CARS50 (Restless or overactive)	0.838	0.034	24.865
CARS58 (Give answers before completed)	0.715	0.049	14.536
CARS62 (I interrupt others)	0.725	0.050	14.401

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.00

OCD

Tabel 3A. OCD Factors With Statements

	Taboo	Clean	Doubt	Ritual	Hoarding
Taboo		E: 0.578 SE:0.091 ESE: 6.338	E:0.840 SE:0.068 ESE:12.343	E:0.738 SE:0.072 ESE: 10.248	E:0.681 SE:0.064 ESE:10.716
Clean			E:0.858 SE:0.051 ESE:16.681	E: 0.844 SE: 0.053 ESE:16.046	E: 0.818 SE:0.053 ESE:15.507
Doubt				E: 0.872 SE:0.042 ESE:20.986	E: 0.803 SE:0.039 ESE:20.547
Rituel					E:0.825 SE:0.042 ESE:19.465
Hoarding					

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 3B. Standardized Factor loadings OCD Taboo Symptoms

OCD Taboo			
	Estimate	Stand. Error	Est./S.E.
YBTA37 (Afraid of hurting myself)	0.883	0.077	11.500
YBTA38 (Hurting others)	0.771	0.076	10.179
YBTA39 (Violent images)	0.827	0.067	12.436
YBTA40 (Blurring out obscenities)	0.782	0.095	8.260
YBTA41 (Acting inappropriate)	0.815	0.062	13.081
YBTA42 (Acting impulsively)	0.779	0.069	11.221
YBTA43 (To steal)	0.648	0.127	5.118
YBTA57 (Sexual thoughts)	0.556	0.101	5.520
YBTA59 (Blasphemy)	0.592	0.103	5.754
YBTA60 (Moral)	0.780	0.070	11.087

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 3C. Standardized Factor loadings OCD Cleaning Symptoms

OCD Cleaning			
	Estimate	Stand. Error	Est./S.E.
YBCL01 (Showering)	0.869	0.067	12.923
YBCL04 (Cleaning House)	0.733	0.074	9.846
YBCL05 (Prevention contamination)	0.752	0.093	8.111
YBCL51 (Body secretions)	0.839	0.089	9.436
YBCL52 (Dirt /bacteria's)	0.782	0.083	9.414
YBCL53 (Fear of contamination)	0.972	0.080	12.153
YBCL55 (Sticky substances)	0.743	0.102	7.321
YBCL56 (Worring about contamination)	0.721	0.128	5.651

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 3D. Standardized Factor loadings OCD Doubt Symptoms

OCD DOUBT			
	Estimate	Stand. Error	Est./S.E.
YBDO06 (Check hurting others)	0.921	0.060	15.446
YBDO07 (Check hurting myself)	0.909	0.060	15.149
YBDO08 (Check catastrophe)	0.728	0.049	14.996
YBDO09 (Check for error)	0.720	0.068	10.616
YBDO10 (Check machinery)	0.811	0.086	9.451
YBDO44 (Fear hurting others)	0.732	0.071	10.332
YBDO45 (Fear responsible disaster)	0.712	0.083	8.589

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 3D. Standardized Factor loadings OCD Ritual Symptoms

OCD Ritual			
	Estimate	Stand. Error	Est./S.E.
YBRI13 (Repeat routine activities)	0.562	0.084	6.685
YBRI15 (Count compulsion)	0.786	0.060	13.202
YBRI20 (Thought Rituals)	0.836	0.088	9.554
YBRI25 (Precautions getting hurt)	0.642	0.110	5.832
YBRI27 (Eating rituals)	0.594	0.109	5.423
YBRI28 (Superstition)	0.588	0.106	5.522
YBRI76 (Lucky numbers)	0.774	0.129	6.019
YBRI77 (Favorite collars)	0.678	0.117	5.783
YBRI78 (Superstition fears)	0.875	0.055	15.835

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000

Table 3E. Standardized Factor loadings OCD Hoarding Symptoms

OCD Hoarding/ symmetry			
	Estimate	Stand. Error	Est./S.E.
YBHO12 (Re –reading /writing)	0.880	0.041	21.541
YBHO16 (Arrange things)	0.929	0.023	40.502
YBHO17 (Applying symmetry)	0.724	0.074	9.804
YBHO19 (Hoarding)	0.750	0.061	12.328
YBHO58 (Hoarding)	0.952	0.025	38.466
YBHO62 (Obsessions on symmetry)	0.945	0.027	35.219
YBHO64 (Things in sequence)	0.695	0.087	8.002
YBHO68 (Miscellaneous)	0.631	0.081	7.788
YBHO70 (Saying exactly wrong thing)	0.803	0.101	7.983

E= Estimator.
SE= Standard Error.
Estimated Standard Error.
P-Value's are all <.0.000