SYMPTOM DIMENSIONS

IN

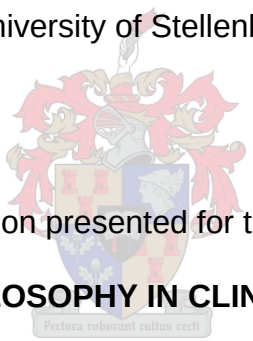
OBSESSIVE - COMPULSIVE DISORDER

Christine Lochner

BA Hons (African Languages; Psychology)

MA (Clinical Psychology)

University of Stellenbosch



Dissertation presented for the degree of

DOCTOR OF PHILOSOPHY IN CLINICAL PSYCHOLOGY

Department of Psychiatry, Faculty of Health Sciences, University of Stellenbosch

Promotor: Prof Dan J. Stein

Co-promotor: Prof Gideon P. de Bruin

2005

DECLARATION:

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously, in its entirety or in part, submitted it at any university for a degree.

Signature: _____ Date: _____

ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by significant heterogeneity. It has been suggested that classification of OCD into more homogeneous subtypes, and identification of their associations with etiological factors (e.g. genetic variants, or psychological trauma), and outcome (e.g. disability and treatment response), may be useful. The identified subtypes are not definitive yet and continue to be subject to revision. The overall objective of this dissertation was to assess comprehensively a sample of OCD patients, and to use cluster analytic methods to delineate valid OCD subtypes.

Methods: Patients meeting DSM-IV criteria for a primary diagnosis of OCD (N=261) on the Structured Clinical Interview for Axis I Disorders - Patient Version (SCID-I/P), with ages ranging from 16 to 71, took part in the study. The newly developed Structured Clinical Interview for the Diagnosis of putative Obsessive-Compulsive Spectrum Disorders (SCID-OCSD) was administered to assess OCD-related conditions not covered by the SCID-I/P. OCD subtyping, based on OCD symptomatology (assessed with the Yale-Brown Obsessive-Compulsive Symptom Checklist [YBOCS-CL]), and based on comorbidity with the OCD spectrum of disorders (assessed with the SCID-OCSD), proceeded along the following lines: Firstly, latent class cluster analysis (LCA), a categorical analogue to traditional factor analysis (FA), and with many advantages compared to FA, was implemented with the (nine) most frequently endorsed OC symptoms. Secondly, in an attempt to remedy some of the limitations of the LCA (e.g. increased potential for computational instability when additional indicators / symptoms were included), cluster analyses (Ward's method) were performed on all of the items of the YBOCS-CL and SCID-OCSD, respectively, for all OCD patients. The associations of cluster scores with demographic variables (age, gender), clinical variables (age of onset, obsessive-compulsive symptom severity and dimensions, level of insight, temperament, childhood trauma, treatment response) and genotypes were then examined,

using Spearman correlation coefficients, one-way analysis of variance (ANOVA), and Mann-Whitney U-tests, where appropriate.

Results: The findings suggested that increased presentation of symptoms characteristic of each of the clusters of cases was associated with specific demographic and clinical characteristics, which substantiated the presence of distinct clinical subtypes of OCD. Cluster analysis of the 45 selected items of the YBOCS-CL in this sample of OCD patients identified 6 separate clusters; these clusters were labelled “Contamination fears / washing”, “Hoarding / collecting”, “Symmetry / ordering / counting / arranging / repeating”, “Sexual”, “Somatic, religious and diverse” and “Harm-related”. Increased presentation of symptoms characteristic of each of the clusters was associated with specific demographic, clinical and, in some cases, genetic characteristics. Of note, the findings indicated the *L/L* (*met/met*) genotype of *COMT Val158Met* polymorphism plays a major role in the increased manifestation of sexual, somatic, religious and diverse, and harm-related symptoms of OCD, as such contributing to the relatively limited data on OC symptom subtypes and genetics. However, the fact that the associated features did not clearly and uniquely differentiate clusters and that clusters were significantly correlated with one another suggested that the delineation of the OCD complex into OC symptom clusters is not the only way to approach the heterogeneity characteristic of OCD. Nevertheless, the significant comorbidity with OCSD’s in the identified clusters (e.g. tics associated with sexual obsessions / compulsions) highlighted the significant relationship of OCD with the OCSD’s. This again raised the question about the way in which the OCSD’s “fit” with the standard OC symptomatology outlined in the YBOCS-CL. A cluster analysis of OCSD’s in OCD patients identified a Tourette’s syndrome / tics subtype of OCD (part of the so-called “reward deficiency” cluster), as well as an impulsivity subtype, and a somatic subtype – each associated with specific clinical and demographic variables. Here, a significant relationship between the identified

clusters and the investigated dopaminergic and serotonergic polymorphisms was not found, suggesting that variants in other genes in these systems should also be explored.

Conclusion: The main finding was that OCD is indeed a heterogeneous disorder that may be subtyped into different symptom dimensions. The identified OCD subtypes with their associated features were to a large extent consistent with previously published data. However, in contrast to factor analysis, LCA provided a novel, appropriate and advantageous statistical analysis strategy for the data. Furthermore, to our knowledge, the attempt to classifiy OCD according to comorbid OCSD's was the first cluster analysis based on a prospective comprehensive interview investigating a range of OCSD's. As such, although the dimensional structure of OCD is still not entirely understood, the categorization of our OCD patients into different groups and the investigation of their respective features have gone beyond the literature and thus add another dimension to the increasing efforts to fully delineate OCD subtypes.

ABSTRAK

Agtergrond: Obsessief-kompulsiewe steuring (OKS) is ‘n neuropsigiatriese toestand wat deur beduidende heterogeniteit gekenmerk word. Daar is voorheen voorgestel dat die klassifikasie van OKS in meer homogene endofenotipes of subtipes, en die identifisering van beduidende assosiasies daarvan met by voorbeeld spesifieke oorsaaklike faktore (bv. genetiese variante, of sielkundige trauma) en uitkomste (insluitend inperking en behandelingsrespons), nuttig kan wees. Die geïdentifiseerde subtipes is nog nie finaal bevestig nie en word daar met die hersiening van bevindinge hieroor volgehou. Die primêre doelstelling van hierdie verhandeling was om ‘n groep pasiënte met OKS deeglik te assesseer, en om tros-analise te gebruik om geldige OKS-subtipes te identifiseer.

Metodes: Pasiënte wat voldoen het aan DSM-IV criteria vir ‘n primêre diagnose van OKS (N=261) volgens die “Structured Clinical Interview for Axis I Disorders – Patient Version” (SCID-I/P), met ouderdomme strekkend vanaf 16 tot 71 jaar, het aan die studie deelgeneem. Die nuut-ontwikkelde “Structured Clinical Interview for the Diagnosis of Putative Obsessive-Compulsive Spectrum Disorders” (SCID-OCSD) is toegepas ten einde OKS-verwante toestande wat nie by die SCID-I/P ingesluit is nie, te assesseer. Subtipering van OKS gebaseer op OKS simptomatologie (soos vasgestel met die Yale-Brown Obsessive-Compulsive Symptom Checklist [YBOCS-CL]), en op komorbiditeit met die OKS spektrum van toestande (soos vasgestel met die SCID-OCSD), het op die volgende wyses geskied: Eerstens, latente klas tros-analise (LKA), ‘n kategoriese analoog vir tradisionele faktor analise (FA), en met baie voordele in vergelyking met FA, is geïmplementeer op die (nege) obsessief-kompulsiewe simptome wat die meeste gerapporteer is. Tweedens, ten einde sommige van die beperkinge van LKA aan te spreek (bv. die verhoogde moontlikheid vir onstabiliteit in die rekenaar-bewerkings wanneer addisioneleindikatore / simptome ingesluit word), is nog ‘n tros-analise (Ward se metode) op al die items van die YBOCS-CL en die SCID-OCSD onderskeidelik, vir alle OKS-pasiënte toegepas. Die assosiasies van die

tros-tellings met demografiese veranderlikes (ouderdom, geslag), kliniese veranderlikes (aanvangsouderdom van OKS, ernstigheidsgraad van obsessiewe-kompulsiewe simptome en dimensies, mate van insig, temperament, trauma in die kindertyd, behandelingsrespons) en genotipes is daarna ondersoek deur gebruik te maak van Spearman korrelasie-koëffisiënte, een-rigting analises van variansie (ANOVA), en Mann-Whitney U-toetse, soos toepaslik.

Resultate: Die bevindinge suggereer dat verhoogde rapportering van simptome kenmerkend van elkeen van die trosse van gevalle met spesifieke demografiese, kliniese en, in sommige gevalle, genetiese eienskappe geassosieërd was, wat die teenwoordigheid van unieke kliniese subtipes van OKS verder ondersteun. Tros-analise van die 45 geselekteerde items van die YBOCS-CL in hierdie groep OKS-pasiente het 6 afsonderlike trosse geïdentifiseer. Hierdie trosse is genoem “Besmettingsvrese / skoonmaak”, “Opgaar / bymekaarmaak”, “Simmetrie / orden / tel / organiseer / sekermaak / herhaal”, “Seksueel”, “Somaties, godsdienstig en divers” en “Skade-verwant”. Verhoogde rapportering van die simptome van elk van die trosse was met spesifieke demografiese, kliniese, en in sommige gevalle, genetiese kenmerke, geassosieërd. Die bevindinge het daarop gedui dat die *L/L* (*met/met*) genotipe van die *COMT Val158Met* polimorfisme ‘n belangrike rol in die manifestasie van seksuele, somatiese, religieuse en diverse, en skade-verwante simptome van OKS kan speel. Hierdie bevinding dra by tot die relatief beperkte beskikbare literatuur oor OK simptoom subtipes en genetika. Aan die ander kant, die feit dat die geassosieërde kenmerke nie die trosse duidelik en uniek van mekaar onderskei het nie en dat die trosse op beduidende wyse met mekaar gekorreleerd was, suggereer dat die kategorisering van die OKS-*kompleks* in OK simptoom-trosse nie die enigste manier is om die heterogeneïteit van OKS te benader nie. Nietemin, die beduidende komorbiditeit met OKS-verwante toestande in die geïdentifiseerde trosse (bv. die assosiasie tussen *tics* en seksuele obsessies / kompulsies), het die betekenisvolle verhouding tussen OKS en die OKS-verwante toestande

beklemtoon. Dit het weer aanleiding gegee tot ‘n vraag na die wyse waarop die OKS-verwante toestande “inpas” by die standaard OK simptomatologie, soos uiteengesit in die YBOCS-CL. ‘n Tros-analise van die OKS-verwante toestande in OKS-pasiënte het ‘n Tourette Sindroom / *tics* subtipe van OKS (deel van die sogenaamde “beloningstekort”-tros), sowel as ‘n impulsiwiteitsubtipe, en ‘n somatiese subtipe geïdentifiseer – wat elkeen met spesifieke kliniese en demografiese veranderlikes geassosieërd was. Hier is nie ‘n beduidende verhouding tussen die geïdentifiseerde trosse en die dopaminergiese en serotonergiese polimorfismes wat ondersoek is, gevind nie, wat moontlik daarop dui dat variante van ander gene in hierdie sisteme ook ondersoek behoort te word.

Gevolgtrekking: Die hoofbevinding was dat OKS is inderdaad ‘n heterogene toestand wat subtipeer kan word in ‘n aantal verskillende simptoom-dimensies. Die geïdentifiseerde OKS-subtipes met hulle geassosieërde kenmerke was in ‘n groot mate ooreenstemmend met voorheen gepubliseerde data. In teenstelling met FA, het die LKA ‘n nuwe, toepaslike en voordelige statistiese analise strategie vir die data gebied. Verder, sover ons weet, was die poging om OKS te klassifiseer volgens die komorbiditeit met OKS-verwante toestande die eerste tros-analise wat gebaseer was op ‘n prospektiewe volledige onderhoud wat die reeks van OKS-verwante toestande ondersoek. Alhoewel die dimensionele struktuur van OKS dus nog steeds nie volkome verstaan word nie, strek hierdie kategorisering van OKS-pasiënte in verskillende groepe en die ondersoek na hulle onderskeidelike kenmerke verder as die bestaande literatuur, en voeg dus nog ‘n dimensie tot die toenemende pogings om die OKS-subtipes af te baken.

ACKNOWLEDGEMENTS

The candidate wishes to express her sincere gratitude to the following persons, without whose help this study would not have been possible:

- Prof Dan Stein, promotor: Director: MRC Unit on Anxiety & Stress Disorders, Department of Psychiatry, University of Stellenbosch, for his expert suggestions, support, guidance, and patience.

- Prof Hanlie Moolman-Smook, from the US/MRC Centre for Molecular and Cellular Biology, who acted as supervisor and consultant of genetic analyses.

- Sian Hemmings and Craig Kinnear, my colleagues from the US/MRC Centre for Molecular and Cellular Biology, who were responsible for all the genotyping and assistance with genetic variant analyses.

- My co-promotor, Prof Deon de Bruin, for his contribution to this project.

- Dr Theunis Kotze (TheoData Statistical Consultation Services, Durbanville) and Prof Daan Nel (Director: Centre for Statistical Consultation, University of Stellenbosch), who acted as statistical consultants for clustering analyses.

- My parents, Jan and Amanda Lochner, for their unconditional love, encouragement, and constant support throughout.

- A special thank you to André Enslin for his support, patience and perseverance.

- The National Research Foundation and the Medical Research Council of South Africa, who awarded me funding and a scholarship respectively, are gratefully acknowledged.

- All the patients who were willing to be interviewed and to share their experiences.

- All colleagues and friends who provided encouragement, support, patience and advice.

CONTENTS

		Page
DECLARATION		ii
ABSTRACT		iii
ABSTRAK		vi
ACKNOWLEDGEMENTS		ix
INTRODUCTION		1
CHAPTER 1:	**BACKGROUND**	4
1.1	Obsessive-compulsive disorder (OCD) in context	4
1.2	A short history of OCD	5
1.3	OCD: DSM-IV diagnostic criteria	6
1.4	Characterization of OCD: Homogeneous or heterogeneous disorder?	7
1.5	OCD as a heterogeneous disorder	8
1.5.1	Phenomenology	8
1.5.2	Psychobiology	10
1.5.3	Family studies / genetics	15
1.5.4	Treatment studies	16
1.6	Subtyping of heterogeneous OCD	25
1.6.1	Subtyping built upon demographic and clinical characteristics	26
i.	Gender	26

ii. Age of onset 29
iii. Course of the disease 30
1.6.2 Subtyping built upon OCD symptomatology 31
i. OCD symptomatology: A dichotomy? 31
ii. OCD symptomatology: A multidimensional approach 31
iii. Studies using factor analysis 32
iv. Studies using cluster analysis 34
v. OCD symptom subtypes: Prevalence 38
vi. OCD symptom subtypes based on OCD symptomatology assessed with the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL): Limitations 38
1.6.3 Subtyping built upon comorbidity 39
1.7 OCD subtypes and associated features 42
1.7.1 OCD subtypes and associated etiological (clinical and genetic) features 42
1.7.2 OCD subtypes and associated outcome 46

CHAPTER 2: METHODS 49
2.1 Participants 49
2.1.1 Inclusion criteria 50
i. Patient group 50
ii. Control group 50
2.1.2 Exclusion criteria 50
2.2 Data collection 51
2.2.1 Interview 51
2.2.2 Rating scales 51

2.2.3 Genotyping 53

2.3 Data analysis 54

CHAPTER 3: PROFILE OF THE OBSESSIVE-COMPULSIVE DISORDER SAMPLE: BASED ON ASSESSMENT WITH THE YALE-BROWN OBSESSIVE-COMPULSIVE SYMPTOM CHECKLIST 55

Abstract 55

3.1 Introduction 56

3.1.1 The YBOCS-CL compared to other obsessive-compulsive symptom checklists 56

3.1.2 The layout of the YBOCS-CL 58

3.1.2.i The individual symptoms 58

3.1.2.ii The major symptom categories 58

3.1.3 Use of the YBOCS-CL in the present OCD sample 59

3.1.3.i Binary vs ordinal data 59

3.1.3.ii “Miscellaneous” and “other” items 60

3.1.3.iii “Current” vs “past” symptomatology 62

3.1.3.iv “Subclinical” vs “clinical” obsessive-compulsive symptomatology 63

3.2 Results 64

3.2.1 Sociodemograpghic findings 64

3.2.2 Clinical findings 64

3.2.2.i Gender and age of onset 64

3.2.2.ii The YBOCS-SS findings 65

3.2.2.iii The Disability Profile (DP) findings 65

3.2.2.iv The YBOCS-CL findings 65

3.2.3	Associated features		69
	3.2.3.a.i	Number of obsessive-compulsive symptoms vs total OCD severity (YBOCS-SS) score	69
	3.2.3.a.ii	Number of obsessive-compulsive symptoms vs total lifetime disability (Disability scale) due to OCD	69
	3.2.3.a.iii	Number of obsessive-compulsive symptoms vs age	69
	3.2.3.a.iv	Number of obsessive-compulsive symptoms vs age of onset	70
	3.2.3.a.v	Number of obsessive-compulsive symptoms vs gender	70
	3.2.3.a.vi	Number of obsessive-compulsive symptoms vs population group (i.e. Caucasian / non-Caucasian)	70
	3.2.3.b.i	Association between individual obsessive-compulsive symptoms and age	70
	3.2.3.b.ii	Association between individual obsessive-compulsive symptoms and age of onset of OCD	71
	3.2.3.b.iii	Association between individual obsessive-compulsive symptoms and gender	73
	3.2.3.b.iv	Association between individual obsessive-compulsive symptoms and population group (i.e. Caucasian vs non-Caucasian)	74
	3.2.3.b.v	Effect of presence / absence of each obsessive-compulsive symptom on the total mean OCD severity (YBOCS-SS) scores	76
	3.2.3.c	The major symptom categories and total OCD	80

severity (YBOCS-SS) and global disability (Disability Profile) scores

3.3 Discussion 81

3.4 Conclusion 85

CHAPTER 4: THE IDENTIFICATION OF OBSESSIVE-COMPULSIVE DISORDER SUBTYPES WITH LATENT CLASS ANALYSIS OF OBSESSIVE-COMPULSIVE SYMPTOMATOLOGY 87

Abstract 87

4.1 Introduction 88

4.2 Methods 90

4.2.1 Subjects and interview 90

4.2.2 Latent Class Analysis (LCA) 91

4.2.3 Data analysis 94

4.3 Results 95

4.3.1 Application of LCA to the YBOCS-CL data 95

4.3.2 Application of LCA to the nine most frequent indicators (OC symptoms) 102

4.3.3 Characterization of the six identified clusters 109

4.3.3.i The relationship of each of the nine most prevalent OC symptoms with the six clusters of cases 110

4.3.3.ii The gender distribution within the six clusters 117

4.3.3.iii The age distribution within the six clusters 117

4.3.3.iv Total OCD severity within each of the six clusters 118

4.3.3.v Comparison amongst clusters in terms of treatment response 120
4.3.3.v.a Response to CBT in the six clusters 120
4.3.3.v.b Response to SRI's in the six clusters 123
4.3.3.vi Comparison amongst clusters in terms of childhood trauma history 127
4.4 Discussion 127
4.5 Limitations 131
4.5.1 Latent Class Analysis 131
4.5.2 Content and number of identified clusters 131
4.5.3 Number of indicators / items included in the analysis 132

CHAPTER 5: THE IDENTIFICATION OF OBSESSIVE-COMPULSIVE DISORDER SUBTYPES WITH CLUSTER ANALYSIS OF OBSESSIVE-COMPULSIVE SYMPTOMATOLOGY 134

Abstract 134
5.1 Introduction 135
5.2 Methodology 135
5.2.1 Subjects, interview and genotyping 135
5.2.2 Cluster analysis of the YBOCS-CL items 138
5.2.3 Data analysis 138
5.3 Results 139
5.3.1 Cluster analysis of the nine most prevalent OC symptoms 139
5.3.2 Cluster analysis of 45 YBOCS-CL items (OC symptoms) 142
5.3.3 Clinical comparison data of the 6 identified clusters 146
5.3.4 Molecular analyses: OC clusters with selected polymorphisms 149

5.4 Discussion 151

5.4.1 CLUSTER 1: The CONTAMINATION FEARS / WASHING cluster 152

5.4.2 CLUSTER II: The HOARDING / COLLECTING cluster 153

5.4.3 CLUSTER III: The SYMMETRY / ORDERING / COUNTING / ARRANGING / CHECKING / REPEATING cluster 153

5.4.4 CLUSTER IV: The SEXUAL cluster 154

5.4.5 CLUSTER V: The SOMATIC, RELIGIOUS AND DIVERSE cluster 155

5.4.6 CLUSTER VI: The HARM-RELATED cluster 156

5.4.7 Genetics findings 156

5.5 Limitations and conclusions 158

CHAPTER 6: CLUSTER ANALYSIS OF OBSESSIVE-COMPULSIVE SPECTRUM DISORDERS IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER 162

Abstract 162

6.1 Introduction 163

6.2 Methods 164

6.2.1 Subjects and interview 164

6.2.2 Genotyping 165

6.2.3 Data analysis 165

6.3 Results 166

6.3.1 Cluster analysis 166

6.3.2 Comparison data 166

6.4 Discussion 169

6.4.1 The REWARD DEFICIENCY cluster 169

6.4.1.i Phenomenology 170

6.4.1.ii Neurobiology 172

6.4.2 The IMPULSIVITY cluster 174

6.4.2.i Phenomenology 176

6.4.2.ii Neurobiology 177

6.4.3 The SOMATIC cluster 178

6.4.3.i Phenomenology 180

6.4.3.ii Neurobiology 182

6.4.4 Clusters and genetics 183

6.5 Conclusion 183

CHAPTER 7: GENERAL DISCUSSION AND CONCLUSION 185

ADDENDUM 1: Reference list 193

ADDENDUM 2: List of tables 237

ADDENDUM 3: List of figures 242

ADDENDUM 4: List of publications resulting from this dissertation 244

ADDENDUM 5: Abbreviations frequently used throughout dissertation 246

ADDENDUM 6: Publications; Conference proceedings; Awards 249

INTRODUCTION

Obsessive-compulsive disorder (OCD) is now recognized as one of the most common psychiatric disorders, associated with substantial morbidity and impaired quality of life. In the clinic, the diagnosis of OCD is made with increasing frequency, and in the research setting, the empirical investigation of OCD has increased. Major advances have recently been made in characterizing the phenomenology and psychobiology of OCD. It has become clear that OCD is not simply a uniform or homogeneous disorder, but rather a disorder characterized by significant heterogeneity that obscures the findings of clinical, natural history and treatment response studies and complicates the search for vulnerability genes.

This dissertation focussed on the classification of OCD into more homogeneous subtypes or symptom dimensions, arguing that subtyping is a useful means of integrating the heterogeneous data on symptomatology, psychobiology, genetics and treatment response. In particular, with the existing literature as background (**Chapter 1**), the overall objective of this study was to assemble, analyze and interpret original data in order to better previous efforts delineating valid OCD subtypes or dimensions and their associated features, with appropriate data classification and association study methods, in a large sample of South African OCD patients. **Chapter 2** includes a general overview of the methodological procedures (including patient recruitment, data collection methods and data analyses) that were implemented in this investigation. Subsequent chapters include a methods section with a detailed description of specific objectives and the procedures followed to achieve these aims. **Chapter 3** provides a description of findings obtained with the YBOCS-CL as

an important introduction to subsequent analyses (**Chapters 4 and 5**), with a comprehensive description and rationale for the use of the YBOCS-CL and the provision of a profile of the present OCD sample based on their YBOCS-CL responses. This section also includes comments on the content and comprehensiveness of the YBOCS-CL as an assessment tool of OC symptomatology. Subtyping based on OCD symptomatology as well as comorbidity (especially with OCD-spectrum conditions) as classifying variables have been two of the most common strategies for identifying OCD subtypes, and has been receiving increasing attention in recent years. The subtyping efforts proceeded along these lines, i.e. firstly based on OCD symptomatology assessed with the YBOCS-CL (**Chapters 4 and 5**), and secondly, given the significant comorbidity of the identified subtypes with the OCD spectrum of disorders, subtyping proceeded based on comorbidity with the OCSD's (assessed with the Structured Clinical Interview for the Diagnosis of putative Obsessive-Compulsive Spectrum Disorders [SCID-OCSD]) (**Chapter 6**). More specifically, **Chapter 4** includes a Latent Class Analysis (LCA), which basically entails different statistical techniques to classify OCD *cases* based on their OC symptomatology as determined by the YBOCS-CL. **Chapter 5,** on the other hand, implements a different statistical technique namely cluster analysis (Ward's Method), and entails the classification of OC symptoms (as *variables*). These were the initial steps in the classification of OCD into more homogeneous subtypes or dimensions. Subsequently, recognizing the importance of comorbidity in subtyping of heterogeneous disorders such as OCD and the significant relationship of OCD with the OCSD's, **Chapter 6** also attempts classification of *variables,* i.e. the cluster analysis (Ward's method) of comorbid OCSD's in patients with OCD as determined by the SCID-OCSD. The associations of the identified clusters or dimensions with other relevant variables including demographic variables (age, gender), clinical variables (age of onset, obsessive-compulsive symptom severity and dimensions, level of insight, temperament/character, treatment response) and genotypes are described. In order to

reduce the chance of type I error, the number of comparisons have been minimalized as far as possible, with priority given to those variables shown to have significant association with the symptom subtypes in previous studies, i.e. childhood interpersonal trauma history and specific genetic variables. **Chapter 7** includes a general discussion of the main findings, with suggestions for clinical practice as well as future research directions.

(Footnote: Tables that were not of immediate importance given the thesis objectives were excluded but may be obtained from the candidate.)

CHAPTER 1

BACKGROUND

The central aim of Chapter 1 is to review the existing literature on the heterogeneity of obsessive-compulsive disorder (OCD), providing an introduction to and motivation for subsequent chapters on the delineation of OCD into different subtypes, each with distinct associated features. It will be argued that subtyping OCD is a useful means of integrating the heterogeneous data on its symptomatology, psychobiology, genetics and treatment response.

1.1 Obsessive-compulsive disorder in context

Epidemiological data from World Health Organisation (WHO) studies indicate that 5 of the 10 most disabling disorders are neuropsychiatric conditions (Murray and Lopez, 1996). In particular, OCD is one of the most common mental disorders; for example, in the Epidemiological Catchment Area study in the USA, it was the fourth most common condition with a life-time prevalence of 2.5% (Karno *et al.*, 1988). OCD is estimated to affect nearly 5 million US citizens (Karno *et al.*, 1988), with a resultant annual impact on the US economy of approximately $ 8.4 billion (DuPont *et al.*, 1995), making it a public health issue of national scope. Moreover, these findings have been confirmed by further surveys conducted internationally (Weissman *et al.*, 1994). The significant negative social and economic impact of OCD on society is also recognized in developing countries such as South Africa (Stein *et al.*, 1996).

1.2 A short history of OCD

The first time a clinical case of OCD was described in psychiatric literature, was during the first half of the 19th century. The rest of the 19th century saw a steady progress in the way OCD was conceptualised, with clinicians like Falret, Morel, Krafft-Ebing and Westphahl offering Psychiatry numerous and varying descriptions of OCD. Interestingly, in as early as the 1870's, heritability was recognized as one of the most prominent etiologic factors in OCD.

In the following years, other diagnostically related categories, e.g. "neurasthenia", and "psychasthenia" were proposed. These categories apparently showed some significant overlap with one another, but also lead to confusion about, and consequently endangering the existence and the conceptualisation of OCD. Nevertheless, the first two to three decades of the 20th century saw Janet and Freud's significant clinical and theoretical contributions to the concept of OCD. After numerous speculations about the concept, Freud finally ended his psychoanalytically - based investigation on OCD in 1926, with the following statement: "Obsessional neurosis is certainly the most interesting and grateful subject of analytic research, but as problem still not solved." (Translated) (Freud, 1926). By the second half of the 20th century, OCD was recognized as a neuropsychiatric condition thought to be caused by early traumatic experiences or environmental factors, warranting treatment. In addition, the last two to three decades saw an increased attention to the influence of genetic factors in the manifestation of this disorder; i.e. a definitive move towards an approach to OCD as a biochemical and neurobiological condition.

1.3 OCD: DSM-IV diagnostic criteria

Today, in the clinic the diagnosis of OCD is made with increasing frequency (Stoll *et al.,* 1992), and in the research setting the empirical investigation of OCD has increased much (Lochner and Stein, 2003a). Despite it still being relatively under-recognized and under-treated, there is growing recognition that OCD is a frequently occurring and disabling neuropsychiatric disorder, associated with substantial morbidity (e.g. unemployment, marital separation or divorce, and lower socio-economic status), and thus significantly impaired quality of life (Karno *et al.*, 1988).

According to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (APA, 1994), OCD is characterized by recurrent obsessions and/or compulsions that cause marked distress, are time-consuming (i. e. requiring more than 1 hour a day), and significantly interfere with the individual's social, academic, or occupational functioning. Obsessions are defined as persistent, intrusive ideas, thoughts, images, or impulses, such as fears of contamination or fears of potential harm to oneself or others, that may be perceived as inappropriate or unreasonable. Compulsions, on the other hand, are repetitive, stereotyped behaviours, such as hand washing or checking behaviours, or covert mental rituals (e.g. silently counting or repeating words) that individuals with OCD feel compelled to perform in response to obsessions, or to prevent some dreaded situation or event. By definition, their insight could waver from good to very poor, but most patients with OCD have good insight and at some point recognize that the obsessions or compulsions are excessive or unreasonable (APA, 1994). Their realisation of the discrepancy between the knowledge that obsessions and compulsions are irrational on the one hand, and the overwhelming urge to perform them on the other hand, contribute to the immense suffering associated with the disorder.

As was noted earlier, there may be different approaches to the characterization of OCD: In the 19th and early 20th century, Freud and other psychoanalysts substituted the early connection between obsessive-compulsive symptoms and psychosis with an emphasis on the concepts of neurosis and character. Contemporary thinking suggested a move away from psychoanalytic theory towards a more neurobiological approach to OCD. Neurobiological research on OCD was given significant impetus by the early finding that this disorder, previously often considered to be treatment refractory, responded to the serotonergic tricyclic, clomipramine. In addition to this neurochemical perspective of OCD as a disorder involving serotonergic mechanisms, it has also been shown to be related to the dopaminergic system (Goodman *et al.*, 1990, 1992). From a neuro-anatomical perspective, OCD is believed to be related to the cortico-striatal system for its role in supporting repetitive, compulsory behaviours (disorder of intellect), and to the amygdala for its role in fear conditioning and anxiety (disorder of emotion) (Rauch and Baxter, 1998). In addition, family and twin studies have provided evidence for a genetic component in OCD.

1.4 Characterization of OCD: Homogeneous or heterogeneous disorder?

In the last few years, the psychobiological approach has gained ground with significant advances in the characterization of the phenomenology and psychobiology of OCD. In particular, studies have addressed the epidemiology (Karno *et al.*, 1988; Weissman *et al.*, 1994), symptomatology (Rasmussen and Tsuang, 1986; Rettew *et al.*, 1992), neuroanatomy (Rauch *et al.*, 1997; Saxena and Rauch, 2000), neurochemistry (Goodman *et al.*, 1990; Zohar and Insel, 1987, 1987), pharmacotherapy (Greist and Jefferson, 1998; Jenike, 1992; Klein, 1990) and psychotherapy (Greist, 1996; Minichiello *et al.*, 1988) of OCD, with some of the findings contributing to the initial conceptualisation of OCD as a relatively homogeneous

and specific neuropsychiatric entity, underpinned by particular mechanisms that manifest in universal symptoms.

At the same time, research findings suggesting the possibility that OCD is not a homogeneous diagnostic entity have become increasingly common in recent years. Indeed, although the cardinal symptoms of OCD (i.e. obsessions / compulsions) are remarkably consistent across cultures, it's specific clinical features and course vary (Leckman *et al.*, 2001; Skoog and Skoog, 1999). The variability in the phenotypic expression has led to the hypothesis that OCD is a heterogeneous disorder and that this heterogeneity obscures the findings of clinical, natural history and treatment response studies and complicates the search for vulnerability genes. This heterogeneity may explain why there have been so many inconsistent findings in studies of OCD.

1.5 OCD as a heterogeneous disorder

The heterogeneity of OCD is evident in a number of respects, including it's phenomenology (Section 1.5.1), psychobiology (Section 1.5.2), genetics (Section 1.5.3) and treatment response (Section 1.5.4) (Lochner and Stein, 2003a).

1.5.1 Phenomenology

The symptoms used to define OCD are diverse and include a range of obsessions and compulsions. The predominant symptoms in OCD have been well documented (e.g. Nestadt *et al.*, 2002; Rasmussen and Tsuang, 1986; Rettew *et al.*, 1992; Rocca *et al.* 1991) and include:

(1) concerns about contamination or illness, along with compulsive cleaning or washing,

(2) obsessive doubt, with subsequent checking rituals,

(3) concerns about, and compulsions regarding, symmetry, orderliness, and numbers,

(4) hoarding/collecting rituals, and

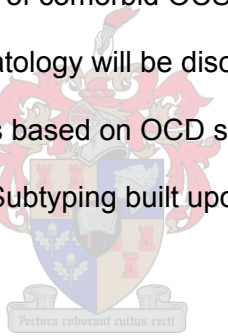
(5) obsessional slowness.

Other symptoms (e.g. religious or sexual obsessions and rituals, and so-called "miscellaneous" symptoms) have also been described. An alternative strategy to focusing simply on specific symptom types has been to explore symptom *clusters*, or "groupings" of various OCD symptoms that may present simultaneously (Baer, 1994; Calamari *et al.*, 1999; Hodgson and Rachman, 1977; Leckman *et al.*, 1997; Summerfeldt *et al.*, 1999; Van Oppen *et al.*, 1995), e.g. obsessions and rituals re both symmetry and hoarding.

In addition, obsessive-compulsive phenomenology show significant overlap with the features of a group of other disorders known as the putative obsessive-compulsive spectrum disorders (OCSD's). It has been suggested that the OCSD's comprise a number of psychiatric and neuropsychiatric conditions that share *enough* phenomenological and psychobiological features with OCD to be meaningfully grouped with it (Hollander, 1993; McElroy *et al.*, 1994; Rasmussen, 1994), arguably adding to the heterogeneity of OCD. Despite consensus in the literature for the existence of an OC spectrum, debate about criteria for inclusion into the OC spectrum continues, with some authors arguing for more *conservative* boundaries, including only OCD, Tourette's disorder, tics, trichotillomania, body dysmorphic disorder and hypochondriasis, whereas others have argued for a "broad" spectrum that may include additional conditions such as eating disorders (anorexia and bulimia nervosa), impulse control disorders (such as pathological gambling and compulsive shopping), stereotypical movement disorders (with or without self-injury), and some personality disorders (including borderline and

obsessive-compulsive personality disorder). One common feature of these conceptual schemes is that OCD is thought to be the prototype for this spectrum of conditions.

Individuals with OCD (compared to other anxiety disorders) are more likely to report a *lifetime* comorbid spectrum condition (Richter *et al.*, 2003), thereby also adding to the heterogeneous presentation of OC phenomenology. Importantly, while most of the literature focuses on the relationship between OCD and spectrum disorders, focus on the comorbidity of OCD spectrum disorders in OCD is on the increase. It has been suggested that a consideration of such comorbidity may well contribute to delineating the heterogeneity of OCD; i.e. the heterogeneous OCD phenotype may possibly be subtyped based on the presence of comorbid OCSD's (Lochner *et al.*, 2005). (Classification of OCD symptomatology will be discussed in more detail under Section 1.6.2.vi "OCD symptom subtypes based on OCD symptomatology assessed with the YBOCS-CL" and Section 1.6.3 "Subtyping built upon comorbidity".)



1.5.2 Psychobiology

Findings from neuropsychiatric, neurochemical, and neuroimmunological studies are relevant here: Several neurological disorders may result in OCD symptoms, although such patients may form only a small proportion of those having OCD (Grimshaw, 1964). Moreover, OCD patients differ in extent and location of neuropsychiatric impairment (Stein *et al.*, 1994), and these differences may also be useful in subtyping the disorder (More on subtyping in Section 1.6). Neuropsychiatric heterogeneity may be seen in studies of neurological soft signs and in neuropsychological function, electroencephalography (EEG), and brain imaging.

A relationship between neurological soft signs and OCD has been suggested. For example, OCD patients have elevated levels of neurological soft signs compared to normal controls (Hollander *et al.*, 1991). Hymas *et al.* (1991) found that patients with obsessional slowness invariably had increased neurological soft signs. In addition, it has been suggested that patients with increased neurological soft signs may have increased ventricular-brain ratio in comparison to normal controls (Stein *et al.*, 1993). Increased neurological soft signs may also predict poor response to pharmacotherapy (Hollander *et al.*, 1991; Thienemann and Koran, 1995). Furthermore, a specific OCD clinical profile may be correlated to organicity; for instance, Thomsen and Jensen (1991) compared 61 child and adolescent OCD patients with 177 matched control patients for organic features as assessed by neurological signs, electrophysiological abnormalities, specific developmental disorder, and attention deficit. Significantly more OCD patients than controls were assigned to the organic class, with neurological soft signs being the most sensitive and specific indicator of organicity. Behavioural problems and loss of temper were significantly more frequent in the non-organic class, whereas symptoms of phobia and depression were more often present in the organic class. Yaryura-Tobias *et al.* (2000) also investigated an "organic" and a control, "non-organic" group of OCD patients and found some differences in their clinical profiles. A subgroup of OCD patients has abnormal EEG's (Stein *et al.*, 1994). Similarly, Deltito (1994) suggested that some OCD patients have symptoms like those of temporal lobe epilepsy, such as irritability, confusion, psychosis, or other cognitive impairments, which may well have implications for treatment. Quantitative EEG patterns have also been reported to differ between responders and non-responders to medication (Prichep *et al.*, 1993).

Functional neuroimaging studies have advanced the understanding of the brain mediation of OCD by orbitofrontal-subcortical circuitry (Baxter *et al.*, 1994), but much is

still unknown (Robinson *et al.*, 1995). Indeed, it has been suggested that phenotypic heterogeneity may account for many of the inconsistencies among previous neuroimaging studies of OCD (Cummings *et al.*, 1988; Rauch and Baxter, 1998; Savage, 1997; Saxena *et al.*, 1998, 2000).

Slowness of thinking (bradyphrenia) and slowness of movement (bradykinesia) are symptoms of subcortical neurological disorders; for example, those of the basal ganglia, such as Parkinson's disease (Cummings *et al.*, 1988; Savage *et al.*, 1997). Similarly, obsessional slowness in OCD patients may reflect basal ganglia damage, but rather than being a separate group of OCD patients, these patients may simply be a subtype with more severe psychopathology.

Functional brain imaging has documented that OCD patients have increased prefrontal activity compared to normal controls (Insel, 1992). Positron emission tomography studies of OCD have consistently identified hypermetabolism in the orbitofrontal cortex, the caudate nucleus, and (sometimes) the anterior cingulate cortex (Baxter *et al.*, 1994; Saxena *et al.*, 1998; Saxena and Rauch, 2000). OCD patients with more motoric symptoms (e.g. tics) may also be more likely than OCD patients without such symptoms to have involvement of the putamen (Rauch and Baxter, 1998), although this hypothesis remains to be validated. It has also been suggested that patients with tic-related OCD may have more abnormal motor cortex excitability than OCD patients without tics (Greenberg *et al.*, 2000). Relatively few studies have explored functional brain imaging in *acquired* OCD (i.e. OCD associated with neurologic disorders). In a review of the brain single positron emission computerized tomography (SPECT) scans of patients with various neurological conditions also presenting with OCD, Hugo *et al.* (1999) reported that all of these patients demonstrated decreased blood flow in the temporal lobes and

cortical perfusion abnormalities in the frontal lobes. Indeed, abnormal blood flow may be seen in a number of different brain regions in acquired OCD (Hugo *et al.*, 1999). In a study investigating OCD associated with brain lesions, Berthier *et al.* (1996) found that in a patient group with acquired OCD, neuroimaging disclosed abnormalities in a variety of regions involving either the cerebral cortex (frontal, temporal, or cingulate regions), the basal ganglia, or both. The study also suggested that patients with focal brain lesions (acquired OCD) had a negative familial history and later age of onset of OCD symptoms than patients with idiopathic OCD (Berthier *et al.*, 1996). There have been some efforts to use factor analyses to identify neural correlates of symptom clusters. For example, Rauch and Savage (Rauch and Savage, 1997) found the severity of religious/aggressive/sexual obsessions and checking was positively related to regional cerebral blood flow in the striatum bilaterally. Distinct trends were also observed for the other factors, or symptom dimensions. These findings provide support for the hypothesis that dysfunction within separate neurocircuitry systems may principally mediate particular symptom clusters. In brief, neurological soft signs are common among OCD patients and may be associated with an "organic" subtype of OCD. Functional neuroimaging studies have suggested that OCD patients have increased prefrontal activity and hypermetabolism in the orbitofrontal cortex, the caudate nucleus, and other regions.

Hollander *et al.* have reported that only some patients' conditions exacerbate after administration of the partial serotonin agonist m-chlorophenylpiperazine (m-CPP) (Hollander *et al.*, 1993a). Interestingly, exacerbation of OCD symptoms after administration of m-CPP is correlated with increased cerebral blood flow in the frontal cortex (Hollander *et al.*, 1995). It may be hypothesized that increased frontal activity in some patients with OCD is in itself a compensatory mechanism. These preliminary

neurobiological findings are consistent with a hypothesis that exacerbation of OCD after administration of a serotonin autoreceptor agonist may be an indication of compensatory postsynaptic serotonergic up-regulation. Such up-regulation may be associated with increased frontal activity and relatively poor response to serotonergic agents (Stein *et al.*, 1999).

Regarding the neuroimmunology findings in OCD: Swedo and Leonard (1994) noted that a proportion of patients with Sydenham's chorea meets diagnostic criteria for OCD and often have tics. Sydenham's chorea is an involuntary movement disorder that develops in some children following a group A beta-hemolytic streptococcal (GABHS) infection. Some of these patients' movements either are or resemble tics. This condition is also characterized by increased antineural antibodies, suggesting that an autoimmune process may be responsible for basal ganglia damage and OCD in these patients (Swedo *et al.*, 1994). Conversely, an increasing body of evidence provides support for the postulate that OCD and tic disorders may arise from poststreptococcal autoimmunity (Allen *et al.*, 1995). The term PANDAS (for "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections") refers to patients with tics and obsessive-compulsive symptoms induced by streptococcal infections (Leonard and Swedo, 2001). Leonard and Swedo (2001) provide five criteria for this condition: presence of OCD or tic disorder; prepubertal symptom onset; sudden onset or episodic course of symptoms; temporal association between streptococcal infections and exacerbation of neuropsychiatric symptoms; and neurological abnormalities.

It has been found that expression of D8/17 (a particular B-lymphocyte antigen) was significantly higher in children with PANDAS, in Sydenham's chorea (Swedo *et al.*, 1997), and in childhood-onset OCD or Tourette's disorder (TD), compared to normal

controls (Murphy *et al.*, 1997). Indeed, the identification of subtypes such as PANDAS may allow for testing of models of pathogenesis and also potentially lead to the development of novel treatment and prevention strategies (Minichiello *et al.*, 1990). Both antibiotic prophylaxis to prevent streptococcal-triggered exacerbations and immunomodulatory interventions (such as intravenous immunoglobulin or therapeutic plasma exchange) have been studied (Leonard *et al.*, 2001). With regard to the latter treatment strategy, long-term (2–5 years) follow-up revealed continued symptom improvement for the majority of patients, particularly when antibiotic prophylaxis had been effective in preventing recurrent streptococcal infections (Leonard *et al.*, 2001).

1.5.3 Family studies / genetics

Family studies of OCD have suggested that OCD is a heterogeneous condition, with some cases being familial and others being isolated (Albert *et al.*, 2002). Early studies completed prior to 1970 suggested that OCD is a familial disorder (Brown, 1942; Kringlen, 1965, 1970; Lewis, 1936; Lo, 1967; Rosenberg, 1967). Prevalence rates among first-degree relatives of OCD probands have been reported ranging between 0.7% and 4.5% (Insel *et al.*, 1983; McKeon and Murray, 1987; Rasmussen and Tsuang, 1986). Findings from more recent systematic studies have provided further support for a familial component for the expression of some forms of OCD (Bellodi *et al.*, 1992; Black *et al.*, 1992; Lenane *et al.*, 1990; Leonard *et al.*, 1992; Nicolini *et al.*, 1993; Pauls *et al.*, 1995; Riddle *et al.*, 1990). In a recent study conducted to determine whether OCD is familial and to investigate possible familial subtypes, it was found that age of onset of OCD is valuable in characterizing a familial subtype (Nestadt *et al.*, 2000). Several studies support the hypothesis that familial loading for OCD is associated with early onset (Lenane *et al.*, 1990; Nestadt *et al.*, 2000). In addition, Pauls *et al.* (1995) found that the relatives of probands with early onset were at higher risk for *both* OCD and tics,

supporting the concept that early age of onset characterizes a familial subtype of OCD. (More on subtyping based on age of onset in Section 1.6.1.ii.)

Furthermore, it has been reported that OCD patients and their family members also have a high prevalence of various putative OCD spectrum disorders (OCSD's) (including body dysmorphic disorder and pathological grooming behaviours) (Bienvenu *et al.*, 2000). Bellodi *et al.* (2001) found that the risk for OCSD's (in particular, OCD and tic disorders) is higher in families of patients with eating disorders, suggesting that eating disorders may also characterize a phenomenological and familial OCD subtype.

The heterogeneity of OCD has possibly confounded genetic investigation, as suggested by many inconsistent findings in studies of OCD. Nevertheless, the genetic study of OCD has made tremendous progress in the last decade. Controlled family studies and segregation analyses provide consistent support for the familial nature of OCD and a major gene locus has been implicated. Arguably, the lack of clear results from studies using molecular genetics could be ascribed to the use of the conventional set of diagnostic criteria that still classifies OCD as a *unitary nosographic entity* (Cavallini *et al.*, 2002). Nevertheless, more recently a segregation analyses have shown that the symmetry / ordering subtype showed a major gene effect for OCD, while both symmetry / ordering and obsessions / checking showed dominant major gene effects in a TS sample with OCD symptoms. Research into the role of different candidate genes in the identified OCD subtypes is scarce, suggesting the need for further work.

1.5.4 Treatment studies

Treatment studies suggest that SRI's are more effective than noradrenergic reuptake inhibitors in the treatment of OCD (Zohar *et al.*, 1987). This result is apparent not only in

adults with OCD, but also in children and adolescents with OCD (Leonard *et al.*, 1989). About 40–60% of OCD patients respond to the first trial of an SRI (Jenike *et al.*, 1992). A proportion of non-responders to a single SRI will respond to administration of a second SRI (Pigott *et al.*, 1990). As was previously mentioned, while serotonin is the neurotransmitter most commonly implicated in obsessive-compulsive and related disorders, there is also evidence for dopaminergic mediation of these conditions (Goodman *et al.*, 1990, 1992). Indeed, augmentation of SRI's with dopamine blockers has been found useful in treatment-refractory OCD (Mohr *et al.*, 2002).

In addition, results from treatment studies suggest that there are multiple factors influencing treatment response. For example, studies are conflicting about whether any particular symptom subtype of OCD is easier to treat or more likely to benefit from particular treatments. (More on OCD symptom subtypes and treatment response under Section 1.7.2 "OCD subtypes and associated outcome".)

Some studies have also suggested that variables such as sex, age, and severity and duration of OCD may predict pharmacotherapy outcome. For example, Alarcon *et al.* (Alarcon *et al.*, 1993) showed that higher initial scores on the Yale-Brown Obsessive-Compulsive Symptoms Severity Scale (YBOCS-SS) were associated with poorer response to treatment. In addition, the combination of longer length of illness, continuous course, and predominance of compulsive behaviours has been found to be associated with poorer response to medication (Alarcon *et al.*, 1993; Ravizza *et al.*, 1995). Different follow-up studies of childhood, adolescent, and adulthood OCD have also related initial severity of OCD to post-treatment severity (Leonard *et al.*, 1993; Mataix-Cols *et al.*, 1999; Thomsen *et al.*, 1995). There are other studies, however, that

have found that these variables did not predict poor response in pharmacotherapy trials (Clomipramine Collaborative Group, 1991; Thoren *et al.*, 1980).

The available literature on level of insight as a predictor of response to behavioural therapy is inconsistent, and the data concerning insight and medication response are sparse (Attiullah *et al.*, 2000). It has been suggested that OCD patients with poor insight may have a different treatment response than patients with better insight (Attiullah *et al.*, 2000), but the relationship between the degree of insight and outcome of therapy remains unclear (Kozak *et al.*, 1994). Recently, in a study evaluating which clinical variables might influence the anti-OCD effect of proserotonergic drugs, non-responders had a higher frequency of poor insight (Erzegovesi *et al.*, 2001); indeed, poor insight was found to be the best predictor of poor drug-treatment response. Nevertheless, the treatment of OCD patients with poor insight may sometimes lead to a shift to good insight with concomitant improvement of OCD severity and depressive status (Matsunaga *et al.*, 2002). Matsunaga *et al.* (2002) also found that in OCD, comorbid schizotypal personality disorders (PD's) compromised prognosis; both OCD with poor insight and comorbid schizotypal PD were found to be associated with failure to gain better insight during treatment.

It has been suggested that people with later onset of OCD (who are more commonly females) have the best chance of responding to medication. For example, in the study by Do Rosario-Campos *et al.* (Do Rosario-Campos *et al.*, 2001), the group with early-onset OCD responded less well to treatment with SRI's than late-onset OCD patients (Again, more on OCD symptom subtypes and treatment response under Section 1.7.2 "OCD subtypes and associated outcome".)

Likewise, another study showed that female OCD patients were more likely than males to respond to therapy with the selective SRI, fluvoxamine (Mundo *et al.*, 1999). It has also been argued that OCD females have lower monoamine oxidase A (*MAO-A*) activity than OCD males (Camarena *et al.*, 2001) and that this association might indicate a beneficial effect of *MAO-A* inhibitors in a particular subtype of OCD females.

It has been suggested that male OCD patients have relatively increased neurological soft signs and tics compared to females (Stein *et al.*, 1994), while neurological soft signs or tics have been associated, in turn, with increased ventricular-brain ratios (Stein *et al.*, 1993) and worse response to SRI's (Hollander *et al.*, 1991; McDougle *et al.*, 1994). Indeed, increased neurological soft signs (associated with males) have been predictive of poorer response to pharmacotherapy in some studies (Hollander *et al.*, 1991) (although in others, this variable did not predict worse outcome at follow-up (Thieneman *et al.*, 1995; Thomsen, 1995)). It should be noted that not all studies agree with the finding that the course of OCD is worse in males (Lensi *et al.*, 1996); arguably, the relationship between male gender and worse course may be largely explained by taking into account those with early brain trauma or similar dysfunction. Indeed, a number of studies have indicated that age, age of onset, and gender are not significant prognostic factors (DeVeaugh-Geiss *et al.*, 1992; Thomsen *et al.*, 1995). In particular, some studies have found that gender has no effect in predicting response to SRI's in OCD (Ackerman *et al.*, 1998).

Comorbidity of mood and anxiety disorders in childhood and adolescent OCD has been found not to predict outcome at follow-up (Thomsen, 1995). In addition, several controlled studies have shown that neither the presence nor the initial severity of depression has any impact on therapeutic outcome in adults with OCD (den Boer, 1997;

Zitterl *et al.*, 1990). The SRI's fluoxetine and fluvoxamine have beneficial effects in OCD, irrespective of the presence or severity of initial depressive symptoms (Goodman *et al.*, 1989, 1990; Perse *et al.*, 1987), and the Clomipramine Collaborative Group (1991) found that comorbid depression did not predict responsiveness to the serotonergic tricyclic, clomipramine. Interestingly, it was found that the tricyclic antidepressant, imipramine improved depressive symptoms in depressed OCD patients (although this improvement did not potentiate the effects of behavioural therapy for OCD) (Foa *et al.*, 1992). Comorbid posttraumatic stress disorder (PTSD) may be associated, however, with worse prognosis of OCD (Gershuny *et al.*, 2002).

A retrospective, case-controlled analysis by McDougle *et al.* found that fluvoxamine alone was less effective in OCD patients with tics than in patients without tics (McDougle *et al.*, 1993). In a continuation of this research, the researchers found (McDougle *et al.*, 1994) that treatment-refractory OCD patients with comorbid chronic tic disorders (such as TS) responded to augmentation of fluvoxamine with a traditional antipsychotic (haloperidol), whereas this strategy was of little benefit for patients without tics. In two subsequent studies, the atypical antipsychotics olanzapine and risperidone (respectively) were added to the treatment of patients refractory to treatment with fluvoxamine alone (Bogetto *et al.*, 2000; McDougle *et al.*, 2000), but no difference was found in response between OCD patients with and without comorbid diagnoses of chronic tic or schizotypal disorder.

The comorbid diagnosis of schizophrenia and OCD (or of OCD with psychotic features) seems to portend a worse prognosis than for either condition alone. Despite the paucity of literature on the topic, there is some evidence that patients with both these conditions may improve on treatment with a combination of antiobsessional and antipsychotic drugs

(Dowling *et al.*, 1995; Ganesan *et al.*, 2001). Nevertheless, it has been noted that administration of atypical antipsychotic agents may be associated with the first onset or worsening of OC symptoms in schizophrenia (Cheung, 2001; de Haan *et al.*, 2002; Khullar *et al.*, 2001).

It has been suggested that comorbid PD's may have prognostic significance in the treatment of OCD (Minichiello *et al.*, 1987; Pfohl *et al.*, 1991). Pfohl *et al.* (1991) noted that in 22 OCD patients who received the Structured Interview for the Diagnosis of Personality Disorder prior to treatment with clomipramine, 11 responders had significantly fewer total Axis II-traits than did the 11 non-responders. Baer *et al.* (1992) have demonstrated that the presence of schizotypal, borderline, and avoidant PD, in tandem with the total number of PD's, did predict poor treatment outcome (with clomipramine). Also, a retrospective analysis of 43 OCD patients demonstrated that those with comorbid schizotypal PD (33%) were comparatively unresponsive to both pharmacotherapy (Jenike *et al.*, 1986) and behavioural therapy (Minichiello *et al.*, 1987). Similarly, there is evidence that schizotypal PD is not the only PD that is a consistent predictor of poor outcome in OCD (Baer *et al.*, 1992). Hermesh *et al.* (1987) reported that in 39 OCD patients, all of those with borderline personality (20%) failed to respond to either pharmacotherapy or behavioural therapy, primarily because of poor compliance. However, some studies have failed to confirm the finding of an association between PD's in OCD patients and (poorer) treatment outcome. In the study by Steketee (1990), comparisons of those OCD patients who did and did not qualify for schizotypal, histrionic, avoidant and dependent, or any other type of PD revealed only marginal associations to treatment gains. In fact, PD patients had slightly better immediate treatment outcome, although this difference was not significant. Similarly, the investigation of Mavissakalian *et al.* (1990) on the relationship between personality and

treatment outcome provided no strong support for the notion that personality factors have prognostic significance in the treatment of OCD.

Importantly, the finding that the presence of particular comorbid PD's in OCD may predict poor treatment outcome is open to more than one interpretation, suggesting either a specific effect of the particular Axis II disorder, or a non-specific effect of increased OCD severity. In view of the particular set of PD's that apparently affect treatment outcome (schizotypal, borderline, avoidant), there is some reason to believe that the first explanation may be correct. Nevertheless, since the total number of PD traits and specific diagnoses are correlated with OCD symptom severity, there is also some basis for taking the second explanation seriously. Additional research is necessary.

In summary, comorbidity of OCD with mood and anxiety disorders does not affect treatment outcome, while comorbid tics and schizophrenia both are associated with worse outcomes. Among comorbid Axis II conditions, schizotypal PD appears to predict worse outcome in the treatment of OCD.

An analysis of differences between the side-effect profiles of clomipramine and more selective SRI's in OCD suggested that good response to both drugs (clomipramine and fluoxetine) was associated with initial nervousness and sexual complaints (Ackerman *et al.*, 1999). More specifically, good response to clomipramine was associated with later age of OCD onset and certain early side-effects that may reflect the sensitivity of responders to clomipramine's serotonergic actions. Replication of the data is necessary.

It has been demonstrated that patients with OCD have increased brain activity in the basal ganglia, that this hyperactivity increases further during exposure to feared stimuli, and that it decreases after successful SRI administration or behavioural therapy (Insel, 1992; Rauch and Savage, 1997). Not all patients respond to this treatment however, suggesting that structures other than the basal ganglia may have a role in mediating OCD symptoms. Indeed, the underlying differences in the neurobiology between responders and non-responders to SRI's are only partly understood. As mentioned earlier, for example, there is evidence that non-responders are more likely to have comorbid tics (McDougle *et al.*, 1993), increased neurological soft signs (Hollander *et al.*, 1991), and atypical EEG's (Prichep *et al.*, 1993).

In addition, functional brain imaging has documented that OCD patients have increased prefrontal activity compared to normal controls (Insel *et al.*, 1992), and it has been suggested that increased blood flow in the frontal regions predicts poor response to medication (Brody *et al.*, 1998). More specifically, it has been found that lower pretreatment metabolism in the right orbitofrontal cortex and anterior cingulate gyrus is associated with a better response to serotonergic drugs (Saxena *et al.*, 2001). It was also found that higher normalized metabolism in the left orbitofrontal cortex region was associated with greater improvement in a behavioural therapy group, but with worse outcome in a fluoxetine-treated group (Brody *et al.*, 1998). These findings indicate that OCD patients with differing patterns of metabolism preferentially respond to behavioural therapy versus medication.

In some, but not all, studies, increased neurological soft signs predict poor response to pharmacotherapy and behavioural treatment (Bolton *et al.*, 2000; Thienemann *et al.*, 1995). Some authors have suggested that OCD patients with abnormal findings on EEG

may respond to anticonvulsant therapy (Prichep *et al.*, 1993). Deltito (1994) found that OCD patients who develop symptoms like those of temporal lobe epilepsy did better when begun on valproate prior to SRI treatment.

Symptoms of OCD may be acutely exacerbated by administration of certain serotonin agonists. Studies of the response of OCD patients to administration of m-CPP have been mixed, with some studies reporting abnormal behavioural and neuroendocrine responses (Hollander *et al.*, 1992, 1994), but with other studies failing to confirm these reports (Goodman *et al.*, 1995). As noted before, it has been suggested that only some patients' conditions exacerbate after administration of m-CPP, and that exacerbation of OCD symptoms in this situation was a negative predictor of response to pharmacotherapy (in particular, SRI's) (Hollander *et al.*, 1993a).

Furthermore, it has been suggested that parental OCD modifies a child's response to medication. Leonard *et al.* (1993) have found that presence of parental Axis I psychiatric diagnosis predicted *poorer* OCD outcome in children. There have also been findings to the contrary, however. In a study to determine the role of familial psychiatric pathology in outpatient treatment with fluoxetine, it was found that OCD patients with parents who have OCD showed a clinically and statistically significant reduction in symptoms following treatment. In addition, Erzegovesi *et al.* (2001) have found that when compared to non-responders, responders to SRI's had a significantly higher frequency of positive family history for OCD in their first-degree relatives. These findings suggest that family psychopathology, especially the presence of OCD, may predict better response to treatment. Further research would be valuable.

In summary, this extensive body of data from studies on the phenomenology, psychobiology, genetics and treatment response of this disorder provides support for the hypothesis of a heterogeneous nature of OCD.

1.6 Subtyping of heterogeneous OCD

As noted earlier, delineating OCD into a number of more homogeneous subtypes may be useful to integrate heterogeneous data on its symptomatology, psychobiology, genetics and treatment response. If distinct subtypes of OCD do exist, one may hypothesize that each of these subtypes is possibly associated with specific clinical variables (e.g. trauma history), as well as treatment response, biological markers, or genetic transmission. Moreover, it has been argued that if reliable and valid subtypes of OCD do exist, failure to identify these subtypes and to adequately characterize OCD patients' heterogeneity will hinder refinements in etiologic theory and treatment intervention (Calamari *et al.*, 1999). Until now, the identification of valid, reliable and consistent subtypes has remained almost elusive however. Nevertheless, there has been a number of different approaches to the identification of OCD subtypes, with most of these efforts giving prominence to subtyping built upon demographic and clinical characteristics (e.g. sex, age of onset of OCD, course of the disease) (Eichstedt and Arnold, 2001; Geller *et al.*, 1998; Minichiello *et al.*, 1990; Noshirvani *et al.*, 1991), presence of comorbid psychiatric conditions (e.g. tics, OCSD's) (Mataix-Cols *et al.*, 2000; Nestadt *et al.*, 2003; Sobin *et al.*, 2000), and nature of obsessive-compulsive symptomatology (Baer, 1994; Calamari *et al.*, 1999; Hantouche and Lancrenon, 1996; Leckman *et al.*, 1997; Mataix-Cols *et al.*, 1999; Summerfeldt *et al.*, 1999). Lately, identification of dimensions or subtypes has focused on using factor analytic techniques on generally recognized OCD symptom checklists.

1.6.1 Subtyping built upon demographic and clinical characteristics

i. Gender

Although there are some inconsistencies, gender-related differences have been observed in OCD symptomatology. Cleaning symptoms (Bogetto *et al.*, 1999; Castle *et al.*, 1995; Khanna and Mukherjee, 1992; Lensi *et al.*, 1996; Marks, 1987; Minichiello *et al.*, 1990; Rachman and Hodgson, 1980; Stern and Cobb, 1978) and aggressive obsessions (Lensi *et al.*, 1996) have been reported to be more common in females with OCD, while primary obsessive slowness (Bogetto *et al.*, 1999), obsessions/compulsions (symmetry and exactness (Lensi *et al.*, 1996; Rasmussen *et al.*, 1986) and numbers (Skoog, 1965; Swedo and Rapoport, 1989), touching rituals (Fischer *et al.*, 1997), and sexual (Bogetto *et al.*, 1999; Lensi *et al.*, 1996) or "odd" (Lensi *et al.*, 1996) symptoms have been found to be more common in OCD males. It should be noted, however, that some studies provide contrasting findings, such as increased contamination obsessions in males (Fischer *et al.*, 1997).

Zohar (1999) suggested that, similar to adults, there may also be gender differences in the symptom types in children and adolescents with OCD (e.g., more checking behaviour in boys, and more cleaning behaviour in girls). Evidence shows that the course of OCD may also be affected by gender. For example, in addition to evidence that OCD has a worse course in males (Castle *et al.*, 1995), some studies indicate that males predominate in childhood OCD (Castle *et al.*, 1995; Lensi *et al.*, 1996; Noshirvani *et al.*, 1991; Rettew *et al.*, 1992) and are more likely to have a chronic rather than episodic course (Castle *et al.*, 1995; Ravizza *et al.*, 1997; Thomsen, 1995). It should be noted, however, that not all studies agree that the course of OCD is worse in males (Lensi *et al.*, 1996).

Several studies have found that gender may significantly affect comorbidity. Increased comorbidity of depression (Castle *et al.*, 1995; Noshirvani *et al.*, 1991), eating disorders (Bogetto *et al.*, 1999; Castle *et al.*, 1995; Kasvikis *et al.*, 1986; Lennkh *et al.*, 1998; Noshirvani *et al.*, 1991; Welner *et al.*, 1976), and panic attacks (Lensi *et al.*, 1996) have been reported in females with OCD, and increased comorbidity of social phobia (Bogetto *et al.*, 1999; Marks, 1987), substance-related disorders (Bogetto *et al.*, 1999; Noshirvani *et al.*, 1991), and hypomanic episodes (Bogetto *et al.*, 1999; Lensi *et al.*, 1996; Perugi *et al.*, 1997) have been reported in OCD males. These findings are generally consistent with the prevalence rates of such disorders in non-OCD populations. Based on reports of increased comorbidity of depression in women with OCD (Castle *et al.*, 1995; Noshirvani *et al.*, 1991), it has been suggested that the greater frequency of later-onset OCD in women is partially explained by the well-known association of depression and OC phenomena (Noshirvani *et al.*, 1991). Furthermore, differential PD pathology between males and females has been noted. For example, in a study of PD's and social and interpersonal features among Japanese patients with OCD, it was found that cluster A PD's, especially schizotypal PD, were more frequently diagnosed in males, and borderline and dependent PD's, in females (Matsunaga *et al.*, 2000).

Evidence from twin and family studies supports a role for gender in the genetics of OCD. For example, a recent segregation analysis of families provided some evidence for a major gene underlying OCD (Nestadt *et al.*, 2000a). Of particular interest in this study was evidence for genetic heterogeneity on the basis of gender of the proband, which supports the hypothesis of different genetic/environmental exposures in at least some families with OCD (Nestadt *et al.*, 2000a). Similarly, on the basis of their segregation analysis, Cavallini *et al.* (1999) suggested a dominant model of transmission with penetrance differing in males and females. The possibility of gender differences in genetic susceptibility for OCD has also

been suggested (Camarena *et al.,* 2001). This particular study replicated the findings of a sexually dimorphic effect of the *MAO-A* gene in OCD (an excess of allele 1 in OCD females with major depressive disorder was confirmed), indicating that OCD females have lower *MAO-A* activity than OCD males.

Arguably, the worse outcomes for OCD males could be explained by early brain trauma or similar neurological dysfunction. It is notable that when compared to female patients, male patients appear to have more increased neurological soft signs (Stein *et al.*, 1994), which include abnormalities of fine motor coordination, as well as involuntary and mirror movements and visual-spatial dysfunction. (Similarly, OCD males are more likely to have tics; see discussion below.) By comparison, females may present with OCD during the menarche (Rasmussen and Eisen, 1988), the premenstrual phase (Williams and Koran, 1997), pregnancy (Diaz *et al.*, 1997; Neziroglu *et al.*, 1992), puerperium (Altshuler *et al.*, 1998; Maina *et al.*, 1999), and even menopause (Lochner *et al.*, 2003). Based on such findings, it may be hypothesized that some forms of OCD may involve gender-specific mechanisms, including hormonal and genetic mechanisms (Camarena *et al.*, 1998; Karayiorgou *et al.*, 1997, 1999). Further research is necessary to delineate the precise mechanisms involved.

In general, there appears to be gender differences in the genetics, course, and clinical manifestations of OCD. Gender differences in comorbid psychiatric disorders generally match the gender differences for these disorders in non-OCD population. Overall, when compared to women with OCD, males with OCD appear to have earlier onset, a more severe course, and more neurological soft signs.

ii. Age of onset

It has been suggested that childhood-onset OCD represents a phenomenologically and etiologically distinct subtype of OCD, bearing a close genetic relationship to tic disorders and possibly sharing a common or similar pathogenesis (Eichstedt and Arnold, 2001; Geller *et al.*, 1998). For example, a recent study by Do Rosario-Campos *et al.* (2001) found that early onset was associated with higher frequencies of sensory phenomena and of comorbid tic disorders, and with higher severity and frequency of tic-like compulsions. Likewise, in contrast to adults, children with OCD often present with *pure* compulsions—for example, washing compulsions and repeating compulsions, without any apparent obsessive thoughts (Swedo *et al.*, 1989). It has also been suggested that patients with a very early onset of OCD (younger than six years old) were more likely to have compulsions rather than obsessions (Honjo *et al.*, 1989; Rettew *et al.*, 1992). These compulsions would typically include elaborate washing or checking rituals without cognitive obsessions (Swedo *et al.*, 1992). In an investigation of possible family subtypes, Nestadt *et al.* (2000) found that age of onset of obsessive-compulsive symptoms in the case proband is strongly related to familiality; no case of OCD symptoms was detected in the relatives of patients whose age of onset was 18 years or older. Similar findings by others (Lenane *et al.*, 1990; Pauls *et al.*, 1995) support the hypothesis that familial loading for OCD is associated with early onset. Thus, early age of onset may be valuable in characterizing a familial subtype of OCD.

To summarize, when compared to later-onset OCD, childhood-onset OCD is associated with higher rates of compulsions and comorbid tic disorders. In addition, childhood-onset OCD appears to be much more strongly genetically transmitted.

iii. Course of the disease

Several studies support theories of OCD as an illness with fluctuating severity (Thomsen, 1995) and varied clinical manifestations that change over time (Rettew *et al.*, 1992). The course of OCD has been differentiated into different groups, including episodic and continuous/chronic (Ravizza *et al.*, 1997), with OCD being chronic in approximately half of all cases (Thomsen and Mikkelsen, 1995). It has been suggested that factors such as age, gender, and severity of childhood OCD symptomatology may play a role in the course of the condition (i.e., as episodic or chronic) (Ravizza *et al.*, 1997). In one study, for example, it was found that in childhood, more females than males have an episodic course of OCD, whereas just as many females as males suffered from OCD, either chronically or episodically, in adulthood (Thomsen, 1995).

In agreement with studies indicating that patients with an episodic course of the disorder may be a distinct subgroup within the whole group of obsessive-compulsive patients, multivariate stepwise discriminant analysis revealed a positive and significant relationship between episodic course on the one hand, and family history of mood disorders, lifetime comorbidity for panic and bipolar II disorders, late age of onset, and negative correlation with generalized anxiety disorder (GAD), on the other (Perugi *et al.*, 1998; Thomsen, 1995). In a retrospective study of 62 OCD patients, the long-term course of OCD and its relationship to depression were investigated. Five courses of OCD were differentiated: continuous and unchanging (27.4%), continuous with deterioration (9.7%), continuous with improvement (24.4%), episodic with partial remission (24.2%), and episodic with full remission (11.3%). There was no difference between primary versus secondary depression on the prognosis of OCD, and there was also no difference between continuous versus episodic course on either primary or secondary depression (Demal *et al.*, 1993). In one study, however, it was found that severity of OCD in childhood plays a determining role in the course and outcome

of OCD; that is, longer duration of obsessive-compulsive symptoms in childhood (chronic course) predicts a poor outcome (presence of OCD) in adulthood (Thomsen, 1995). Furthermore, some studies have found a correlation between continuous course and poorer response to pharmacotherapy (Alarcon *et al.*, 1993; Ravizza *et al.*, 1995). It remains unclear what factors predict a chronic deteriorative course (Rasmussen and Eisen, 1991).

1.6.2 Subtyping built upon OCD symptomatology

As noted previously, a focus on the nature of OCD symptomatology as a classifying variable has been one of the most common strategies for identifying OCD subgroups, and has been receiving increased attention in recent years.

i. OCD symptomatology: A dichotomy?

Earliest efforts to subtype OCD suggested a broad distinction between obsessions and compulsions. This dichotomy continues to be recognized in current diagnostic systems such as the DSM-IV (APA, 1994). However, it has increasingly been suggested that the diversity of the presentation of OCD necessitates a more multidimensional approach.

ii. OCD symptomatology: A multidimensional approach

Even approaching the matter from a multidimensional perspective is not without restrictions. In particular, attempts to dissect dimensions or subtypes of OCD have limitations – either by excluding some of the "miscellaneous" symptoms included in some of the OCD-scales, or by using restricted symptom scales or even inadequate statistical packages. Moreover, symptom-based taxonomies have often only focused on OCD patients' major or most prominent compulsions (e.g. checking, or washing) (e.g. Hodgson and Rachman, 1977). Such classifications are then based on a single, dominant compulsion and therefore limited,

as most patients tend to present with multiple types of obsessions and compulsions. Although the formation of OCD symptom subtypes based on a single dominant compulsion continues to be used as a subtyping strategy (e.g. Matsunaga *et al.*, 2001), some researchers have cautioned that grouping OCD patients based solely on behavioural similarities may be problematic (Summerfeldt *et al.*, 1999) and that a more comprehensive approach incorporating more than just compulsive behaviour or rituals is needed.

Because of the complex patterns of obsessions and compulsions characteristic of OCD, the multivariate statistical methods of cluster and factor analysis have been applied as a useful way to identify the latent dimensions of symptom measures or to classify heterogeneous data into "smaller" more homogeneous categories. Generally speaking, these methods were specifically designed to reduce a number of variables and to detect structure in the relationships between variables, i.e. to *classify variables* (Kim and Mueller, 1978, 1978).

iii. Studies using factor analysis

As noted earlier, lately most of these studies have used factor analysis of OCD symptoms that were assessed by specific symptom scales as a way of subtyping OCD. In short, the purpose of factor analysis is to find a new set of variables, fewer in number than the original variables, which express that which is common among the original variables (Cattell, 1978, p16). For example, an early principal-components factor analysis of the 30 item of the Maudsley Obsessional Compulsive Inventory (MOCI) in 100 patients yielded four factors: checking, cleaning, slowness, and doubting (Hodgson and Rachman, 1977). The MOCI comprises only 30 items however, which are biased towards the symptoms of cleaning and checking, while other symptoms, such as aggressive obsessions and hoarding compulsions, are underrepresented (Baer, 1994). Van Oppen *et al.* (1995) evaluated the factor structure

of a similar scale — the Padua Inventory (Sanavio, 1988) — and five factors were identified: impulses, washing, checking, rumination, and precision.

The widely recognized YBOCS-CL is a clinician-rated measure that is more comprehensive than the earlier scales (Goodman *et al.*, 1989). More recently, it was emphasized that an objective approach relying upon *exploratory* factor analysis or similar *data reduction* / classification techniques using the YBOCS-CL to detect empirical grouping in large standardized arrays of symptoms is needed (Summerfeldt *et al.*, 1999). The YBOCS-CL corrects the item-selection bias of the MOCI and Padua Inventory (Baer, 1994). Improving on these limitations characteristic of the other scales, factor analytic studies of *a priori* clinically derived symptom categories or individual OCD symptoms using the YBOCS-CL have consistently found that these fall into 3 to 6 factors, namely aggressive / checking, contamination, symmetry / ordering and hoarding symptoms (Baer, 1994; Calamari *et al.*, 1999; Cavallini *et al.*, 2002; Denys *et al.*, 2004; Feinstein *et al.*, 2003; Leckman *et al.*, 1997; Mataix-Cols *et al.*, 1999; Summerfeldt *et al.*, 1999).

These symptom dimensions appear to be common in the majority of analyses, despite somewhat different methodological approaches. In particular, Baer's factor analysis of the YBOCS-CL yielded three factors: symmetry/hoarding, contamination/cleaning, and "pure obsessions" (Baer, 1994). Similarly, the 1996-study by Hantouche and Lancrenon also reported a symptomatic clustering of obsessions and compulsions into these three major categories (1996). Partially similar, Leckman *et al.* (1997) more recently identified four different dimensional factors using the YBOCS-CL, including obsessions and checking, symmetry and ordering (including other compulsions such as counting, arranging and repeating), cleanliness and washing, and hoarding. Using the same instrument and implementing confirmatory factor analysis, Summerfeldt *et al.* (1999) confirmed these

findings with their specification of obsessions/checking, symmetry/ordering, contamination/cleaning, and hoarding. A principal components analysis by Mataix-Cols *et al.* (1999) identified five factors explaining as much as 65.5% of the variance in outcome, i.e. symmetry/ordering, hoarding, contamination/cleaning, aggressive/checking, and sexual/religious obsessions. In addition, a very recent factor analysis of the clinically-derived categories and the individual items of the YBOCS-CL rendered results with considerable overlap with factor clusters from prior studies (Feinstein *et al.*, 2003).

Importantly, in factor analysis, variance is partitioned between factors and one person may have loadings on all of the identified factors (Baily, 1994); i.e. at any one time, OCD patients may have symptoms from more than one of these identified factors.

In summary, to date, a number of factor analysis studies have been published, assessing more than 2000 patients (Baer, 1994; Cavallini *et al.*, 2002; Feinstein *et al.*, 2003; Foa *et al.*, 2002; Hantouche and Lancrenon, 1996; Leckman *et al.*, 1997, 2003; Mataix-Cols *et al.*, 1999, 2002; Summerfeldt *et al.*, 1999; Tek and Ulug, 2001). In all of these studies 3 to 6 OC factors or dimensions have been identified, accounting for almost 70% of the variance (Mataix-Cols *et al.*, 2005).

iv. Studies using cluster analysis

In cluster analysis variables are grouped together according to the high correlations they have with one another (Cattell, 1978). In addition, in contrast to factor analysis, in cluster analysis, patients are unambiguously assigned to these identified groups created by maximizing between-group differences and minimizing within-group variability on the chosen set of measures; in other words, each patient falls into only one cluster. (Conversely, as noted before, in factor analysis, an object may have loadings on all of the identified factors.)

Use of cluster analysis has gained ground in recent years, with some investigators suggesting that cluster analysis may be a superior method for identifying OCD subtypes (Calamari *et al.*, 1999).

A cluster analysis of the items of the YBOCS-CL by Calamari *et al.* (1999) identified five definitive symptom-based groupings based on the YBOCS-CL, including harming, hoarding, contamination, certainty, and obsessionals; the core symptoms of these identified subgroups being comparable to factors identified in the previous factor analysis studies with the YBOCS-CL (Baer, 1994; Leckman *et al.*, 1997; Summerfeldt *et al.*, 1999). In a recent attempt to replicate and extend their previous symptom-based subgroup taxonomy also using cluster analysis, Calamari *et al.* (2004) suggested that the rules for determining the number of symptom subgroups supported a more complex model. In addition, with their between-sample comparisons, the contamination subgroup came out as the only stable subgroup in both a 5- and 7-group taxonomy. A harming subgroup was consistently identified as well. Between-sample stability was not so strong for symmetry, certainty, and obsessionals subgroups. Hoarding as a distinctive subgroup was unstable in the separate samples. However, when they combined their present sample with the 1999-sample, a reliable hoarding subgroup was found. In summary, they presented with both a 5- and 7-subgroup taxonomy, with greater support for the 7-subgroup model; this model being the most complex (and probably the most clinically impractical) symptom-based taxonomy to date. In addition, their findings emphasized the need for using larger clinical samples to identify OCD-subgroups.

A summary of all published OCD classification studies (i.e. factor and cluster analyses) of OC symptoms using the YBOCS-CL are listed in Table 1.

TABLE 1. OCD classification studies using the YBOCS-CL

Study	Year	Nr of patients	Analysis technique	Total variance explained (%)	Nr of factors / clusters	Identified factors / clusters
Baer, 1994	1994	107	Principal components analysis, current symptoms	48%	3	1. Symmetry and hoarding 2. Contamination and cleaning 3. Pure obsessions
Hantouche & Lancrenon, 1996	1996	615	Principal components analysis, current symptoms	32.5%	3	1. Predominantly compulsive 2. Predominantly obsessive 3. Mixed
Leckman *et al.*, 1997	1997	292	Principal components analysis, lifetime symptoms	63.5%	4	1. Obsessions and checking 2. Symmetry and ordering 3. Cleanliness and washing 4. Hoarding
Calamari *et al.*, 1999	1999	106	Cluster analysis	65.5%	5	1. Harming 2. Hoarding 3. Contamination 4. Certainty 5. Obsessional
Summerfeldt *et al.*, 1999	1999	203	Confirmatory factor analysis, current symptoms	Not available	4	1. Aggressive, sexual, religious, somatic obsessions and checking 2. Symmetry and repeating, ordering and counting 3. Contamination and cleaning, washing 4. Hoarding obsessions and compulsions
Mataix-Cols *et al.*, 1999	1999	354	Principal components analysis, current symptoms	62.5%	5	1. Symmetry and ordering 2. Hoarding 3. Contamination and cleaning 4. Aggressive and checking obsessions 5. Sexual and religious obsessions
Tek and Ulug, 2001	2001	45	Principal components analysis, current symptoms	65.5%	5	1. Contamination / cleaning 2. Symmetry / ordering 3. Aggressive / counting 4. Sexual / religious obsessions 5. Checking / hoarding compulsions
Cavallini *et al.*, 2002	2002	180	Principal components analysis, lifetime symptoms	59.87%	5	1. Contamination / washing 2. Hoarding 3. Aggressive 4. Symmetry 5. Repetitive rituals
Mataix-Cols *et al.*, 2002	2002	153	Principal components analysis, current symptoms	Not available	5	1. Aggressive / checking 2. Contamination / washing 3. Symmetry / ordering

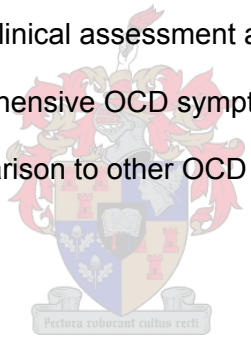
						4. Hoarding 5. Sexual / Somatic
Feinstein *et al.*, 2003	2003	160	1.) Principal components analysis performed on clinically derived categories, current symptoms	54.2%	4	1. Symmetry / ordering / counting / arranging / repeating / need to touch 2. Aggressive and contamination obsessions / checking / cleaning compulsions 3. Hoarding 4. Religious / sexual obsessions (pure obsessions)
			2.) Principal components analysis performed on individual items, current symptoms	39.3%	4	1. Harm obsessions / checking 2. Disgust with contaminants / cleaning compulsions 3. Sexual obsessions 4. Hoarding / symmetry / repeating
Calamari *et al.*, 2004	2004	220	Cluster analysis	Not available	7	1. Contamination 2. Harming 3. Hoarding 4. Symmetry 5. Obsessionals 6. Certainty 7. Harming / Contamination
Denys *et al.*, 2004	2004	335	Principal components analysis, current symptoms	41.7%	5	1. Contamination / cleaning 2. Aggressive / sexual, religious, somatic obsessions 3. Somatic obsessions and checking 4. Symmetry and perfectionism 5. High risk assessment and checking

v. *OCD symptom subtypes: Prevalence*

In terms of prevalence of the various OCD symptom subtypes, an examination of 65 studies that classified patients according to such subtypes found that patients with primarily cleaning or checking compulsions predominated, accounting for 75% of the treatment population (Ball *et al.*, 1996). Patients with multiple compulsions or other compulsions such as exactness, counting, hoarding, or slowness rituals were underrepresented, making up only 12% of the subjects—which is markedly less than clinical epidemiological estimates (Ball *et al.*, 1996).

vi. OCD symptom subtypes based on OCD symptomatology assessed with the YBOCS-CL: Limitations

In general, the YBOCS-CL has been chosen as an OCD-scale to be factor / cluster analysed because of its extensive use in OCD clinical assessment and research. As noted before, this checklist is indeed a relatively comprehensive OCD symptom measure, with a bigger range of symptoms that are assessed in comparison to other OCD symptom measures (see Addendum 8 for a copy of this scale).



However, it has been suggested that alternative comprehensive measures of OCD symptoms with well established psychometrics are needed, given that the YBOCS-CL provides for relatively limited assessment of several types of obsessions and compulsions, i.e. symptoms that are related to the subgroups identified in some of the more complex models. In addition, one may argue that only very basic assessment of hoarding symptomatology, of symmetry and exactness, of somatic concerns, and of counting and ordering is found on the YBOCS-CL. In addition, the so-called “other” and “miscellaneous” categories contain items / symptoms that are idiosyncratic and heterogeneous, respectively, and although important symptoms are included in these categories, these sections have no logical coherence or empirical support. Calamari *et al.* (2004), focusing on developing a symptom-based OCD subgroup taxonomy using cluster

analysis, suggested that the instability that was observed in their identified subgroups (such as "obsessionals", "hoarding", and "symmetry") have resulted from the limitations of the measurement of symptoms important to these subtypes. In fact, they noted that a much more comprehensive assessment of symptoms than that which can be accomplished with a modification of the YBOCS-CL will likely be needed to comprehensively measure the complex symptom heterogeneity of OCD.

Nevertheless, despite these limitations, one has to bear in mind that currently the YBOCS-CL is one of the most comprehensive measures of OCD symptomatology available. Future efforts to subtype OCD (based on symptomatology) will probably continue using this measure until it has been modified and/or a better or more comprehensive measure of OCD symptoms is established.

1.6.3 Subtyping built upon comorbidity

Another approach to subtyping OCD may be to consider issues of comorbidity. Indeed, there is growing interest in the categorization of OCD as a heterogeneous phenomenon into more homogeneous subtypes by examining comorbidity (Nestadt *et al.*, 2003). OCD patients often report comorbid psychiatric conditions. In fact, comorbidity in OCD appears to represent the rule rather than the exception, with this condition being commonly comorbid with a number of psychiatric conditions: After major depressive disorder, the most common comorbid disorders reported in patients with OCD are other anxiety disorders (e.g. posttraumatic stress disorder), eating disorders, alcohol abuse, and the putative OCSD's. For instance, in their attempt to characterize psychopathological classes of disorders related to OCD to distinguish more homogeneous phenotypes with distinct etiologies, Nestadt *et al.* (2003) suggested that the OCD phenotype is expressed in two different subgroups based on the presence of additional clinical

syndromes that frequently accompany the condition. One of the subgroups was characterized by panic disorder / agoraphobia and tic disorders, and the other by generalized anxiety disorder, major depressive disorder (recurrent), and the OCSD's. Subtyping based on such comorbidity is not the main focus in the current thesis; however, future work on the structure of comorbid disorders in OCD should address the inclusion of all of these conditions.

Increasing attention has also been paid to the fact that individuals with OCD are likely to report a lifetime comorbid obsessive-compulsive spectrum condition (Richter *et al.*, 2003), with a recent clinical study suggesting that just more than half of their participants with OCD currently met criteria for at least one putative OCSD, and that 67.1% had a lifetime history of at least one comorbid OCSD (du Toit *et al.*, 2001). Subsequently, it has also been suggested that the heterogeneous OCD phenotype may comprise a number of *subtypes* based on the presence of such comorbid OCSD's, each with specific pathophysiological mechanisms and treatment outcomes. For example, as mentioned before, many patients with OCD have comorbid tics and/or TD, and patients with comorbid tics may have a particular phenomenology, neurobiology (e.g. involving the dopamine system), requiring somewhat different treatments. In addition to tics or TD, there are other commonly comorbid OCD spectrum conditions in patients with OCD, e.g. body dysmorphic disorder (BDD) and hypochondriasis, trichotillomania, stereotypic movement disorder and self-injury, as well as bulimia nervosa, kleptomania and pathological gambling. However, while the majority of OCD patients suffer from at least one comorbid OCSD (du Toit *et al.*, 2001), there has been relatively little systematic investigation of the structure and implications of such comorbidity. Nevertheless, based on existing data, one might hypothesize that comorbid OCD and OCSD's in general fall into a number of homogeneous *groups*, including:

1.) patients with tics or other involuntary movements (including TD);

2.) a group of patients with somatic obsessions (including the somatoform disorders of

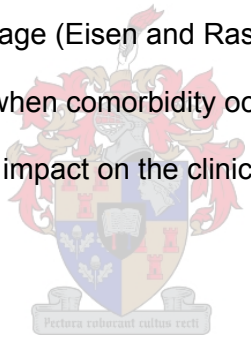
BDD, hypochondriasis;

3.) patients with stereotypic or grooming symptoms (including trichotillomania (TTM), stereotypical movement disorder (SMD) and self-injury), and

4.) patients demonstrating impulsive features (including eating disorders such as bulimia nervosa, kleptomania, and pathological gambling).

More research is needed to investigate these hypotheses.

In addition to OCD subtyping based on comorbidity with OCSD's, emerging evidence shows that OCD may be comorbid with psychotic conditions (Attiullah *et al.*, 2000). For instance, it was found that compared to OCD patients without psychosis, patients with OCD and psychotic features were more likely to be male, be single, have a deteriorative course, and have had their first professional contact at a younger age (Eisen and Rasmussen, 1993). Data from a study by Perugi *et al.* (1997) also indicate that when comorbidity occurs with bipolar and unipolar affective disorders, it has a differential impact on the clinical characteristics, comorbidity, and course of OCD.



A range of comorbid Axis II disorders has also been found in OCD patients, with those of cluster C the most prevalent (Baer *et al.*, 1990; Bejerot *et al.*, 1998; Black *et al.*, 1993; Matsunaga *et al.*, 1998; Mavissakalian *et al.*, 1990, 1990; Thomsen and Mikkelsen, 1993). Existence of a schizotypy subtype of OCD, associated with three clinical features that have previously been associated with psychosis, i.e. counting compulsions, learning disabilities, and phobia, has also been suggested (Eisen *et al.*, 1993; McDougle *et al.*, 1990; Norman *et al.*, 1996; Sobin *et al.*, 2000). OCD with schizotypy has also been associated with poor insight that remained poor even after treatment (Matsunaga *et al.*, 2002).

Overall, OCD has high rates of comorbidity with a number of Axis I and II disorders. Among the Axis I disorders, OCSD's are among those most often comorbid with OCD. Focussing on conditions that may be etiologically related to OCD and possibly due to the same underlying mechanisms, may enhance the probability of finding susceptibility genes for OCD. Preliminary data suggest that *dissecting* comorbidity in OCD, and perhaps comorbidity with OCSD's in particular, is a useful way of subtyping OCD; e.g. OCD with tics may represent a genetically meaningful subtype. Much additional work remains to be done.

1.7 OCD subtypes and associated features

In summary, in recent years increasing attention has been paid to subtyping OCD, and specifically subtyping based upon demographic and clinical characteristics (e.g. age of onset of OCD), obsessive-compulsive symptomatology and comorbidity patterns. Findings suggest relative consistency. Most authors agree that childhood-onset OCD is a valid subtype of OCD that is associated with higher rates of compulsions and comorbid tic disorders, and is strongly genetically transmitted. Findings rendered by the other two approaches (i.e. symptomatology, comorbidity patterns) to subtyping OCD are currently a somewhat more contentious matter emphasizing the need for further research. Nevertheless, one may hypothesize that ultimately the utility of any subtyping approach awaits evaluations of subtype-related differences in etiological processes including clinical (e.g. trauma history) and genetic features, as well as outcome (treatment) studies.

1.7.1 OCD subtypes and associated etiological (clinical and genetic) features

Increased subtyping efforts have indeed been accompanied by a number of studies investigating the matter of OCD subtypes and their associated features: For example, in a

study by Khanna and Mukherjee (1992) it was suggested that checkers can be sociodemographically and clinically differentiated from washers, emphasizing the importance of exploration of features associated with the main obsessive-compulsive symptomatology. It was found that checkers were more likely to be single and male and have an earlier age of onset, with the mixed group on the other hand (patients who are both washers and checkers) appearing to be a female-dominated variant of the checkers group. Furthermore, drawing on the work of Janet (reviewed by Pitman (1987)), Rasmussen and Eisen (1991) have suggested that OCD can be subtyped on the basis of three core features—namely, abnormal risk assessment, pathological doubt, and incompleteness. These core features were shown to be related to the clinical features of OCD and to comorbid disorders. More specifically, it was suggested that symptoms involving incompleteness are likely to be associated with tics and compulsive personality traits, while other symptoms are likely to be associated with increased anxiety and comorbid anxiety disorders (Rasmussen and Eisen, 1991). Baer (1994) has provided empirical data partially consistent with such a hypothesis, noting that the "symmetry/hoarding" cluster of symptoms, which is often characterized by incompleteness, was significantly related to tics (TS or chronic tic disorder) and to obsessive-compulsive personality disorder. Another study found a significantly higher rate of sexual and religious obsessions, and a significantly lower rate of checking rituals, in OCD patients with comorbid bipolar disorder, compared to nonbipolar OCD patients (Perugi *et al.*, 1997). Frost *et al.* (2000) found that, compared to non-hoarding OCD and other anxiety disorder patients, OCD patients with hoarding scored higher on anxiety, depression, and social disability.

In addition, clinicians have long described the emergence of obsessive-compulsive symptoms in the aftermath of psychological or emotional trauma. However, this concept lost ground as psychodynamic theories about OCD became less popular and as neurobiological data on OCD emerged. Certainly, clinicians should be reminded not to confuse OCD and PTSD (Pitman,

1993). Nevertheless, there is recent work suggesting that in some cases of OCD, psychological trauma may play a role (de Silva and Marks, 1999; Trumbull *et al.*, 2001). More work is needed to determine whether there is a significant association between a history of specific traumatic experiences and OCD subtypes, and if so, what the implications are.

In contrast, however, to the above findings that linked OCD symptomatology at baseline with other clinical variables (such as comorbidity), a prospective longitudinal study of 79 children and adolescents with OCD (Rasmussen *et al.*, 1986) found no significant relationship between the type of OCD symptom at baseline and age, gender, and duration of illness. Similarly, in a series of 250 OCD patients, Rasmussen and Eisen (1988) found no significant relationship between the type of symptom and age at onset, gender, course of illness, or comorbid conditions. It is nevertheless possible that the above studies did not include enough subjects having potentially unique symptoms (Takeuchi *et al.*, 1997), and thus lacked the power to show a relationship between rarer symptoms and demographic or clinical variables. For example, it has been suggested that "obsessional slowness" (the tendency towards pathological orderliness and having to undertake tasks in a precise and particular pattern), as originally characterized, can be differentiated from slowness secondary to rituals (Rachman, 1974). Later authors have argued, however, that such cases can invariably be reanalyzed as secondary to obsessions, compulsions, or avoidance strategies (Galderisi *et al.*, 1995; Veale *et al.*, 1993), and therefore do not carry particular clinical significance. Notably, symptoms may differ in OCD patients along several other clinical variables, such as insight, duration of illness, continuity of symptoms, ratio of obsessions to compulsions, bizarreness of obsessions, fixity of belief, control over symptoms, resistance to symptoms, and overall severity.

In terms of neurochemistry / genetics, Cavallini *et al.* (2002) have suggested a trend towards positive association between their fifth factor, including counting and repeating rituals, and an

insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR). In another study, the symmetry/ordering subtype also showed greater inheritance of OCD (Alsobrook *et al.*, 1999). Interestingly, in a recent factor analysis of obsessive-compulsive symptomatology in patients with Tourette's disorder, Leckman *et al.* (2003) identified two symptom dimensions; i.e. aggressive, sexual, and religious obsessions and checking compulsions (Factor 1) and symmetry and ordering obsessions and compulsions (Factor 2), and found that familial factors (genetic or environmental) contribute significantly to OCD symptom dimension phenotypes in families with Tourette's disorder. Rauch *et al.* (1998) have also suggested that OCD patients with higher scores on the so-called "obsessional" factor showed a positive correlation with blood flow in the striatum bilaterally. Importantly however, findings on the relationship between symptom dimensions and some of these variables have not always been consistent across studies.

In summary, the dimensional structure of OCD symptoms is still not fully delineated. Nevertheless, continued attempts to quantify phenotypic OC traits may help to identify more robust endophenotypes. Very little work has been carried out to identify endophenotypes for OCD, with the possible exception of structural and functional neuroimaging studies. OCD "endophenotypes" can be conceptualized as "latent genetically influenced traits, which may be related only indirectly to the classic (OC) symptoms defined in the DSM-IV" (Gottesman *et al.*, 1997). As such, endophenotypes (whether physiological, psychological, functional or structural in nature) reflect an underlying susceptibility to the OCD phenotype. Therefore, the rationale for using endophenotypes when studying an illness such as OCD, is based on the assumption that the number of genes required to produce variations in OCD traits may be fewer (and thus possibly easier to identify) than those involved in producing the OCD diagnosis (Gottesman and Gould, 2003).

1.7.2 OCD subtypes and associated outcome

Arguably, the nature of the delineated OCD subtypes will have implications for associated impairment and treatment outcome. For example, returning to some of the findings from the above mentioned treatment studies:

Some studies have found that cleaning symptoms may respond best to exposure methods (Buchanan *et al.*, 1996; Rachman and Hodgson, 1980), whereas checking rituals predicted poorer outcome in some behavioural therapy studies (Basoglu *et al.*, 1988; Rachman and Hodgson, 1980). Other studies have, however, not found differences in treatment response between patients with cleaning and checking (Foa and Goldstein, 1978). More recently, it has been suggested that improvement with behavioural therapy is more likely only with patients having *either* cleaning *or* checking compulsions, but not both (Ball *et al.*, 1996). There is a relative absence of documentation concerning the outcome of behavioural therapy for obsessive-compulsive symptoms other than cleaning and checking; other subgroups (such as patients with ordering compulsions, hoarding rituals, or obsessional slowness) have rarely been included in trials of such therapy (Ball *et al.*, 1996). This lack of data is perhaps not surprising in that some studies have suggested that patients with non-cleaning compulsions may be more likely not to enter behavioural therapy (Marks *et al.*, 1988). Even so, several studies have found that patients with non-cleaning compulsions and obsessions (e.g., those with obsessional slowness or in whom obsessions predominate) are unresponsive to behavioural therapy (Basoglu *et al.*, 1988; Christensen *et al.*, 1987; Clark *et al.*, 1982; Marks, 1987; Minichiello *et al.*, 1988).

It has been suggested that washing symptoms do worse with SRI's (Alarcon *et al.*, 1993; Ravizza *et al.*, 1995). Hoarding symptoms have also been associated with worse response to

treatment with SRI's (Black *et al.*, 1998; Mataix-Cols *et al.*, 1999) as well as premature drop-out from behaviour therapy (Mataix-Cols *et al.*, 2002). Furthermore, high scores on hoarding and sexual/religious symptoms have also been found to predict poor treatment response (Mataix-Cols *et al.*, 2002). Similarly, somatic obsessions have been reported to condition a poor prognosis for drug treatment (Erzegovesi *et al.*, 2001). In another treatment study, a subgroup of OCD patients with principal symmetry obsessions responded to treatment with the monoamine oxidase inhibitor phenelzine whereas other symptom groups did not (Jenike *et al.*, 1997).

In addition to treatment response, disease outcome may also refer to the extent of the disability or functional impairment associated with the symptoms. Indeed, treatment response and disability are related concepts, i.e. only partly but not entirely similar. For instance, it may be argued that a treatment responder spends significantly less time on his OC symptoms, he/she has fewer OC symptoms and experiences less distress due to the illness after receiving treatment compared to a non-responder. On the other hand however, treatment response is related but not necessarily synonymous with less "disability" or less functional impairment. The concept of disability includes impairment in a number of different domains of functioning including family life, school / work, marriage, friendship, activities of daily living etc. In fact, patients presenting with different OCD symptom dimensions may have similar treatment response, but may differ in terms of the extent and nature of their associated disability. For example, as noted earlier, it has been found that "hoarding" is associated with higher scores on anxiety, depression, family and social disability measures than other subtypes of OCD (Frost *et al.*, 2000). Data on the issue of disability and symptom subtypes are lacking, but one may argue that efforts to determine the extent to which the identified symptom dimensions or subtypes determine outcome (i.e. both treatment outcome, disability), may contribute to a more

precise determination of the pathogenesis of OCD symptoms for a more accurate projection of future outcomes, and ultimately, for better treatment.

In conclusion, studies of the phenomenology, psychobiology, genetics and family relationships, and neuro-imaging of OCD support the view that **OCD is not simply a homogeneous entity. Rather, increasing evidence suggests that OCD indeed is a heterogeneous disorder, with different subtypes or dimensions that are characterized by differing pathophysiological mechanisms and treatment outcomes. Classification of OCD into a number of possibly more homogeneous subtypes has been shown to provide a useful means of integrating data on its symptomatology, neurobiology, and treatment response.** In addition, existing data support the significant association between some of the identified subtypes of OCD and specific clinical variables (e.g. trauma history), treatment response, biological markers, or genetic transmission in OCD. Until now, the identification of valid, reliable, meaningful and consistent OCD subtypes has remained elusive however, justifying more research into this area to also facilitate refinements in etiologic theory and prediction of outcome for each identified subtype. Replication and consistency of findings will contribute to more effective treatment intervention and management of disability associated with this condition.

CHAPTER 2

METHODS

2.1 Participants

The study was based on existing data obtained from patients participating in the Genetics of Anxiety Disorders Project (MRC Unit on Anxiety Disorders; project number: 99/013, approved by the Institutional Review Board of the University of Stellenbosch), as well as additional data, which the candidate and her colleagues collected over a period of 4 years. In total, 282 participants with obsessive-compulsive disorder (OCD) were recruited during this time and included in this project. Due to a number of reasons, there were a few patients who were excluded from the analyses: For example, those patients who scored less than 8 on the so-called Yale-Brown Obsessive-Compulsive Symptoms Severity Scale (YBOCS-SS), which may be indicative of *subclinical* OCD, were excluded. Other reasons for patient exclusion include the following: Self-report questionnaires which were not completed or returned to the research unit, or where there was a change of address without giving notice to the researchers so that those patients could not be followed up when additional material was added to the interview schedule. Each of the subsequent chapters will indicate the exact number of the total group of participants that was actually included in the various analyses.

To be eligible, patients had to meet the Diagnostic and Statistic Manual of Mental Disorders 4th Edition (DSM-IV) (APA, 1994) criteria for a primary diagnosis of OCD on the Structured Clinical Interview for Axis I Disorders - Patient Version (SCID-I/P) (First *et al.*, 1998), and had to provide written informed consent for the study. Patients were recruited from a wide range of sources (the OCD Association of South Africa, community based primary care practitioners, and

specialist psychiatrists). Inclusion into this project was subject to informed consent from all relevant parties and was guided by the inclusion and exclusion criteria.

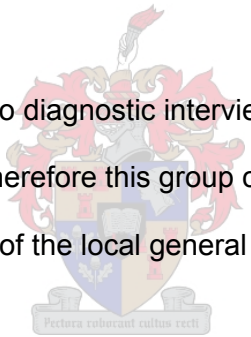
2.1.1 Inclusion criteria:

i. Patient group:

- The patient has a primary DSM-IV diagnosis of OCD, with or without any obsessive-compulsive spectrum disorders (OCSD's).
- The patient or his/her parents has given signed informed consent.
- The patient was willing to comply with study procedures.

ii. Control group:

- Controls did not undergo diagnostic interviews and were randomly selected from a community sample; therefore this group can be assumed to be a *convenience* sample, representative of the local general population.



2.1.2 Exclusion criteria:

- Patients with any *primary* Axis I disorders *other than OCD* (as determined with the SCID-I/P and -OCSD clinical interview).
- Patients who did not appear to comprehend adequately the aims and practical implications of this protocol.
- Patients who did not provide consent after reading the information and consent forms.

2.2 Data collection

2.2.1 Interview

After recruitment of a participant, and obtaining written informed consent, each individual was subjected to a semi-structured interview, either personally performed by the candidate or other experienced clinical researchers employed at the MRC Unit on Anxiety and Stress Disorders. Demographic data, including current age, age at onset of the illness, ethnicity, highest education level and current employment status, were obtained. The SCID-I/P, and selected parts of the Structured Clinical Interview for Axis II Disorders - Patient Version (SCID-II/P) (including OC, avoidant, schizotypal and borderline personality disorders) (First *et al.*, 1998) were used to assess comorbidity. Both these structured diagnostic instruments are used very frequently in Psychiatry research. In addition, a newly developed Structured Clinical Interview for the Diagnosis of putative Obsessive-Compulsive Spectrum Disorders (SCID-OCSD) (du Toit *et al.*, 2001) was administered to assess OCD-related conditions not covered by the SCID-I/P.

2.2.2 Rating scales

The Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL) and Severity Scale (YBOCS-SS) (Goodman *et al.*, 1989b, 1989c) were used allowing assessment of the typology and severity of obsessive-compulsive symptoms, respectively. Each of the 74 items of the YBOCS-CL represents a single obsessive or compulsive symptom. These items are sometimes grouped together into 13 to 14 *broad* or *major* symptom categories based on their core characteristics. This scale was developed in 1986, has very frequently been used in research and clinical settings since, and is generally assumed to have good validity and reliability (although data on the psychometric properties of the YBOCS-SS is relatively limited).

Patients' level of insight into the senselessness or excessiveness of their OC symptoms was assessed using the relevant YBOCS-SS item (Goodman *et al.*, 1989c).

The presence/absence of tics (current and/or past) was clinically assessed.

For patients who had received an adequate trial of pharmacotherapy with a serotonin reuptake inhibitor (SRI) (i.e. at least 10 weeks on the medication with a minimum of 6 weeks on mid-range dose) and/or formal cognitive behaviour therapy (CBT) (i.e. 8 or more sessions with an expert OCD/CBT psychotherapist), response was assessed on the global improvement item of the Clinical Global Impression (CGI) scale; subjects with CGI scores of 1 ("very much improved") or 2 ("much improved") were defined as treatment responders (Guy, 1976), with the rest defined as *non*-responders or *treatment resistant / refractory*.

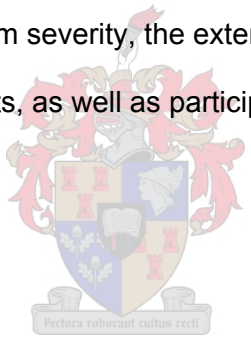
The Childhood Trauma Questionnaire (CTQ) (Bernstein *et al.*, 1994) was used as a self-report questionnaire to assess the nature and severity of childhood trauma. Subscales of the CTQ include measures of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Reliability and validity of the CTQ had been well researched and the scale appears to be a useful measure of childhood trauma (Bernstein *et al.*, 1997).

The Disability Profile questionnaire (DP) (Schneier *et al.*, 1994) was included in the clinical interview to assess current (past two weeks) and lifetime impairment in eight domains (alpha coefficients: 0.87 for current rating, and 0.90 for lifetime rating). Each item is rated separately for current and for most severe lifetime disability on a 5-point, descriptively anchored scale ranging from 0 (no impairment) to 4 (severe impairment). It was initially developed for use in patients with social anxiety disorder (SAD). Nevertheless, as the DP has since been used in a number of studies to assess disability in patients with other anxiety disorders (Mogotsi *et al.*,

2000), this scale was administered in the present interviews with OCD patients. However, test-retest and inter-rater reliability have not yet been established for this scale (Mendlowicz and Stein, 2000).

The self-report Temperament and Character Inventory (TCI) (Cloninger *et al.*, 1994) was also used to measure behaviours associated with seven personality dimensions, namely novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence.

In conclusion, these assessment scales and semi-structured questions allowed the researcher to diagnose each individual according to DSM-criteria (APA, 1994), and to assess OCD symptomatology, overall OCD symptom severity, the extent of disability or impairment due to OCD, temperament and character traits, as well as participants' history of interpersonal trauma.



2.2.3 Genotyping

DNA was extracted from venous blood (10-30 ml) in a Caucasian subset of OCD patients and controls, including patients and controls from the genetically homogeneous Afrikaner population, and was genotyped for polymorphisms in genes involved in monoamine function, which had previously been hypothesized to be relevant to OCD (Hemmings *et al.*, 2003). The polymorphisms investigated were: a 48 base pair (bp) variable number of tandem repeats (VNTR) in the third exon of dopamine receptor type 4 (*DRD4*) (Lichter *et al.*, 1993), a 40bp VNTR in the 3' untranslated region of dopamine transporter (*DAT*) (Vandenbergh *et al.*, 1992), a 44bp insertion/deletion polymorphism in the promoter region of the serotonin transporter (*5-HTTLPR*) (Heils *et al.*, 1996) and single nucleotide polymorphisms in the serotonin receptor type 1B serotonin receptor type 1B ($5HT_{1B}$, previously referred to as $5HT_{1DB}$) (*G861C*) (*G861C*)

(Sidenberg *et al.*, 1993), the serotonin receptor type 2A (*5-HT$_{2A}$*) (*T102C*) (Warren *et al.*, 1993), tyrosine hydroxylase (*TH*) (Val81Met) (Ishiguro *et al.*, 1998), catechol-O-methyl transferase (*COMT*) (Val58Met) (Karayiorgou *et al.*, 1997) and monoamine oxidase A (*MAO-A*) (*C1460T/EcoR*V) (Hotamisligil and Breakefield, 1991). Previously described genotyping protocols (Hemmings *et al.*, 2003) were followed.

2.3 Data analyses

The data analyses were performed using different statistical procedures, each of which will be discussed in the appropriate sections in the chapters that follow.

CHAPTER 3

PROFILE OF THE OBSESSIVE-COMPULSIVE DISORDER SAMPLE: BASED ON ASSESSMENT WITH THE YALE-BROWN OBSESSIVE-COMPULSIVE SYMPTOM CHECKLIST

Abstract

The Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL) is considered to be an important instrument in the comprehensive assessment of patients' obsessive-compulsive symptom profile and has extensively been used in the data collection phase of most obsessive-compulsive disorder (OCD) research. In this chapter, it was aimed to lay the groundwork for the subsequent investigations with:

(1) firstly, a review of available descriptive data on the YBOCS-CL, with

(2) secondly, a discussion of the rationale for using the YBOCS-CL in these investigations, and then,

(3) finally, provision of a profile of the present OCD sample based on their YBOCS-CL responses.

This profile includes for example, the frequencies in which the major obsessive-compulsive symptom categories were reported, the mean number of symptoms reported by the patients and the frequency with which each individual item of the YBOCS-CL (i.e. symptom) was reported, as well as the association of each of these items / symptoms with specific demographic (gender, age, population) and clinical variables (total OCD severity and disability). The findings suggest that the present sample is not dissimilar to OCD samples used in other investigations. Thus, analyses and findings using this patient population and checklist would arguably render information comparable and applicable to other OCD patients.

3.1 Introduction

The Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL) is an important instrument in the comprehensive assessment of patients' obsessive-compulsive symptom profile and has extensively been used in the data collection phase of most obsessive-compulsive disorder (OCD) research. In this chapter, it was aimed to lay the groundwork for the subsequent investigations (e.g. Chapter 4) with:

(1) firstly, a review of available descriptive data on the YBOCS-CL, with

(2) secondly, a discussion of the rationale for using the YBOCS-CL in these investigations, and then,

(3) finally, provision of a profile of the present OCD sample based on their YBOCS-CL responses.

3.1.1 The YBOCS-CL compared to other obsessive-compulsive symptom checklists

The YBOCS-CL was initially developed as an ancillary instrument to assist in the scoring of the Yale-Brown Obsessive-Compulsive Symptoms Severity Scale (YBOCS-SS) (Goodman *et al.*, 1989b, 1989c). There has been renewed and increased interest in the use of the YBOCS-CL in OCD studies as it has been shown to have a number of advantages over other measures of OCD symptoms. For instance, it gained popularity with the increasing dissatisfaction with self-administrative measures of OCD such as the Maudsley Obsessive-Compulsive Inventory (MOCI) and the Padua Inventory (PI) (Goodman and Price, 1992; Taylor, 1998), on the grounds that it covers more symptoms and that the other scales are strongly influenced by *non*-OCD symptoms such as depression (Frost *et al.*, 1996). Furthermore, the YBOCS-CL measures symptoms independently from overall illness severity compared to the other self-administered

measures of OCD symptoms where the symptom scores are confounded by overall illness severity, as the same subscale is used to measure both the presence of a given symptom and its severity.

Ironically, while the YBOCS-SS has been extensively studied in the past decade, and despite its frequent use in studies of OCD symptomatology, not much is known about the psychometric properties of the ancillary YBOCS-CL (Mataix-Cols *et al.*, 2004) except for its factor structure (Baer, 1994; Hantouche and Lancrenon, 1996; Leckman *et al.*, 1997; Mataix-Cols *et al.*, 2002, 1999; Summerfeldt *et al.*, 1999) and test-retest reliability (Mataix-Cols *et al.*, 2002). To rectify the situation, Mataix-Cols *et al.* (2004) have recently assessed its convergent and divergent (discriminant) reliability with a comparison of the YBOCS-CL with the MOCI and the PI. To establish convergent validity, it must be showed that measures that should be related *are* in reality related, i.e. one should be able to show a correspondence or *convergence* between similar constructs. For example, if the contamination / washing subscales of the YBOCS-CL, MOCI and PI correlate significantly, the convergent validity of these scales is adequate. On the other hand, to establish discriminant validity, it must be showed that measures that should *not* be related, are in reality *not* related, i.e. one should be able to *discriminate* between dissimilar constructs. For example, there must be weaker correlations between non-corresponding symptom subscales such as the contamination / washing subscale of the MOCI and the checking subscale of the YBOCS-CL. The findings of the above-mentioned study suggest that the convergent reliability of the YBOCS-CL was generally poor when correlated with self-administrative instruments (such as the MOCI and the PI). Mataix-Cols *et al.* (2004) suggested that this finding could partially be explained by the incomplete coverage of some OCD symptoms in these self-administered scales. The divergent reliability of the YBOCS-CL was adequate and it appeared to be a relatively pure measure of OCD symptomatology, independent from overall symptom severity and state variables. The use of this scale is likely to

continue and/or increase; thus further research of the psychometric properties of this scale is warranted.

3.1.2 Layout of the YBOCS-CL

3.1.2.i The individual items

As noted before, the version of the YBOCS-CL (Goodman *et al.*, 1989b, 1989c) used in this investigation comprises 74 items with each item representing a single obsessive or compulsive symptom. Responses are scored on a continuum, i.e. each of the YBOCS-CL items is scored 0 (not present), 1 (the symptom is present but not considered to be a primary concern), or 2 (the symptom is present and considered a principal problem).

3.1.2.ii The major symptom categories

In addition to the division made between obsessions and compulsions, users of the scale have divided the items of the YBOCS-CL into a number of broad "major" symptom categories based on similarities amongst the various items. The major symptom categories with an example item of each are presented in Table 1.

TABLE 1. The major symptom categories with example items

OBSESSIONS	EXAMPLE ITEMS
Aggressive or harm-related obsessions	E.g. "fear that I might harm others"
Contamination obsessions	E.g. "concerns with dirt or germs"
Sexual obsessions	E.g. "content involves homosexuality"
Hoarding / saving obsessions	I.e. an obsession with hoarding of objects, for reasons other than for their monetary or sentimental value
Religious obsessions	E.g. "concern with sacrilege or blasphemy"

Symmetry obsessions	E.g. “obsession with the need for symmetry or exactness”
Somatic or body-focused obsessions	E.g. “concern with illness or disease”
COMPULSIONS	**EXAMPLE ITEMS**
Cleaning or washing compulsions	E.g. “excessive or ritualized handwashing”
Checking	E.g. “checking locks, stove, appliances, etc”
Repeating rituals	E.g. “re-reading or re-writing”
Counting	I.e. the compulsion to count most things with which the person comes into contact, e.g. to count lampposts when driving
Ordering and arranging	I.e. constantly tidying up or arranging things to be “perfect”, “symmetrical” or “in the right order”
Hoarding compulsions	I.e. keeping or saving useless things, e.g. piling up old newspapers or keeping junkmail
Mental compulsions	E.g. “special words, images, or numbers repeated mentally to neutralise anxiety (e.g. lucky numbers)”

3.1.3 Use of the YBOCS-CL in the present OCD sample

3.1.3.i Binary vs ordinal data

Somewhat different from previous investigations where the YBOCS-CL was used, the responses of the participants in this project to these items were categorical and binary (present / absent).

More specifically, in these assessments,

a.) a score of 2 was given if the symptom was present only in the past,

b.) a score of 1 if the symptom was currently present, and

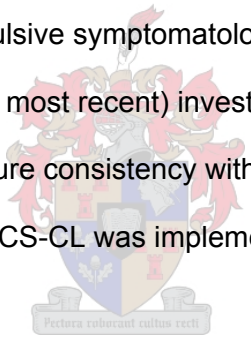
c.) a score of 0 was given if the symptom was absent.

In other words, in most of the data collection interviews, distinctions between “principal/primary” and “present, but not primary” symptoms (as was the case in previous factor analysis studies), were not made. Importantly, in the cluster analyses of data described in Chapters 4, 5 and 6, statistical techniques appropriate for this type of data were selected, but also comparable to

those used in other investigations. (Currently, data collected using the *usual* pattern of administration, i.e. similar to that used in previous investigations, are also increasing.)

3.1.3.ii "Miscellaneous" and "Other" items

In addition to the easily "classifiable" and clinically well-recognized OCD symptoms targeted under the major symptom categories, the YBOCS-CL also contains a number of items assessing 'miscellaneous' and 'other' OCD symptoms: The 'miscellaneous' category includes symptoms that patients sometimes present with but which do not 'comfortably' fit into any of the specific symptom categories. Summerfeldt *et al.* (2003) recently suggested that there are reliable associations among the established symptom dimensions and a number of these miscellaneous symptoms of OCD, providing justification for incorporating these items into a data reduction analysis of obsessive-compulsive symptomatology. However, following the example of most of the earlier (and some of the most recent) investigations with the YBOCS-CL, it was decided to exclude these items to ensure consistency with most of these previously reported factor analysis studies where the YBOCS-CL was implemented (Baer, 1994; Leckman *et al.*, 1997; Summerfeldt *et al.*, 1999).



The 'other' items allow the interviewer to include symptoms specific to the participant being rated (i.e. instead of just indicating the presence / absence of an already described symptom, the interviewer has to enter the patient's description of his/her symptom *verbatim*). As the content of these customized items were expected to be unique for each person, and the item content therefore not standardized, it was argued that inclusion of these items in the analyses would not be psychometrically sound, and were also excluded from the analyses.

In summary, after the above-mentioned exclusions, 45 items remained and were used for the subsequent analyses (Table 2). In other words, this investigation (of, for example, the

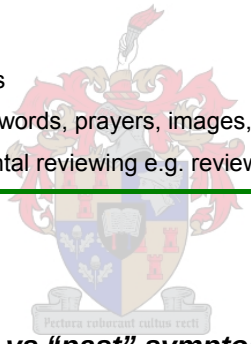
frequencies of the major symptom categories and the mean number and median of items / symptoms endorsed by the respondents, as well as the frequency with which each item was reported,) has focused on these 45 items.

Table 2 provides a list of the 45 items that were included in the current and subsequent analyses, after exclusion of the 'miscellaneous' and 'other' items:

TABLE 2. The 45 YBOCS-CL - items included in the current and subsequent analyses

Item nr	Item description
1	Fear that I might harm myself
2	Fear that I might harm others
3	Violent or horrific images
4	Fear of blurting out obscenities or insults
5	Fear of doing something else embarrassing
6	Fear that I will act on unwanted impulses (e.g. to stab friend)
7	Fear that I will steal things
8	Fear that I will harm others because of not being careful enough (e.g. hit/run MVA)
9	Fear that I will be responsible for something else terrible happening (e.g. fire, burglary)
10	Concerns or disgust with bodily waste or secretion (e.g. urine, faeces and saliva)
11	Concern with dirt or germs
12	Excessive concern with environmental contaminants (e.g. asbestos, radiation, toxic waste)
13	Excessive concern with household items (e.g. cleaners, solvents)
14	Excessive concern with animals (e.g. insects)
15	Bothered by sticky substances or residues
16	Concerned that I will get ill because of contaminant
17	Concerned that I will get others ill by spreading contamination (aggressive)
18	No concern with consequences of contamination other than how it might feel
19	Forbidden or perverse sexual thoughts / images / impulses
20	Content (of obsession) involves children or incest
21	Content (of obsession) involves homosexuality
22	(Obsession with) sexual behaviour toward others (aggressive)
23	Hoarding / Saving obsessions
24	Concerned with sacrilege and blasphemy
25	Excessive concern with right / wrong, morality

26	Obsession with need for symmetry or exactness - Accompanied by magical thinking (e.g. concerned that mother will have accident unless things are in the right place)
27	Obsession with need for symmetry or exactness - Not accompanied by magical thinking
28	Concern with illness or disease
29	Excessive concern with a body part or an aspect of appearance (e.g. dysmorphophobia)
30	Excessive or ritualised handwashing
31	Excessive or ritualised showering, bathing, teeth brushing, grooming or toilet routine
32	Compulsions involving cleaning of household items or other inanimate objects
33	Other measures (than those in item 32) to prevent or remove contact with contaminants
34	Checking locks, stove, appliances, etc.
35	Checking that I did not / will not harm others
36	Checking that I did not / will not harm self
37	Checking that nothing terrible did / will happen
38	Checking that I did not make a mistake
39	Checking tied to somatic obsessions
40	Re-reading or re-writing
41	Need to repeat routine activities (e.g. in / out door, up / down from chair, i.e. repeating rituals)
42	Counting compulsions
43	Ordering / Arranging compulsions
44	Hoarding / Collecting compulsions
45	Mental compulsions (e.g. special words, prayers, images, numbers repeated mentally or repeated in set manner to neutralise anxiety; mental reviewing e.g. reviewing of conversations)



3.1.3.iii "Current" vs "past" symptomatology

In addition, following the example of Baer (1994) and Summerfeldt *et al.* (1999), only ratings of *current* symptoms (i.e. present = 1, or absent = 0) were included in the analyses, since inaccuracies or bias in participants' recall of *non-current* (past) symptoms may have influenced results. In other words, for the sake of the current analyses, symptoms reported as "past only", were marked as "currently absent".

3.1.3.iv "Subclinical" vs "clinical" obsessive-compulsive symptomatology

Assessment of total OCD severity with the YBOCS-SS renders scores from 0 to a maximum of 40. Patients with scores less than 8 may be considered to have *subclinical* OCD (Goodman *et al.*, 1989c), i.e. the total severity of the obsessive-compulsive symptoms is not considered to be severe enough to warrant a diagnosis of *clinical* OCD. In order to establish a sample of patients all with *clinically significant* OCD, it was decided to exclude those few patients who had YBOCS-SS scores less than 8 from the study sample (i.e. those with OCD of *subclinical* severity). These patients may perhaps have been treatment responders, i.e. with a significant reduction in their OC severity scores after treatment.

In conclusion, in this chapter it was aimed to lay the groundwork for subsequent investigations where responses to the YBOCS-CL were analyzed. This *scene-setting* chapter includes an investigation and discussion of a number of issues including, for example, the frequencies of the major symptom categories (as they are currently categorized in the YBOCS-CL) and the mean number and median of items / symptoms presented by these patients, as well as the frequency with which each item was endorsed. In order to further expand the comprehensiveness of this sample profile, data on the associations between some of the items / symptoms with sociodemographics (gender, age, population group) and clinical variables (total impairment and total OCD severity) are also presented.

3.2 Results

3.2.1 Sociodemographic findings

The YBOCS-CL was originally administered to 282 OCD patients, with ages ranging from 16 to 71. From this group, only 261, i.e. those with an OCD severity score higher than 7 (i.e. mild to severe OCD), were included (N=261: mean age: 34.1 ± 12.9). 56% of the total sample obtained a higher education diploma or university / college degree after successful completeion of high school.

Population group stratification was important for subsequent genetic investigations: A subset of the total sample was Caucasian (N=230), including subjects from the genetically homogeneous Afrikaner population (N=110). Their DNA was extracted from venous blood and was genotyped for polymorphisms in genes involved in monoamine function.

The non-Caucasian subset of the sample (N=31) included subjects from the so-called 'colored' (N=8), Malay (3), Black (N=1), Indian / Asiatic (11) and so-called "other ethnic group" (including Portuguese, Italian etc) (N=8) communities of South Africa. Notably, given the focus of this study on recruiting subjects from the Caucasian (and Afrikaner) population groups, the sample studied here is not representative of the stratification of the entire South African population.

3.2.2 Clinical findings

3.2.2.i Gender and age of onset

Of the 261 patients, 130 were female (mean age: 36.7 ± 14.5) and 131 male (mean age: 31.6 ± 10.5). Onset age of OCD ranged from 2 to 51 years (mean: 17.8 ± 10.3).

3.2.2.ii The YBOCS-SS findings

Scores on the YBOCS-SS ranged from 8 to 39 (i.e. from mild to very severe), with a mean score of 21.1 ± 6.4.

3.2.2.iii The Disability Profile (DP) findings

Total disability scores on the DP ranged from 1 to 30 (the maximum score possible is 32), i.e. patients reported varying degrees of disability, from very little to major disability or impairment due to OCD, with a mean total score of 12.1 ± 5.8.

3.2.2.iv The YBOCS-CL findings

The patients reported a mean of 12 (current) OCD symptoms (as listed in the YBOCS-CL), with the number of symptoms endorsed by individuals ranging between 0 and 42. Table 3 presents the items from the one that was reported most frequently, i.e. “Mental compulsions”, through to the one least often reported, i.e. “Fear will steal things”, together with the number of patients (and percentage of the total sample) that reported the particular symptom.

TABLE 3. Frequencies in which YBOCS-CL - items were reported (N=261) – in descending order

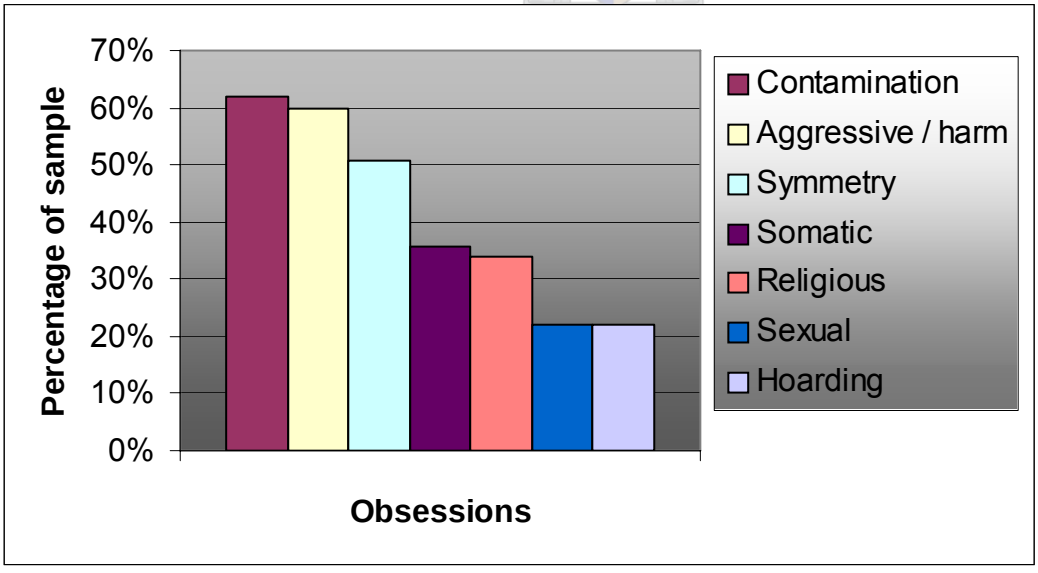
Item nr	Item description	Number of times an item was reported (frequency)	Percentage (%) of patients reporting this symptom
45	Mental compulsions (e.g. special words, images, numbers repeated mentally to neutralize anxiety)	169	64.8%
38	Checking that did not make mistake	140	53.6%
40	Re-reading or re-writing	126	48.3%
11	Concern with dirt or germs	123	47.1%

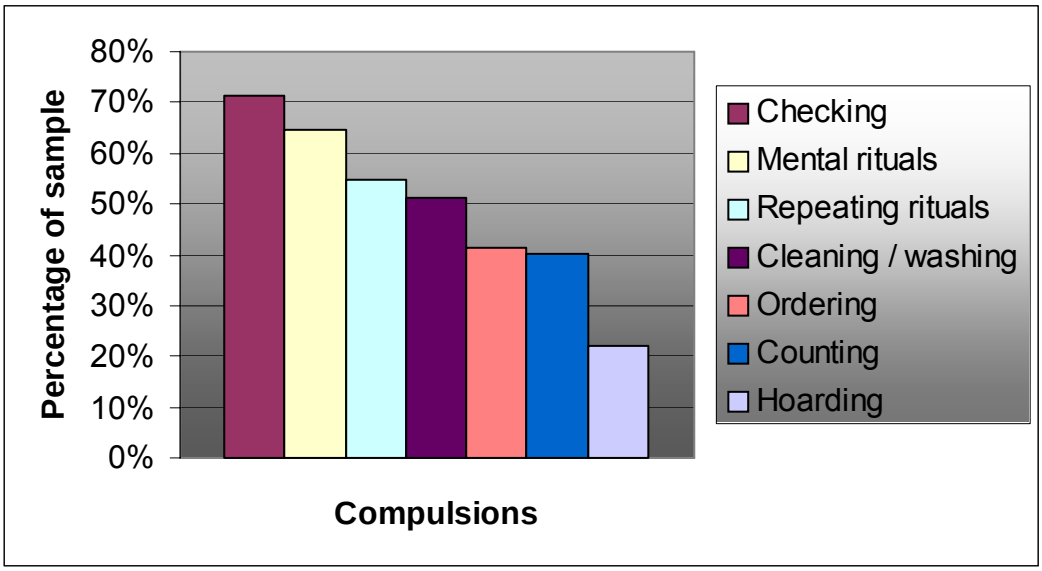
43	Ordering / Arranging compulsions	108	41.4%
34	Checking locks, stoves, appliances, etc.	105	40.2%
42	Counting compulsions	105	40.2%
30	Excessive or ritualised handwashing	100	38.3%
27	Obsession with need for symmetry or exactness - Not accompanied by magical thinking	95	36.4%
10	Concerns or disgust with bodily waste or secretion (e.g. urine, faeces and saliva)	90	34.5%
31	Excessive or ritualised showering, bathing, toothbrushing, grooming or toilet routine	83	31.8%
32	Involves cleaning of household items or other inanimate objects	83	31.8%
2	Fear I might harm others	81	31.0%
37	Checking that nothing terrible did / will happen	78	29.9%
33	Other measures (other than cleaning / washing) to prevent or remove contact with contaminants	76	29.1%
9	Fear will be responsible for something terrible happening	75	38.7%
41	Need to repeat routine activities (e.g. in / out door, up / down from chair)	75	28.7%
25	Excess concern with right / wrong, morality	74	28.4%
35	Checking that did not / will not harm others	70	26.8%
28	Concern with illness or disease	69	26.4%
5	Fear of doing something else (other than blurting out obscenities or insults) embarrassing	66	25.3%
8	Fear will harm others because not careful enough (e.g. hit / run MVA)	66	25.3%
16	Concerned will get ill because of contaminant	66	25.3%
15	Bothered by sticky substances or residues	65	24.9%
3	Violent or horrific images	58	22.2%
23	Hoarding / Saving obsessions	58	22.2%
44	Hoarding / collecting compulsions	58	22.2%
13	Excessive concern with household items (e.g. cleaners, solvents)	56	21.5%
24	Concerned with sacrilege and blasphemy	55	21.1%
12	Excessive concern with environmental contaminants (e.g. asbestos, radiation, toxic waste)	52	19.9%
19	Forbidden or perverse sexual thoughts / images / impulses	52	19.9%
26	Obsession with need for symmetry or exactness – Accompanied by magical thinking	50	19.2%
36	Checking that did not / will not harm self	48	18.4%
1	Fear that I might harm myself	46	17.6%
4	Fear of blurting out obscenities or insults	46	17.6%
14	Excessive concern with animals (e.g. insects)	46	17.6%
6	Fear will act on unwanted impulses (e.g. to stab friend)	45	17.2%

39	Checking tied to somatic obsessions	45	17.2%
29	Excessive concern with body part or aspect of appearance (e.g. dysmorphophobia)	43	16.5%
17	Concerned will get others ill by spreading contamination (aggressive)	35	13.4%
21	Content involves homosexuality	27	10.3%
18	No concern with consequences of contamination other than how it might feel	24	9.2%
20	Sexual obsessions: Content involves children or incest	23	8.8%
22	Sexual behaviour toward others (aggressive)	14	5.4%
7	Fear will steal things	9	3.4%

The distribution of 14 selected major symptom categories in the present sample was tabulated (Table 4), with the most common symptoms being contamination, aggressive and symmetry obsessions, and checking, mental rituals and repeating.

TABLE 4. Frequencies of the major symptom categories of the YBOCS-CL in 261 OCD patients





Symptom category	Number / percentage of patients reporting items within this symptom category	
	N	%
OBSESSIONS		
Contamination	162	62.1%
Aggressive / harm	156	59.8%
Symmetry	132	50.6%
Somatic	93	35.6%
Religious	89	34.1%
Sexual	58	22.2%
Hoarding	58	22.2%
COMPULSIONS		
Checking	186	71.3%
Mental rituals	169	64.8%
Repeating rituals	143	54.8%
Cleaning / washing	134	51.3%
Ordering	108	41.4%
Counting	105	40.2%
Hoarding	58	22.2%

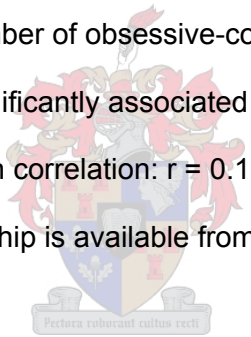
3.2.3 Associated features

3.2.3.a.i Number of obsessive-compulsive symptoms vs total OCD severity (YBOCS-SS) score:

The number of obsessive-compulsive symptoms reported was significantly associated with the total OCD severity (Pearson correlation: $r = 0.27$; $p < 0.001$). (A figure illustrating this relationship is available from the candidate upon request.)

3.2.3.a.ii Number of obsessive-compulsive symptoms vs total lifetime disability (Disability scale) due to OCD:

The number of obsessive-compulsive symptoms reported was also significantly associated with the total lifetime disability (Pearson correlation: $r = 0.19$; $p=0.009$). (A figure illustrating this relationship is available from the candidate.)



3.2.3.a.iii Number of obsessive-compulsive symptoms vs age:

Patients' age at the time of interview and the number of symptoms that they reported were not significantly related; however there was a tendency for younger patients to present with an increased number of OCD symptoms (Pearson correlation $r = - 0.11$; $p = 0.07$).

3.2.3.a.iv **Number of obsessive-compulsive symptoms vs age of onset:**

Patients with a younger age of onset of OCD had a significantly increased number of obsessive-compulsive symptoms (Pearson correlation r = - 0.19; p = 0.003).

3.2.3.a.v **Number of obsessive-compulsive symptoms vs gender:**

The number of symptoms reported by males and females was similar; the mean number of obsessive-compulsive symptoms reported by males and females was 12 (SD: 8) and 11 (SD: 7) respectively.

3.2.3.a.vi **Number of obsessive-compulsive symptoms vs population group (i.e. Caucasian / non-Caucasian):**

The Caucasian and non-Caucasian population groups did not differ significantly in terms of the number of symptoms reported; both groups reported a mean number of 12 (with standard deviations of 8 and 7, respectively) symptoms.

3.2.3.b.i **Association between individual obsessive-compulsive symptoms and age:**

Six of the harm-related obsessions (item number 1, 2, 3, 4, 6, 9), harm-related checking (item number 36, 37), and forbidden or perverse sexual thoughts / images / impulses (item number 19, 21) were significantly associated with patients of a younger age compared to those who did not report these items. Patients with concerns with illness or disease (somatic obsessions) (item

number 28) or excessive or ritualized handwashing (item number 30) were also younger at the time of the interview. Patients with hoarding symptoms (item number 23 and 44) as well as those who reported counting compulsions (item number 42) were significantly older than those without hoarding. (Student's t-test) (A table illustrating these associations is available from the candidate upon request.)

The significant relationship found between age and the various major symptom categories confirmed the present findings of significant associations found between age at the time of the interview and the individual symptoms. (Student's t-test) (A table illustrating these associations is available from the candidate upon request.)

3.2.3.b.ii Association between individual obsessive-compulsive symptoms and onset age of OCD:

Patients with aggressive or harm-related obsessions (items number 1, 2, 3, 5, 6, and 9) had a significantly younger age of onset of OCD compared to those who did not report these items. In addition, patients reporting forbidden or perverse sexual thoughts / images / impulses (item number 19), an obsession with symmetry or exactness (accompanied by magical thinking, item number 26), an excessive concern with some part of his/her appearance (e.g. dysmorphophobia, item number 29), compulsive checking (item number 35, 38), as well as *repeating* rituals (re-

reading or re-writing) (item number 40) were also significantly associated with younger age of onset of OCD compared to those without these symptoms (Table 5). (Student's t-test)

TABLE 5. Statistically significant associations between individual obsessive-compulsive symptoms and onset age

Item nr	Item description	Onset age (SD)		t	P
		With item / symptom	Without item / symptom		
1	Fear that I might harm myself	15.5 (7.1)	18.3 (10.8)	2.1	0.04
2	Fear that I might harm others	14.6 (8.0)	19.2 (10.9)	3.6	<0.001
3	Violent or horrific images	14.9 (8.1)	18.7 (10.7)	2.8	0.006
5	Fear of doing something embarrassing	14.9 (7.8)	18.7 (10.8)	2.9	0.004
6	Fear that I will act on unwanted impulses	14.7 (8.1)	18.5 (10.6)	2.1	0.04
9	Fear that I will be responsible for something terrible happening	14.4 (8.1)	19.3 (10.8)	3.9	<0.001
19	Forbidden or perverse sexual thoughts / images / impulses	15.3 (7.3)	18.5 (10.8)	2.4	0.02
26	Obsession with need for symmetry or exactness (with magical thinking)	14.5 (9.0)	18.6 (10.5)	2.4	0.02
29	Excessive concern with body part or an aspect of appearance	13.5 (7.2)	18.6 (10.6)	3.6	0.001
35	Checking that did not / will not harm others	15.7 (8.9)	18.6 (10.7)	2.0	<0.05
38	Checking that did not make mistake	16.3 (9.4)	19.6 (11.0)	2.5	0.01
40	Re-reading or re-writing	15.2 (8.0)	20.4 (11.7)	4.0	<0.001

The significant associations found between individual symptoms and onset age of OCD were confirmed by the associations found between the various major symptom categories and age of onset of OCD. (Student's t-test)

(A table illustrating these associations is available from the candidate upon request.)

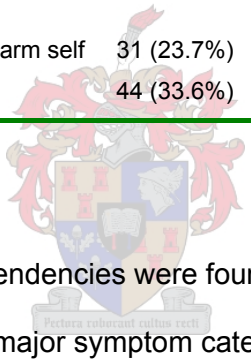
3.2.3.b.iii Association between individual obsessive-compulsive symptoms and gender:

Significantly more females than males reported an excessive concern with animals or insects (a contamination obsession; item number 14), an obsession with the need for symmetry or exactness (not accompanied by magical thinking) (item number 27), excessive cleaning of household items or other inanimate objects (item number 32), and counting compulsions (item number 42). More males reported sexual obsessions e.g. “forbidden or perverse sexual thoughts / images / impulses” (item number 19) and sexual obsessions concerning children or incest (item number 20), concern with illness or disease (item number 28), as well as harm-related checking (i.e. checking that he/she did not harm self) (item number 36) (Table 6). (Chi - squared test)

(Table 6 follows on the next page.)

TABLE 6. Statistically significant associations between individual obsessive-compulsive symptoms and gender

Item nr	Item description	Gender (with symptom / item)		χ^2	p
		Male (n=131)	Female (n=130)		
14	Excessive concern with animals or insects (contamination obsession)	16 (12.2%)	30 (23.1%)	5.4	0.02
19	Forbidden or perverse sexual thoughts / images / impulses	37 (28.2%)	15 (11.5%)	11.7	0.001
20	Content involves children or incest (sexual obsession)	17 (13.0%)	6 (4.6%)	5.9	0.02
27	Obsession with need for symmetry or exactness (Not accompanied by magical thinking)	40 (30.5%)	55 (42.3%)	3.9	<0.05
28	Concern with illness or disease	42 (32.1%)	27 (20.8%)	4.3	0.04
32	Involves cleaning of household items or other inanimate objects	33 (25.2%)	50 (38.5%)	5.3	0.02
36	Checking that did not / will not harm self	31 (23.7%)	17 (13.1%)	4.9	0.03
42	Counting compulsions	44 (33.6%)	61 (46.9%)	4.8	0.03



Similar tendencies were found in the associations between gender and the major symptom categories. (Chi - squared test)
(A table illustrating these associations is available from the candidate upon request.)

3.2.3.b.iv Association between individual obsessive-compulsive symptoms and population group (i.e. Caucasian vs non-Caucasian):

Caucasian patients more often reported hoarding obsessions and compulsions (item number 23 and 44), whereas non-Caucasians more often reported excessive or ritualised handwashing,

showering and cleaning of household items or other inanimate objects (item number 30, 31 and 32) (Table 7). (Chi - squared test)

There is a tendency (perhaps particularly in South Africa) to want to exclude population group / race unless there are clear reasons where it might come in. It was decided to include this information here, given the focus on genetics in subsequent investigations (see following chapters). For genetics, inclusion of population / race can be important because some variants are found more often in some groups.

TABLE 7. Statistically significant associations between individual obsessive-compulsive symptoms and population group

Item nr	Item description	Population group (with symptom / item)		χ^2	p
		Caucasian (n=230)	Non-Caucasian (n=31)		
23	Hoarding / saving obsessions	56 (24.3%)	2 (6.5%)	6.3	0.01
30	Excessive or ritualized handwashing	83 (36.1%)	17 (54.8%)	3.9	<0.05
31	Excessive or ritualized showering, etc.	68 (29.6%)	15 (48.4%)	4.2	0.04
32	Involves cleaning of household items or other inanimate objects	68 (29.6%)	15 (48.4%)	4.2	0.04
44	Hoarding / collecting compulsions	56 (24.3%)	2 (6.5%)	6.3	0.01

Investigation of the associations between gender and the major symptom categories rendered similar findings. (Chi - squared test)

(A table illustrating these associations is available from the candidate upon request.)

3.2.3.b.v Effect of presence / absence of each obsessive-compulsive symptom on the total mean OCD severity (YBOCS-SS) scores:

As noted before, OCD severity scores (on the YBOCS-SS) ranged from 8 to 39 (i.e. from mild to very severe), with a mean score of 21.1 $\pm$ 6.4. Table 8 indicates the impact of the presence or absence of 45 YBOCS-CL items on the total OCD severity score. Focussing on, for example, the 9 most frequently occurring OC symptoms (highlighted in yellow), it is clear that if any of these are present, the mean severity score is more than the 95% upper bound. Presence of item nr 31 ('Excessive or ritualised showering, bathing, etc.') was associated with the highest severity score. Similar trends were noticed for the other cleaning / washing compulsions, emphasizing the strong impact that contamination symptoms may have on general OCD severity. On the other hand, it is not clear why presence of item nr 19 ('Forbidden or perverse sexual thought / images / impulses') was associated with a decrease in the total YBOCS-SS score.

(Table 8 follows on the next page.)

TABLE 8. Effect of presence / absence of each obsessive-compulsive symptom on the total mean OCD severity (YBOCS-SS) scores*

YBOCS-CL item label		Mean YBOCS-SS-score if absent	YBOCS-CL item number	Mean YBOCS-SS-score if present	
Fear that I might harm myself		20.97	Item nr 1	21.39	
Fear that I might harm others		20.98	Item nr 2	21.19	
Violent or horrific images		21.03	Item nr 3	21.09	
Fear of blurting out obscenities or insults		20.62	Item nr 4	23.04	More than 95% limit
Fear of doing something else embarrassing		21.05	Item nr 5	21.05	
Fear that I will act on unwanted impulses (e.g. to stab friend)		21.05	Item nr 6	21.02	
Fear that I will steal things		21.05	Item nr 7	20.89	
Fear that I will harm others because of not being careful enough (e.g. hit/run MVA)		20.78	Item nr 8	21.82	
Fear that I will be responsible for something else terrible happening (e.g. fire, burglary)		20.57	Item nr 9	22.23	More than 95% limit
Concerns or disgust with bodily waste or secretion (e.g. urine, faeces and saliva)		20.65	Item nr 10	21.80	
Concern with dirt or germs	Less than 5% limit	19.34	Item nr 11	22.96	More than 95% limit
Excessive concern with environmental contaminants (e.g. asbestos, radiation, toxic waste)		20.79	Item nr 12	22.08	More than 95% limit
Excessive concern with household items (e.g. cleaners, solvents)		20.64	Item nr 13	22.52	More than 95% limit
Excessive concern with animals (e.g. insects)		20.82	Item nr 14	22.09	More than 95% limit
Bothered by sticky substances or residues		20.40	Item nr 15	23.00	More than 95% limit
Concerned that I will get ill because of		20.96	Item nr 16	21.29	

contaminant					
Concerned that I will get others ill by spreading contamination (aggressive)		20.81	Item nr 17	22.57	More than 95% limit
No concern with consequences of contamination other than how it might feel		20.82	Item nr 18	23.20	More than 95% limit
Forbidden or perverse sexual thoughts / images / impulses	More than 95% limit	21.44	Item nr 19	19.44	Less than 5% limit
Content (of obsession) involves children or incest		21.08	Item nr 20	20.74	
Content (of obsession) involves homosexuality		21.22	Item nr 21	19.56	Less than 5% limit
(Obsession with) sexual behaviour toward others (aggressive)		21.04	Item nr 22	21.21	
Hoarding / Saving obsessions		20.90	Item nr 23	21.55	
Concerned with sacrilege and blasphemy		21.00	Item nr 24	21.20	
Excessive concern with right / wrong, morality		20.99	Item nr 25	21.18	
Obsession with need for symmetry or exactness - Accompanied by magical thinking (e.g. concerned that mother will have accident unless things are in the right place)		20.60	Item nr 26	22.94	More than 95% limit
Obsession with need for symmetry or exactness - Not accompanied by magical thinking	Less than 5% limit	20.08	Item nr 27	22.73	More than 95% limit
Concern with illness or disease		20.63	Item nr 28	22.22	More than 95% limit
Excessive concern with a body part or an aspect of appearance (e.g. dysmorphophobia)		20.66	Item nr 29	23.00	More than 95% limit
Excessive or ritualised handwashing	Less than 5% limit	19.83	Item nr 30	23.01	More than 95% limit
Excessive or ritualised showering, bathing,	Less than 5% limit	19.63	Item nr 31	24.08	More than 95% limit

teeth brushing, grooming or toilet routine					
Compulsions involving cleaning of household items or other inanimate objects	Less than 5% limit	19.87	Item nr 32	23.58	More than 95% limit
Other measures (than those in item 32) to prevent or remove contact with contaminants	Less than 5% limit	20.22	Item nr 33	23.05	More than 95% limit
Checking locks, stove, appliances, etc.		20.39	Item nr 34	22.02	More than 95% limit
Checking that I did not / will not harm others		20.92	Item nr 35	21.40	
Checking that I did not / will not harm self		21.15	Item nr 36	20.58	
Checking that nothing terrible did / will happen		20.53	Item nr 37	22.26	More than 95% limit
Checking that I did not make a mistake	Less than 5% limit	19.36	Item nr 38	22.50	More than 95% limit
Checking tied to somatic obsessions		21.00	Item nr 39	21.27	
Re-reading or re-writing	Less than 5% limit	20.01	Item nr 40	22.16	More than 95% limit
Need to repeat routine activities (e.g. in / out door, up / down from chair, i.e. repeating rituals)		20.44	Item nr 41	22.55	More than 95% limit
Counting compulsions	Less than 5% limit	20.06	Item nr 42	22.51	More than 95% limit
Ordering / Arranging compulsions	Less than 5% limit	19.96	Item nr 43	22.58	More than 95% limit
Hoarding / Collecting compulsions		20.71	Item nr 44	22.22	More than 95% limit
Mental compulsions (e.g. special words, prayers, images, numbers repeated mentally or repeated in set manner to neutralise anxiety; mental reviewing e.g. reviewing of conversations)	Less than 5% limit	19.73	Item nr 45	21.76	

* The 9 most frequently occurring OC symptoms are highlighted in yellow

3.2.3.c. The major symptom categories and total OCD severity (YBOCS-SS) and global disability (Disability Profile) scores

Given the heterogeneous nature of OCD symptomatology and the relatively large number of individual items / symptoms listed in the YBOCS-CL, it was decided to not only focus on total OCD severity and disability in the OCD group as a whole, but also to present data on the total OCD severity (YBOCS-SS) and disability (Disability Profile) scores in each of the major symptom categories (Table 9). Findings are consistent with the previous investigation of the effect of the presence / absence of each obsessive-compulsive symptom on the total OCD severity (YBOCS-SS) scores. Turning the attention to the symptom categories in particular, the findings suggest that, although not *statistically* different from the others, contamination compulsions, obsessions with symmetry/exactness and ordering/arranging compulsions were the three symptom categories associated with the highest total OCD severity scores, whereas the (three) highest disability scores were associated with religious obsessions, hoarding compulsions and aggressive/ harm-related obsessions.

TABLE 9. Total OCD severity (YBOCS-SS) and disability (Disability Profile) scores in each of the major symptom categories

OCD symptom category	Total severity score			Total disability score		
	N*	Mean	SD	N**	Mean	SD
Aggressive obsessions	156	21.2	6.3	115	13.1	6.3
Contamination obsessions	162	22.3	6.3	114	12.8	5.8
Sexual obsessions	58	19.6	5.4	48	12.7	6.5

Hoarding obsessions	58	21.6	6.1	38	12.8	5.3
Religious obsessions	89	21.2	6.0	57	13.9	6.3
Symmetry obsessions	132	22.7	6.3	94	11.9	5.4
Somatic obsessions	93	22.3	6.2	70	12.6	5.8
Contamination compulsions	134	22.9	6.2	97	12.6	5.6
Checking	186	21.9	6.2	134	12.6	5.6
Repeating rituals	143	22.1	5.8	103	12.1	5.0
Counting compulsions	105	22.5	6.4	69	12.3	5.8
Ordering compulsions	108	22.6	6.8	81	11.5	4.74
Hoarding compulsions	58	22.2	6.0	39	13.2	5.3
Mental compulsions	169	21.8	6.1	115	12.0	5.7

N*, N** = number of OCD patients who presented with one / more obsessive-compulsive symptoms included in the specified symptom category, for whom there were severity or disability data available, respectively

3.3 Discussion

In this chapter it was aimed to lay the groundwork for the subsequent investigations with a review of available descriptive literature on the YBOCS-CL, subsequent provision of a rationale for using this instrument in this project, together with a profile of the present OCD sample based on their YBOCS-CL responses. The findings suggest that the male:female ratio, age of onset of OCD, the mean number and content of obsessive-compulsive symptoms reported, as well as the mean and range of the total OCD severity score are similar to those of previous OCD investigations. Moreover, the significant associations found between the number of OC symptoms, as well as individual symptoms and symptoms categories, with specific sociodemographic (gender, age, population) and clinical variables (total OCD severity and disability) respectively, are also relatively similar to those found in the OCD literature (APA, 1994; Castle *et al.*, 1995; Cavallini *et al.*, 2002, 1999; Goodman *et al.*, 1989a; Rasmussen and Tsuang, 1984; Weissman *et al.*, 1994). (Regarding the findings of signiciant associations, it is important to take into consideration that with such a large sample size, the power may guarantee statistical significance to even relatively modest findings.)

This investigation is consistent with data (APA, 1994) indicating an age of onset of OCD ranging from childhood to adulthood, with mean age of onset in adolescence or early adulthood. In addition, similar to other samples, the gender ratio in this sample was more or less equal, suggesting that OCD may also be equally common in males and females in the South African population. Furthermore, similar to the data on the prevalence of the various OCD symptom subtypes, an examination of 65 studies that classified patients according to such subtypes, found that patients with primarily cleaning or checking compulsions predominated, accounting for 75% of the treatment population (Ball *et al.*, 1996).

The finding that the number of symptoms reported ranges from none (0) to forty-two (42) is interesting, deserving comment, given that only patients with *clinical* OCD were included in the sample. In other words, there arguably were patients with a diagnosis of OCD in the study sample who did not report any of the YBOCS-CL symptoms that were selected for use in the investigations. There are several possible explanations for this: For example, the patient may have presented only with the so-called *miscellaneous* and/or *other* symptoms that were excluded from the analyses. Moreover, the patient could also have presented with OC symptoms that are not currently included in the YBOCS-CL, but which also do not fit into any of the existing, even *miscellaneous* or *other*, symptom categories. Absence of YBOCS-CL items reported may also reflect on the patient's level of insight, i.e. in some patients, poor insight may hamper the ability to identify and accurately report symptoms. These ideas suggest that, although the YBOCS-CL is considered to be one of the most, if not *the* most, comprehensive symptoms checklists available today, there are grounds for improvement or expansion of the current range of symptoms that are assessed.

The statistically significant associations found between the individual symptoms and sociodemographic variables such as age at the time of the interview, onset age of OCD, gender

and population group, respectively, were confirmed as expected by the associations found between the various major symptom categories and these variables. In particular, a number of harm-related obsessions (as well as harm-related checking), sexual obsessions, somatic obsessions, and cleaning rituals were associated with younger age at the time of the interview, whereas hoarding and counting showed an association with increased age. Earlier age of onset of OCD was found to be associated with harm-related obsessions, obsessive concerns with symmetry or exactness, somatic obsessions, compulsive checking and other repeating rituals (e.g. re-reading). Similarly, it has been suggested that, in contrast to adults, children with OCD often present with *pure* compulsions, such as washing and repeating compulsions (Swedo *et al.*, 1989). It has also been suggested that patients with a very early onset of OCD (i.e. younger than six years old) are more likely to have compulsions rather than obsessions (Honjo *et al.*, 1989; Rettew *et al.*, 1992). These compulsions would typically include elaborate washing or checking rituals without cognitive obsessions (Swedo *et al.*, 1992). Nevertheless, despite some differences between child and adult OCD, there appears to be much continuity between the clinical presentation of OCD in childhood and that in adulthood (Flament *et al.*, 1988; Rapoport *et al.*, 1992; Rasmussen and Tsuang, 1986; Swedo *et al.*, 1989; Toro *et al.*, 1992; Wever and Rey, 1997).

Consistent with most of the existing OCD data (Lochner and Stein, 2003a), it was found that females more often had specific contamination obsessions with some cleaning rituals, symmetry concerns and counting whereas males on the other hand more often had sexual obsessions, somatic obsessions (e.g. with illness / disease) and harm-related checking. However, as was indicated earlier, the relationship between symptom clusters and variables such as age and gender has not always been consistent across studies.

In contrast to the present and other existing data linking OCD symptomatology and specific sociodemographic variables, there are a number of studies that have suggested that type of OCD symptom at baseline was not related to a number of variables, including age, age of onset, gender, illness course or comorbidity (Rasmussen and Eisen, 1988; Rasmussen and Tsuang, 1986). It may nevertheless be argued that these studies did not include enough subjects having potentially unique symptoms (Takeuchi *et al.*, 1997) and thus may have lacked the power to show a relationship between (rarer) symptoms and demographic or clinical variables. Further work is needed to investigate this matter.

Furthermore, the number of symptoms reported may also differ in OCD patients along several other variables, such as overall severity and/or disability. The findings here indeed suggest that an increase in the number of obsessive-compulsive symptoms is significantly related to increased overall severity and disability. This does make sense on one level, i.e. given the way the instrument is structured, an OCD patient who has very severe contamination symptoms will assumably report multiple contamination symptom items. On a different level, this finding encourages further investigation given the fact that the clinical experience of the candidate and her colleagues suggests that the presentation of even a very few OC symptoms may be associated with severe OCD or extreme disability – however, whereas this is possible, it is statistically less likely. Admittedly, these may have been a few isolated cases. Nevertheless, based on these findings, it may be concluded that generally, patients with more symptoms experience worse OCD or disability, and vice versa. In addition, the present findings suggest that some obsessive-compulsive symptoms and categories may be associated with higher global severity or more disability than others; the differences were not significant however. Nonetheless, comparably, Frost *et al.* (2000) found that, compared to non-hoarding OCD and other anxiety disorder patients, OCD patients with hoarding scored higher on anxiety, depression, as well as social disability. Additional research is required to determine the extent

(significance) to which the severity / disability scores differs amongst the different symptom categories. In addition, levels of severity or disability may possibly in turn be related to outcome with medication or behaviour therapy; these data were not controlled for treatment stage however, necessitating more work in this area. Arguably, some categories may show a better response (i.e. decreased global severity and disability) to specific drugs or psychotherapies. For example, a principal components analysis by Mataix-Cols *et al.* (1999) has suggested that higher scores on the hoarding dimension predicted poorer outcome following treatment with serotonin reuptake inhibitors, after controlling for baseline severity. Therefore, it may be concluded that this type of data (symptom dimensions) may be useful in, for example, treatment studies where patients usually are categorized as OCD / non-OCD (or control) only, and not according to their primary obsessive-compulsive symptomatology.

3.4 Conclusion

In conclusion, the YBOCS-CL remains an important instrument in the comprehensive assessment of patients' obsessive-compulsive symptom profile. Also in this patient sample, the YBOCS-CL findings arguably provided a good indication of their OC related characteristics, e.g. the frequencies in which the major OC symptom categories were reported, the mean number of symptoms reported by the patients and the frequency with which each individual item of the YBOCS-CL (i.e. symptom) was reported, as well as the association of each of these items / symptoms with specific demographic (gender, age, population) and clinical variables (total OCD severity and disability). It may be suggested that the clinical profile of this present sample of OCD patients is not dissimilar to that of OCD patients in other investigations elsewhere. Subsequent analyses and findings using this patient population and checklist will arguably render information comparable to most other OCD patients.

This work forms the background to Chapters 4 and 5, which aimed to identify OCD subtypes based on their obsessive-compulsive symptomatology assessed with the YBOCS-CL.

CHAPTER 4

THE IDENTIFICATION OF OBSESSIVE-COMPULSIVE DISORDER SUBTYPES WITH LATENT CLASS ANALYSIS OF OBSESSIVE-COMPULSIVE SYMPTOMATOLOGY

Abstract

There is increasing evidence that obsessive-compulsive disorder (OCD) is a heterogeneous disorder, with clinical subtypes that are characterized by differing pathophysiological mechanisms and treatment response. This study aimed to identify clusters of OCD cases based on their obsessive-compulsive (OC) symptomatology assessed with the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL). By means of specialized computer software, latent class analysis (LCA) was applied to the data matrix, which in its entirety consisted of the categorical responses of 261 OCD patients to 45 selected items of the YBOCS-CL. The procedure for LCA was to fit a one-class solution first, followed by two-, three-, and four-class solutions and so forth, until the best solution was obtained for the items of the YBOCS-CL included in the analysis to develop an empirically based typology. The "best fit" comprised six (6) clusters or patient subtypes when the nine (9) most frequently occurring obsessive-compulsive symptoms were included in the analysis. To gain insight into the cluster structure, the ways in which clusters of cases differed with respect to specific demographic variables (age, gender) and clinical variables (OC symptoms, total OCD severity, treatment response, childhood trauma history) were investigated. Clusters I to VI were labelled 'Mental compulsions', 'Maximal disorder', 'Minimal disorder', 'No checking compulsions, 'Checking compulsions', and 'Pure contamination compulsions / washing', respectively. The clusters did not differ significantly in terms of the clinical features investigated. Nevertheless, some of the

clusters identified with LCA broadly resembled some of the current sub-classifications of OCD suggested in the literature.

4.1 Introduction

Chapter 1 of this dissertation provides a review of the extensive obsessive-compulsive disorder (OCD) literature which suggests that OCD is a heterogeneous condition, with clinical subtypes that are characterized by differing pathophysiological mechanisms and treatment outcomes (Lochner and Stein, 2003a). This heterogeneity has possibly confounded the findings of clinical, natural history and treatment response studies and has complicated the search for vulnerability genes, as suggested by the many inconsistent findings in studies of OCD. For example, responsivity to treatment and prognosis may vary according to obsessive-compulsive (OC) symptoms (Erzegovesi *et al.*, 2001; Mataix-Cols *et al.*, 1999), suggesting that there is a spectrum of different OC symptoms which may have different biological underpinnings. Furthermore, there is a lack of clear results from OCD studies using molecular genetics which could arguably be ascribed to the use of the conventional set of diagnostic criteria that still classifies OCD as a *unitary nosographic entity* (Cavallini *et al.*, 2002) instead of focusing on the different "entities" or phenotypes of OCD.

It has been suggested that success in accurate and detailed measurement of OCD phenotypes and an adequate characterization of OCD patients' heterogeneity are likely to facilitate refinements in genetic, neurobiological, environmental and treatment studies (Calamari *et al.*, 1999, 2004; Miguel *et al.*, 2005) and may lead to greater clarity concerning course, treatment strategies and outcome. There have been numerous attempts to identify OCD subtypes, with the most common strategy being a focus on OCD symptoms as classifying variables. Factor

and cluster analyses are the statistical approaches used most often to subtype OCD symptomatology or OCD cases. In summary, most efforts to classify OCD symptoms assessed with symptoms checklists such as the Yale Brown Obsessive-Compulsive Disorder Symptoms Checklist (YBOCS-CL) have consistently found that these fall into 3 to 6 symptom dimensions or factors, including aggressive / checking, contamination, symmetry / ordering and hoarding symptoms (Baer, 1994; Calamari *et al.*, 1999; Cavallini *et al.*, 2002; Denys *et al.*, 2004; Feinstein *et al.*, 2003; Leckman, 1993; Mataix-Cols *et al.*, 1999; Summerfeldt *et al.*, 1999). Furthermore, it has been suggested that each of the different factors may be associated with different demographic, clinical and genetic features (Lochner and Stein, 2003a); findings in this regard have, however not always been consistent across studies, indicating the need for further research.

In addition to the standard *data reduction* procedures, there is another statistical classification method currently gaining ground given its many advantages over above these methods with their apparent limitations, i.e. latent class analysis (LCA). LCA is used to empirically determine typologies of *categorical* data (i.e. data indicating, for example, the absence or presence of a particular symptom) on specific disorders as it occurs in clinical and epidemiological samples. It has been suggested that similarity amongst such OCD case characteristics can be of assistance in understanding more of the heterogeneous phenomenon of OCD. However, although this method has been increasingly used in studies to capture the natural clustering of specific pathology, it has of yet been used in very few studies with OCD samples (e.g. Nestadt *et al.*, 2003).

This investigation of the naturally occurring empirical typology of OCD was an empirical attempt at providing answers to the question of whether there is a single broad “OCD” phenotype with specific features and a common etiology, or whether there are a number of distinct types with

different features and etiologies within this broad framework. In other words, it was firstly aimed to determine the number of clusters / classes that renders the best fit for the data analysed and secondly, to characterize these OCD clusters of cases.

4.2 Methods

4.2.1 Subjects and interview

Two hundred and eighty two patients with OCD (N=282), with ages ranging from 16 to 71, took part in the study. From this group, only those with an OCD severity score on the Yale-Brown Obsessive-Compulsive Symptoms Severity Scale (YBOCS-SS) higher than 7 (i.e. mild to severe OCD) were included (N=261: mean age: 34.1 ± 12.9). Of the 261 patients, 130 were female (mean age: 36.7 ± 14.5) and 131 male (mean age: 31.6 ± 10.5).

These patients were referred to this Research Unit from a wide range of sources (the OCD Association of South Africa, specialist psychiatrists, and community based primary care practitioners). They were interviewed by a clinical psychologist with expertise in the field (the candidate), and met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994) criteria for OCD on the Structured Clinical Interview for Axis I Disorders (SCID-I) (First *et al.*, 1998). Referring clinicians were contacted to establish, where possible, a longitudinal expert opinion on the diagnostic status of the patient.

As noted previously, the YBOCS-CL was the assessment measure of choice given its extensive use in OCD research. Previous factor analytic studies based their work on the assumption that the YBOCS-CL is a comprehensive checklist of OC symptomatology rendering responses of *continuous* (or ordinal) nature (i.e. absent, present, principal or prominent). In contrast, the

responses of the participants to the YBOCS-CL in this project were categorical and binary (present / absent). In other words, the OC symptoms were defined as binary '0; 1' - indicator measurements and therefore it was possible to display any combination of symptoms as a string of zeroes and ones. A 'zero' represented symptom absence and a 'one' the presence of a particular OC symptom. With this data collection, distinction was not made between symptoms considered "primary / principal" and "present" as was the case in some previous studies.

When an adequate trial of pharmacotherapy with a serotonin reuptake inhibitor (SRI) (i.e. at least 10 weeks on the medication with a minimum of 6 weeks on mid-range dose) or cognitive-behavioural therapy (CBT) (i.e. 8 or more sessions with an expert OCD/CBT psychotherapist) had been undertaken, responsivity to pharmacotherapy / psychotherapy was assessed using the global improvement item of the Clinical Global Impression (CGI) scale (Guy, 1976).

The self-report Childhood Trauma Questionnaire (CTQ), was used to assess the nature and severity of possible childhood interpersonal trauma in the patients. Sub-scales of the CTQ include measures of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Reliability and validity of the CTQ have been well researched and the scale appears to provide a useful measure of childhood trauma (Bernstein *et al.*, 1997).

4.2.2 Latent class analysis

As noted before, traditional factor analysis (FA) is the data-mining model that was used most often in past studies of OC symptomatology to extract a relatively small number of meaningful "factors" or symptom dimensions from a large number of OC symptoms or variables. However, in recent times this method has been increasingly criticised for its limitations in practice,

including the requirement that all variables should be continuous, and the assumption of multivariate normality to justify a linear model.

Cluster analysis is theoretically similar to FA, and refers to the classification of similar objects (e.g. OC symptoms or OCD patients) into meaningful classes or groups, when both the *number* of classes and the *composition* or form of the classes are to be determined (Everitt, 1993; Kaufman and Rousseeuw, 1990). When cluster analysis is applied to objects with categorical *attributes* (e.g. data on the presence or absence of symptoms, such as data rendered by the present assessment of OCD symptoms with the YBOCS-CL), it is sometimes called *latent class analysis* (LCA) (Bartholomew and Knott, 1999; Goodman, 1974; Lazarsfeld and Henry, 1968; Uebersax, 2000); i.e. LCA is actually considered a "categorical analogue" to the traditional FA and therefore is appropriate for implementation in the current investigation. In addition, LCA has been shown to have many advantages above FA, and does not have the above limitations, making it an attractive choice for the present data analyses.

LCA yields a probabilistic clustering approach, where each "object" (in this case, the OCD patient) is assumed to belong to one class or cluster, and it is taken into consideration that there may be some uncertainty about an object's / patient's cluster membership. Vermunt and Magidson (2002b) suggested that probably one of the most important reasons for the increased popularity of LCA as a statistical tool for cluster analysis is the fact that presently high-speed computers make these computationally intensive methods practically applicable. In addition, latent class clustering is very flexible in the sense that both simple and complicated distributional forms can be used for the observed variables within clusters. Another advantage of this approach is that no decisions have to be made about the scaling of the observed variables: For example, when working with normal distributions with unknown variances, the results will be the same irrespective of whether the variables are normalized or not. (This is

very different from the standard non-hierarchical cluster methods, where scaling is always an issue.)

LCA can be divided into two major classes, namely: (1) clustering of *measurements* (variables), and (2) clustering of *cases*. To illustrate, for cluster analysis of measurements / variables, the *columns* of the array in Table 1 may be partitioned according to similarity (e. g. correlations, distance measures, etc). In cluster analysis of cases the *rows* of this array are grouped together according to case characteristics.

TABLE 1. The two major classes of cluster analysis

	Variable Dimension (or Measurement Dimension)							
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	.....	Item 10
Case Sample Dimension (or Observations Dimension)									

4.2.3 Data analysis

By means of Latent Gold 3.0, a computer program appropriate for LCA, cluster analysis of the OCD *cases* included in this data matrix was done; the data matrix in its entirety consisted of 261 OCD patients who responded to the 45 selected items of the YBOCS-CL, i.e. the data matrix comprised a 261 X 45 table (patients X symptoms).

As discussed before (Chapter 2: Methods), the example of other researchers (e.g. Baer (1994) and Summerfeldt *et al.* (1999)) was followed by including ratings of *current* symptoms (i.e. present=1, or absent=0) in the analysis, since inaccuracies or bias in participants' recall of non-current symptoms may have influenced results. (In other words, symptoms reported only as "past" symptoms, were for the sake of the current analysis marked as "absent").

The YBOCS-CL that was implemented actually comprised 74 items with each item representing a single obsessive or compulsive symptom. Interestingly, in addition to the easily categorized and clinically well-recognized OCD symptoms, the YBOCS-CL also contains a number of 'other' and 'miscellaneous' OCD symptoms. The 'other' items allow the interviewer to include symptoms specific to the participant being rated. As the content of these customized items was expected to be unique for each person, and the item content therefore not standardized, inclusion of these items in the present analysis would not have been psychometrically sound, and were therefore excluded from the analysis. Similarly, the so-called 'miscellaneous' obsessive and compulsive items were also excluded from these analyses.

The procedure for LCA entailed testing each model in an iterative fashion, i.e. a one-class solution was fitted first, followed by two-, three-, and four-class solutions and so forth, until the "best" solution was obtained. The best fitting solution was determined by the evaluation of the chi-squared test statistic for fit. Another criterion taken into consideration to ensure that this

was the best model likelihood was based on the fact that the difference between the log-likelihood of the previous and the current class approximated a chi-squared distribution - if this difference was greater than the critical chi-squared statistic, then the current class provided a better fit to the data than the previous class.

A further aim of the study was to investigate the association of the identified clusters with additional data not included in the LCA, i.e. specific demographic information (age, gender distribution) and clinical variables including specific OC symptoms, treatment response, total OCD severity and trauma history.

4.3 Results

4.3.1 Application of LCA to the YBOCS-CL data

One of the first lessons learned when implementing the cluster analysis approach of LCA, was that a sparse learning set could affect the outcome of the analysis adversely. For example, if the number of nominal indicators (the OC symptoms) used in the cluster analysis was large with respect to the number of cases (261 observations or cases for this study), the procedure of LCA resulted in asymptotic problems in the estimation process. In this analysis it was clear from the outset that all 45 YBOCS-CL items could not be included in the clustering process if reliable output was to be obtained.

There were numerous combinations (absence / presence) of the 45 OC symptoms that could have been studied or investigated. If, for example, ten symptoms were studied, there were 1024 ($=2^{10}$) different combinations (on the vertices of a hypercube) of strings consisting of zeroes and ones. (See the Methods section in this chapter for an explanation of 'zeroes' and

'ones'.) Not all of these 1024 different combinations were represented in the outcomes, as evident in the learning sample of 261 individuals (observations). If each of the 261 individuals in this sample had a different set of the ten selected OC symptoms, there would still have been a set of 763 (1024-261) combinations (or outcomes) not represented in the learning set, likely due to very low probabilities of those particular outcomes.

Tables 2, 3, and 4 provide illustrations of the marginal frequency and joint frequencies of the zero/one-combinations for some of the YBOCS-CL items reported most frequently.

TABLE 2. Marginal frequency table of the <u>two</u> most frequently occurring OC symptoms as assessed with the YBOCS-CL

	Absent	**Present**	**Marginal rate or incidence**
Mental compulsions **(Item nr 45)**	92	169	64.8%
Checking that did not make mistake **(Item nr 38)**	121	140	53.6%

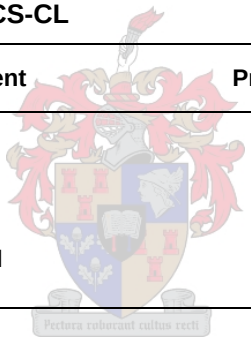


TABLE 3. Joint frequency table of the <u>two</u> most frequently occurring OC symptoms as assessed with the YBOCS-CL

Checking that did not make mistake (Item nr 38)	**Mental compulsions (Item nr 45)**	**Frequency**	**Relative Incidence**
Absent	Absent	60	23.0%
Absent	Present	61	23.4%
Present	Absent	32*	12.3%
Present	Present	108**	41.4%

* The minimum cell frequency for the two most frequently occurring OC symptoms was equal to 32 (i.e. reported by 12.3% of the sample.

** The maximum cell frequency was 108 (incidence: 41.1%).

Turning the attention to the four most frequently reported OC symptoms (Table 4), it is clear that the minimum cell frequency was equal to 3 (incidence: 1.1%) whereas the maximum cell frequency was 42 (incidence: 16.1%). If the occurrences of these four OC symptoms were approximately evenly distributed throughout the sixteen cells described by these indicators, the frequencies would have varied approximately between 10 and 22 (expected count = 261 / 16 ≈ 16).

TABLE 4. Joint frequency table of the <u>four</u> most frequently occurring OC symptoms as assessed with the YBOCS-CL

Item nr 11[a]	Item nr 40[b]	Item nr 38[c]	Item nr 45[d]	Frequency of individuals*,**	Relative Incidence
Absent	Absent	Absent	Absent	**33**	**12.6%**
Absent	Absent	Absent	Present	**30**	**11.5%**
Absent	Absent	Present	Absent	4	1.5%
Absent	Absent	Present	Present	12	4.6%
Absent	Present	Absent	Absent	5	1.9%
Absent	Present	Absent	Present	9	3.4%
Absent	Present	Present	Absent	6	2.3%
Absent	Present	Present	Present	**39**	**14.9%**
Present	Absent	Absent	Absent	19	7.3%
Present	Absent	Absent	Present	13	5.0%
Present	Absent	Present	Absent	9	3.4%
Present	Absent	Present	Present	15	5.7%
Present	Present	Absent	Absent	3	1.1%
Present	Present	Absent	Present	9	3.4%
Present	Present	Present	Absent	13	5.0%
Present	Present	Present	Present	**42**	**16.1%**

Item nr 45[d]	Mental Compulsions	**Item nr 40[b]**	Re-reading or re-writing
Item nr 38[c]	Checking that did not make mistake	**Item nr 11[a]**	Concern with dirt or germs

* Frequency of individuals with the preceding combination

** The four highest frequencies of individuals with the preceding combination are in bold type.

From the Stem-and-Leaf Diagram (Figure 1) of the frequencies present in the sixteen cells, it can be deduced that only five observed frequencies were contained in the interval between 10 and 22. The high frequencies of OC symptoms (i.e. 30, 33, 39 and 42) especially confirmed the presence of clustering (Table 4).

FIGURE 1. Stem-and-Leaf Diagram of the frequencies of individuals / cases present in the 16 cells in the joint distribution of the four highest OC symptoms (items nr 11, 40, 38 and 45)

Stem	Leaves
0	34
0	56999
1	233
1	59
2	
2	
3	03
3	9
4	2
4	

The distribution of the cell frequencies for higher dimensional tables was also investigated - for example, when using the nine indicators (items / OC symptoms) with the highest marginal incidences. In the study of these nine OC symptoms, 512 (=2^9) different sequences of 'Absent' and 'Present' strings or cells could be formed to describe any outcome. A Stem-and-Leaf Diagram (Figure 2) was constructed for the frequencies present in the 512 cells in the joint distribution of the nine most frequently occurring OC symptoms. The majority of the cells were empty (or zero), i.e. 362 out of 512 possible combinations (cells) of the nine OC symptoms. In other words, no individual cases satisfied these 362 OC symptom combinations. From the

frequency distribution, it is clear that a further 107 cells contained single occurrences. The rest of the distribution is also available in Figure 2. The largest frequency in this 9-way table was 25 occurring in the cell where all the OC symptoms were absent. In contrast, in the cell where all nine OC symptoms were present, the frequency was 8. Again, both these relatively high frequencies confirm the presence of clustering.

(Figure 2 follows on the next page.)

FIGURE 2. Stem-and-Leaf Diagram of the frequencies present in the 512 cells in the joint distribution of the nine most frequently occurring OC symptoms*

Stem	Leaves	Frequency of cells
Empty Cells	00000 00000 00000 00000 00000 00000…… 00000 00	362
1	00000 00000 …… 00000 00000 00	107
2	00000 00000 00000 00000 00	22
3	00000 00000	10
4	00000 00	7
5		0
6		0
7		0
8	0	1
9	0	1
10	0	1
11		0
12		0
13		0
14		0
15		0
16		0
17		0
18		0
19		0
20		0
21		0
22		0
23		0
24		0
25	0	1
	Total number of cells	**512**

*The nine most frequently occurring YBOCS-CL items are items nr 11, 27, 30, 34, 38, 40, 42, 43, and 45

If the unusual assumption of evenly distributed occurrences over the 512 cells were made, the expected count per cell was 0.51 (261 / 512). By this criterion the 9-way table would be assumed to be sparse. The same conclusion was reached by studying the observed marginal frequency table. Forty-three of the cell frequencies were equal to 2 or more, confirming the

presence of clustering within this 9-way table. It may be observed that the proportion of very small frequencies increased as the dimensions increased (compare the proportion of small frequencies in Tables 3 and 4).

Importantly, the deductions made and models derived after the application of any statistical technique depend on the data used as a learning set. In this investigation, various groups (partitions) of the OC symptoms were used as exploratory learning sets. The frequency of 25 (the maximum) originated from the cell (absent, absent …… absent); thus, for 25 individuals none of the nine OC symptoms were present. From the experience gained in applying LCA, it was learned that estimation problems occurred when applied to data that would have given rise to sparse frequency arrays.

Importantly, when using additional indicators in LCA, the potential for computational instability increased. Interestingly, the one OC symptom definitely not considered for methodological reasons due to its low prevalence (only 9 out of a total sample of 261 cases), was YBOCS-CL item nr 7: 'Fear will steal things'.

In summary, the motivation for concentrating on the nine most prevalent OC symptoms for LCA as assessed with the YBOCS-CL was that the LCA technique selected for application worked efficiently when the multi-way contingency table was not too sparse. For the 9-way table under consideration, 362 of the cells were equal to zero. However, the Latent Class technique appeared to handle sparse data better than a likelihood estimation approach for higher order interactions. The extra benefit of this approach was to confirm the presence of clusters in the data for the nine most prevalent OC symptoms. Similar to multi-way contingency table analysis, the estimation and inferential process was more efficient when the marginal rates or

probabilities (of the different OC symptoms) were close to 50%. This was the case for the nine most prevalent OC symptoms.

4.3.2 Application of LCA to the nine most frequent indicators (OC symptoms)

The cluster module of LCA offered an opportunity to find 'optimal' partitions (clusters) of the 261 observations / cases. Given the fact that in this type of analysis the definitions and context of the OC symptoms are of importance, the 9 most frequently reported OC symptoms are listed below with their YBOCS-CL item numbers and the frequency of occurrence of each (Table 5).

TABLE 5. The YBOCS-CL item descriptions and numbers of the nine most prevalent OC symptoms and the frequency of occurrence of each in 261 OCD patients

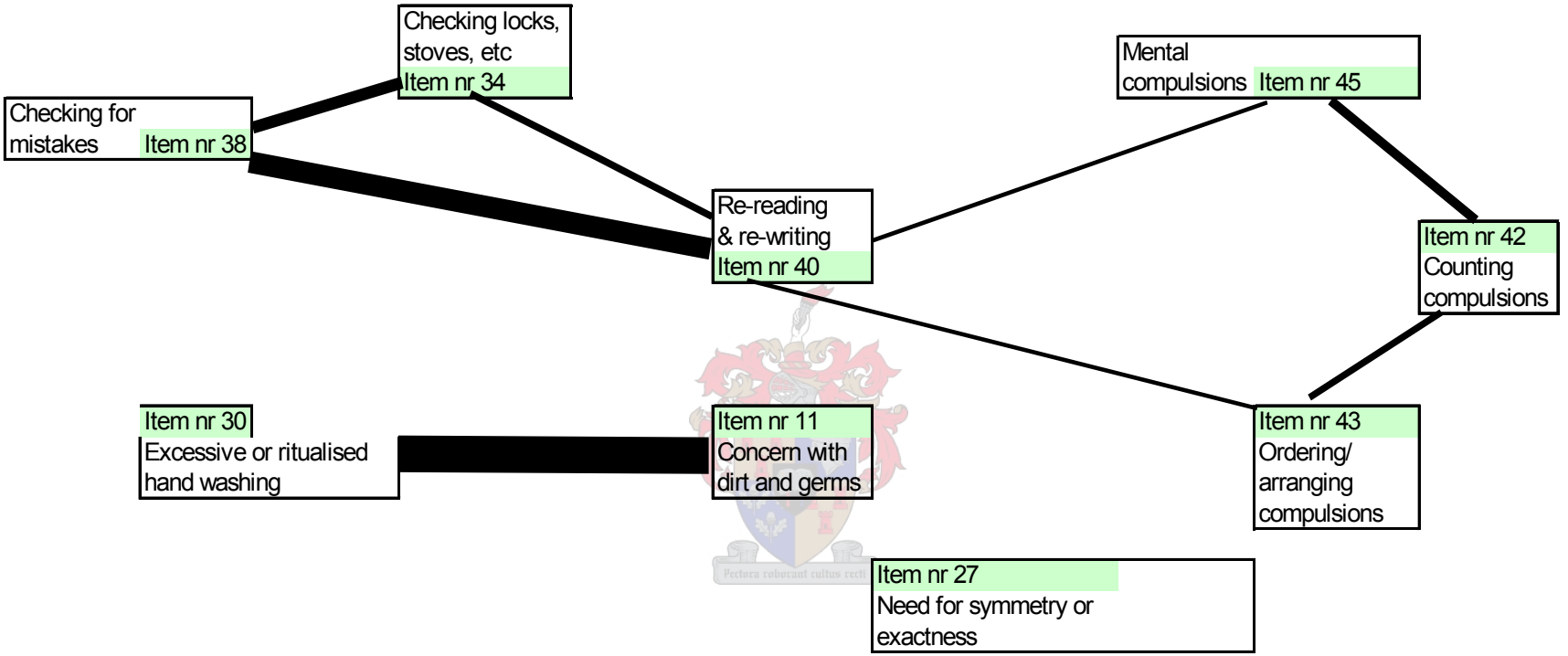
Order	Item number	Frequency / Number of times an item was reported	Item description
1	45	169	Mental compulsions
2	38	140	Checking that did not make a mistake
3	40	126	Re-reading or re-writing
4	11	123	Concern with dirt or germs
5	43	108	Ordering / arranging compulsions
6	34	105	Checking locks, stove, appliances, etc.
7	42	105	Counting compulsions
8	30	100	Excessive or ritualised hand washing
9	27	95	Need for symmetry or exactness not accompanied by magical thinking

An investigation of the associations amongst the nine most prevalent YBOCS-CL items / OC symptoms suggested that some of these items were very strongly related to one another (e.g. YBOCS-CL items number 11 and 30, and 38 and 40 respectively). Surprisingly, item nr 27 ("Need for symmetry or exactness not accompanied by magical thinking") was neither significantly associated with item nr 43 ("Ordering / arranging compulsions"), nor with any of the

other eight OC symptoms (Table 6). These associations amongst the nine YBOCS-CL items may have had an impact on the way in which the clusters were formed. For example, one of the cells in this 9-way table contained 25 individuals (see Figure 2) in a particular cell indicating that there was clustering present where the mean or expected number of individuals per cell was 0.51.

Pectora roborant cultus recti

TABLE 6. Graphical display of associations between the nine most prevalent symptoms*



* The thicker the connecting line between items, the stronger the association (all significant)

Table 7 provides information used to decide on the optimal number of clusters present when the information in the nine most frequent indicators (OC symptoms) was utilised. Basically, as noted before, the procedure of LCA requires fitting a one-class solution first, followed by two-, three-, and four-class solutions and so forth, until the best solution is obtained. More specifically, if the Bootstrap p-value for each cluster set was significant (e. g. $p<0.05$), it indicated that 'Model fit' was not achieved.

A measure of model 'fit' was whether the added information, proceeding from an 'N-cluster' to an 'N+1-cluster', was significant. For example, the Four-cluster model displayed sufficient fit on the 5% level (Bootstrap p-value 0.0623); however, the information added by the fourth cluster was highly significant (p-value of the difference: 7.49E-10). Subsequently, studying the test statistics of the Five-cluster model, it could be observed that the fit of the model has improved (Bootstrap p-value = 0.1175), but the p-value of the difference suggests that it was still useful to include the fifth cluster. At the level of the Six-cluster model, the fit improved further (Bootstrap p-value = 0.1963); however, the p-value of the difference was equal to 2.2% suggesting that it may be useful to include an additional cluster. Considering the Seven-cluster model, it was evident that the fit was still sufficient but that the seventh cluster did not add much to the improvement of the fit, given that the p-value of the difference was now not significant (0.35567). In conclusion, the Six-cluster model provided the best fit for the data used.

(Table 7 follows on the next page.)

TABLE 7. Model fitting statistics for the nine indicators (OC symptoms) occurring most frequently

1-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	502	p-value		
L-squared (L^2)	748.6667	5.10E-12	0	0

Calculated measures

Bootstrap p-value - L^2 estimate Not calculable; p-value = 0

2-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	492	p-value		
L-squared (L^2)	489.3347	0.52	0	0

Calculated measures

Bootstrap p-value - L^2 estimate Not calculable; p-value = 0

3-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	482	p-value		
L-squared (L^2)	405.9986	0.99	0.001	0.0005

Calculated measures

Bootstrap p-value - L^2 estimate 583.6697

4-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	472	p-value		
L-squared (L^2)	364.1514	1	0.0623	0.0038

Calculated measures

Bootstrap p-value - L^2 estimate	*520.0649*	
Associated degrees of freedom		*10*
Difference between measures of fit		*63.60*
p-value of the difference		*7.49E-10*

5-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	462	p-value		
L-squared (L^2)	335.1637	1	0.1175	0.0051

Calculated measures

Bootstrap p-value - L^2 estimate	*498.3485*	
Associated degrees of freedom		*10*
Difference between measures of fit		*21.72*
p-value of the difference		*0.016616*

6-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	452	p-value		
L-squared (L^2)	309.3184	1	0.1963	0.0063

Calculated measures

Bootstrap p-value - L^2 estimate	*477.5052*	
Associated degrees of freedom		*10*
Difference between measures of fit		*20.84*
p-value of the difference		*0.022213*

7-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	442	p-value		
L-squared (L^2)	290.2815	1	0.197	0.0063

Calculated measures

Bootstrap p-value - L^2 estimate	*467.1411*	
Associated degrees of freedom		*10*
Difference between measures of fit		*11.02*
p-value of the difference		*0.355666*

8-Cluster Model

Chi-Squared Statistics			Bootstrap p-value	Standard error
Degrees of freedom (df)	432	p-value		
L-squared (L^2)	275.533	1	0.1533	0.0057

Calculated measures

Bootstrap p-value - L^2 estimate	*462.059*	
Associated degrees of freedom		*10*
Difference between measures of fit		*5.08*
p-value of the difference		*0.885631*

Focussing the attention to the comparison of the Six-Cluster solution with a Four-Cluster solution (which also demonstrated good fit) (Table 8), it may be suggested that a Four-Cluster solution may be advantageous to describe a simpler structure in the data. Nevertheless, the sample size allowed the identification of the six clusters, which arguably rendered a better understanding of the relevant data. Importantly, the two solutions did not show a significant difference (Test statistic chi-squared = 592.83; p value = 0.000).

TABLE 8. Frequencies of patients with a Six-cluster solution vs a Four-cluster solution*

Six-cluster solution	Four-cluster solution				
	I	II	III	IV	Total
I	58				58
II		54	1		55
III	3		3	47	53
IV	29		8		37
V	4	20	9		33
VI			25		25
Total	94	74	46	47	261

*Test statistic chi-squared = 592.83; p value = 0.000

Focussing the attention on the comparison between the Six-cluster and Four-cluster solution with the genders separated, the findings again suggested that the solutions (Four- vs Six-) were similar (males: Test statistic chi-squared = 305.11; p value = 0.000; females: Test statistic chi-squared = 286.69; p value = 0.000).

4.3.3 Characterization of the six identified clusters

The cluster sizes (i.e. number of patients included in each) were equal to 58, 55, 53, 37, 33 and 25 for the six clusters, respectively. The 261 cases were more or less evenly distributed amongst the six clusters with the smallest frequency in Cluster 6 (N=25).

Based on their associated clinical features, the identified clusters can be described and labelled as follows:

The first cluster was largest (58 cases) with strong associations with the OC symptoms of checking for mistakes, mental compulsions (including the repeating of special words, images, numbers, prayers, mental counting, list-making and reviewing of conversations) and re-reading / re-writing and was therefore labelled '*Predominantly mental compulsions*'. Cluster II was associated with the highest OCD severity scores for both genders and was labelled '*Maximal*

disorder'. Cluster III was labelled '*Minimal disorder*' as the patients in Cluster III had the lowest mean OCD severity score and the lowest frequency of associated OC symptoms. Cluster IV was *negatively* associated with checking, i.e. none of the patients included in this cluster reported checking for mistakes or very few reported checking of doors, locks etc, and was therefore labelled '*No checking compulsions*'. Given the very strong positive association with checking (for mistakes) (100% of patients on Cluster V), Cluster V was labelled '*Checking compulsions*'. A very strong positive association with contamination fears and related compulsions was noted for Cluster VI, justifying the label of '*Pure Contamination compulsions / washing*'.

To gain further insight into the structure of these identified clusters, attention was turned to the way in which clusters differed with respect to (i) the nine OC symptoms included in the LCA, (ii) gender and (iii) age distribution, (iv) total OCD-severity, (v) treatment response, and (vi) childhood trauma history.

4.3.3.i The relationship of each of the nine most prevalent OC symptoms with the six clusters of cases

In the next few tables, the findings of the present investigation of the relationship of the six clusters with each of the nine most frequently reported OC symptoms are shown. The column percentages of the absence and presence of the corresponding YBOCS-CL item were calculated for each cluster and compared to the general rate of this particular YBOCS-CL item within the study sample. The data are presented in order of decreasing occurrence frequency of the YBOCS-CL items.

The most frequently occurring YBOCS-CL item, item nr 45 ('Mental compulsions'), was positively associated with Cluster I (88%) and negatively associated with Cluster III (28%) (Table 9).

TABLE 9. The distribution of the absence or presence of YBOCS-CL item nr 45 'Mental compulsions' in the six clusters

		Cluster Number and Label						
Item nr 45	Data	**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	Total
Absent	Count	7	14	38	8	10	15	92
	Column %	12%	25%	72%	22%	30%	60%	35%
Present	Count	51	41	15	29	23	10	169
	Column %	88%	75%	28%	78%	70%	40%	65%
Column Totals		58	55	53	37	33	25	261

In Table 10, the strong positive associations between YBOCS-CL item 38 ('Checking that did not make a mistake') and Clusters V (100%), II (95%) and I (91%) are shown. This OC symptom also showed a strong negative association with Clusters IV (0%), VI (0%) and III (4%).

TABLE 10. The distribution of the absence or presence of YBOCS-CL item nr 38 'Checking that did not make a mistake' in the six clusters

		Cluster Number						
Item nr 38		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	5	3	51	37	0	25	121
	Column %	9%	5%	96%	100%	0%	100%	46%
Present	Count	53	52	2	0	33	0	140
	Column %	91%	95%	4%	0%	100%	0%	54%
Column Totals		58	55	53	37	33	25	261

YBOCS-CL item nr 40 ('Re-reading or re-writing') was positively associated with Clusters I (76%) and II (76%). It showed a negative association with Cluster III (6%) (Table 11).

TABLE 11. The distribution of the absence or presence of YBOCS-CL item nr 40 'Re-reading or re-writing' in the six clusters

		Cluster Number						
Item nr 40		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	14	13	50	29	12	17	135
	Column %	24%	24%	94%	78%	36%	68%	52%
Present	Count	44	42	3	8	21	8	126
	Column %	76%	76%	6%	22%	64%	32%	48%
Column Totals		58	55	53	37	33	25	261

YBOCS-CL item nr 11 ('Concern with dirt or germs') was reported absent by all of the cases included in Cluster I, i.e. no association between this OC symptom and Cluster I (0%), but it

showed a positive association with Clusters II (96%) and VI (96%). This OC symptom (item nr 11) was also, to a lesser extent, positively associated with Cluster V (85%), and, also to a lesser extent, negatively associated with Cluster III (17%) (Table 12).

TABLE 12. The distribution of the absence or presence of YBOCS-CL item nr 11 'Concern with dirt or germs' in the six clusters

		Cluster Number						
Item nr 11		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	58	2	44	28	5	1	138
	Column %	100%	4%	83%	76%	15%	4%	53%
Present	Count		53	9	9	28	24	123
	Column %	0%	96%	17%	24%	85%	96%	47%
Column Totals		58	55	53	37	33	25	261

There was a strong positive link between YBOCS-CL item 43 ('Ordering / arranging compulsions') and Cluster II (87%), while there was a strong negative link with Clusters III (0%), V (12%) and VI (16%), respectively (Table 13).

(Table 13 follows on the next page.)

TABLE 13. The distribution of the absence or presence of YBOCS-CL item nr 43 'Ordering / arranging compulsions' in the six clusters

		Cluster Number						
Item nr 43		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	30	7	53	13	29	21	153
	Column %	52%	13%	100%	35%	88%	84%	59%
Present	Count	28	48	0	24	4	4	108
	Column %	48%	87%	0%	65%	12%	16%	41%
Column Totals		58	55	53	37	33	25	261

The OC symptom described by YBOCS-CL item nr 34 ('Checking locks, stove, appliances, etc.') was positively linked to Cluster II (69%) whereas this item showed a negative association with Clusters VI (8%), III (13%) and IV (16%), respectively (Table 14).

TABLE 14. The distribution of the absence or presence of YBOCS-CL item nr 34 'Checking locks, stove, appliances, etc.' in the six clusters

		Cluster Number						
Item nr 34		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	25	17	46	31	14	23	156
	Column %	43%	31%	87%	84%	42%	92%	60%
Present	Count	33	38	7	6	19	2	105
	Column %	57%	69%	13%	16%	58%	8%	40%
Column Totals		58	55	53	37	33	25	261

Table 15 indicates the positive association of item nr 42 ('Counting compulsions') with Clusters II (65%) and IV (65%), and the strong negative association with Clusters III (0%) and VI (4%).

TABLE 15. The distribution of the absence or presence of YBOCS-CL item nr 42 'Counting compulsions' in the six clusters

		Cluster Number						
Item nr 42		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	27	19	53	13	20	24	156
	Column %	47%	35%	100%	35%	61%	96%	60%
Present	Count	31	36	0	24	13	1	105
	Column %	53%	65%	0%	65%	39%	4%	40%
Column Totals		58	55	53	37	33	25	261

Table 16 indicates that YBOCS-CL item nr 30 ('Excessive or ritualized handwashing') was not associated with Cluster I (0%), but was definitely positively associated with Cluster VI (100%). In addition, this OC symptom also showed a strong positive association with Clusters II (75%) and V (79%), and a strong negative association with Cluster III (4%).

(Table 16 follows on the next page.)

TABLE 16. The distribution of the absence or presence of YBOCS-CL item nr 30 'Excessive or ritualised hand washing' in the six clusters

		Cluster Number						
Item nr 30		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	58	14	51	31	7	0	161
	Column %	100%	25%	96%	84%	21%	0%	62%
Present	Count	0	41	2	6	26	25	100
	Column %	0%	75%	4%	16%	79%	100%	38%
Column Totals		58	55	53	37	33	25	261

YBOCS-CL item nr 27 ('Need for symmetry or exactness not accompanied by magical thinking') was definitely not associated with Clusters III (0%) and V (0%). This OC symptom was positively associated with Cluster II (82%) (Table 17).

TABLE 17. The distribution of the absence or presence of YBOCS-CL item nr 27 'Need for symmetry or exactness not accompanied by magical thinking' in the six clusters

		Cluster Number						
Item nr 27		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Absent	Count	35	10	53	17	33	18	166
	Column %	60%	18%	100%	46%	100%	72%	64%
Present	Count	23	45	0	20	0	7	95
	Column %	40%	82%	0%	54%	0%	28%	36%
Column Totals		58	55	53	37	33	25	261

4.3.3.ii The gender distribution within the six clusters

The gender distribution within the six clusters (Table 18) was relatively even except for Clusters IV and VI which included as few as 13 (35%) and as many as 15 (60%) males, respectively.

TABLE 18. The gender distribution within the six clusters

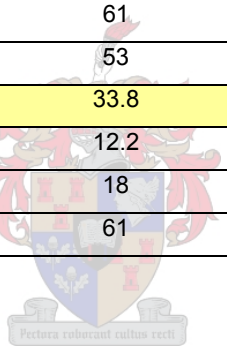
		Cluster Number						
Gender		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Male	Count	28	26	30	13	19	15	131
	Column %	48%	47%	57%	35%	58%	60%	50%
Female	Count	30	29	23	24	14	10	130
	Column %	52%	53%	43%	65%	42%	40%	50%
Total		58	55	53	37	33	25	261
Column %		100%	100%	100%	100%	100%	100%	100%

4.3.3.iii The age distribution within the six clusters

In Table 19 the descriptive statistics of the age at the time of the interview of the patients were studied with respect to gender within the six clusters. The average age of the male group (31.6 years) was younger than that of the female group (36.7 years). The lowest average age for males was 25.6 years in Cluster V, whereas the highest average age was 38.1 years for males in Cluster II. For females, the lowest average age was 34.3 years in Cluster VI, and the highest average age was 39.2 years in Cluster III. It was interesting to observe that for the males the difference between the minimum and maximum average age within the clusters was more than 12 years and much less for the corresponding range for the females (5 years).

TABLE 19. The descriptive statistics of age with respect to gender within the six clusters

		Cluster Number						
Gender		**I** *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	**Total**
Male	Count	28	26	30	13	19	15	131
	Average age	35.3	38.1	29.6	27.5	25.6	28.7	31.6
	StdDev	11.5	9.8	8.4	8.6	9.4	9.2	10.5
	Min	16	24	18	16	16	16	16
	Max	55	54	55	47	59	44	59
Female	Count	30	29	23	24	14	10	130
	Average age	35.3	36.0	39.2	37.9	36.8	34.3	36.7
	StdDev	12.9	14.4	14.2	15.1	17.9	15.9	14.5
	Min	16	18	18	16	16	19	16
	Max	59	69	61	63	65	71	71
Count	All	58	55	53	37	33	25	261
Average age	All	35.3	37.0	33.8	34.2	30.4	30.9	34.1
StdDev	All	12.1	12.3	12.2	14.0	14.5	12.3	12.9
Min	All	16	18	18	16	16	16	16
Max	All	59	69	61	63	65	71	71



4.3.3.iv Total OCD severity within each of the six clusters

In the total sample, OCD severity scores (on the YBOCS-SS) ranged from 8 to 39 (i.e. from mild to very severe), with a mean score of 21.1 ± 6.4. In a comparison of the medians of the YBOCS-SS scores in all six clusters (using Kruskal-Wallis One-way ANOVA on ranks), it was found that the clusters did not differ significantly from one another (Figures & tables illustrating the comparison of medians amongst the clusters are available from the candidate upon request.)

Turning the attention to the possible associations between the total OCD severity score and the genders within each of the different clusters, Table 20 indicates that OCD severity was the

mildest in males in Cluster III (15.7). A similar tendency was observed for the females in Cluster III (20.0). However, compared to the males where a relatively big difference was noted between the smallest and second smallest mean severity score (15.7 → 19.1), the difference between the smallest and second smallest mean for females with OCD was much less (20.0 → 20.6). For both males (24.7) and females (23.4) in Cluster II, OCD severity was highest. Compared to the other clusters, the standard deviation of the mean OCD severity score for females in Cluster IV was largest (SD = 8.2), suggesting a large variation in OCD severity in the female patients included in this cluster.

TABLE 20. The associations between the total OCD severity score and the genders within each of the clusters

		Cluster Number						
		I *Predominantly mental compulsions*	**II** *Maximal disorder*	**I** *Minimal disorder*	**IV** *No checking compulsions*	**V** *Checking compulsions*	**VI** *Pure Contamination compulsions / washing*	
Gender								**Total**
Male	Count	28	26	30	13	19	15	131
	Average OCD severity score (YBOCS-SS)	21.7	24.7	15.7	19.1	22.7	21.0	20.7
	Standard deviation	5.5	5.3	4.2	4.9	6.1	6.5	6.1
	Minimum	9	16	8	10	10	9	8
	Maximum	38	36	24	26	33	32	38
Female	Count	30	29	23	24	14	10	130
	Average OCD severity score (YBOCS-SS)	20.6	23.4	20.0	20.6	21.9	21.9	21.4
	Standard deviation	6.2	5.8	6.9	8.2	7.1	6.0	6.7
	Minimum	10	12	9	10	12	16	9
	Maximum	33	35	35	37	39	33	39
Count		58	55	53	37	33	25	261
Average OCD severity score (YBOCS-SS)		21.1	24.0	17.6	20.1	22.4	21.4	21.0
Standard deviation		5.8	5.5	5.9	7.2	6.5	6.2	6.4
Minimum		9	12	8	10	10	9	8
Maximum		38	36	35	37	39	33	39

4.3.3.v Comparison amongst clusters in terms of treatment response

Focussing the attention to the treatment response in the six identified clusters, 41 and 177 of the total sample of patients (in 6 clusters) reported an adequate treatment trial of CBT and SRI, respectively. (Tables illustrating the frequency of patients in each cluster treated with CBT and SRI's are available from the candidate.)

4.3.3.v.a Response to CBT in the six clusters

The six clusters did not differ significantly from one another in terms of their response to CBT (Table 21). Of the 22 patients in Cluster I who received an adequate trial of CBT, 68% (N=15) reported improvement (whether it was minimal, much or very much). Similarly, twenty-two (N=22) of Cluster II received CBT, with 68% of those reporting improvement. In Cluster III, the improvement was more marked, i.e. 90% of the patients with prominent Cluster III-symptoms reported improvement. 79% of Cluster IV (N treated = 14), 57% of Cluster V (N treated = 14) and 70% of Cluster VI (N treated = 10) reported improvement of their illness when treated with CBT. Interestingly, only one person (in Cluster II) was much worse after receiving CBT. From Table 21 it is also clear that response to CBT was better for patients with lower total OCD severity.

TABLE 21. OCD severity scores of patients according to response to CBT in Clusters I – VI: All patients (N = 261)

		RESPONSE TO CBT: CGI – IMPROVEMENT CATEGORIES							
CLUS-TERS		Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	(blank)	Total
I	Patient frequency	2	6	7	6	1	—	36	58
	Mean severity score (Y-BOCS-SS)	17.50	22.67	16.29	21.33	25.00	—	21.83	21.10
	StdDev	4.95	7.53	4.64	3.67	—	—	5.82	5.81
	Minimum	14	10	10	15	25	—	9	9
	Maximum	21	30	24	25	25	—	38	38
II	Patient frequency	5	3	7	6	—	1	33	55
	Mean severity score (Y-BOCS-SS)	22.60	23.00	23.14	23.17	—	22.00	24.73	24.02
	StdDev	5.73	10.44	5.08	3.60	—	—	5.72	5.54
	Minimum	18	16	16	17	—	22	12	12
	Maximum	32	35	30	28	—	22	36	36
III	Patient frequency	3	11	12	3	—	—	24	53
	Mean severity score (Y-BOCS-SS)	20.33	15.64	17.50	18.33	—	—	18.13	17.60
	StdDev	12.70	4.41	3.94	1.53	—	—	6.70	5.88
	Minimum	13	9	12	17	—	—	8	8
	Maximum	35	24	25	20	—	—	30	35
IV	Patient frequency	1	5	5	3	—	—	23	37
	Mean severity score (Y-BOCS-SS)	12.00	16.00	19.80	20.33	—	—	21.35	20.08
	StdDev	—	5.24	10.21	0.58	—	—	7.21	7.19
	Minimum	12	10	10	20	—	—	10	10
	Maximum	12	22	34	21	—	—	37	37
V	Patient frequency	1	2	5	6	—	—	19	33
	Mean severity score (Y-BOCS-SS)	24.00	22.50	23.60	19.83	—	—	22.74	22.36
	StdDev	—	6.36	4.28	6.43	—	—	7.33	6.47
	Minimum	24	18	16	12	—	—	10	10
	Maximum	24	27	26	27	—	—	39	39
VI	Patient frequency	—	2	5	3	—	—	15	25
	Mean severity score (Y-BOCS-SS)	—	21.00	21.60	21.67	—	—	21.27	21.36
	StdDev	—	4.24	6.66	11.68	—	—	5.66	6.18
	Minimum	—	18	14	9	—	—	14	9
	Maximum	—	24	32	32	—	—	33	33
Total patient frequency		12	29	41	27	1	1	150	261
Total Mean severity score (Y_BOCS-SS)		20.42	18.76	19.78	21.00	25.00	22.00	21.86	21.05
Total StdDev		7.40	6.53	6.00	5.11	—	—	6.58	6.42
Total Minimum		12	9	10	9	25	22	8	8
Total Maximum		35	35	34	32	25	22	39	39

Pectora roborant cultus recti

4.3.3.v.b Response to SRI's in the six clusters

The six clusters did not differ significantly from one another in terms of their response to medication (Table 22). Thirty-six Cluster I-patients were treated with at least one adequate trial of medication (SRIs), with 86% reporting improvement. Eighty-two percent (82%) of 28 patients in Cluster II reported improvement with medication. Of the 38 patients in Cluster III who were treated with medication, 79% reported improvement. Eighty-two percent (82%) of Cluster IV (N treated = 22), 69% of Cluster V (N treated = 26) and 82% of Cluster VI (N treated = 17) reported improvement of their OC symptoms when treated with medication. Again, as with CBT, there was only one person (in Cluster IV) who reported that the illness was very much worse after medication treatment.

Pectora roborant cultus recti

TABLE 22. OCD severity scores of patients according to response to medication in Clusters I – VI: All patients (N = 261)

CLUS-TERS		RESPONSE TO MEDICATION: CGI-IMPROVEMENT CATEGORIES							
		Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	(blank)	Total
I	Patient frequency	5	18	8	5	—	—	22	58
	Mean severity score (Y_BOCS-SS)	14.00	21.28	21.00	21.80	—	—	22.45	21.10
	StdDev	5.70	7.09	4.28	3.83	—	—	4.68	5.81
	Minimum	9	10	14	15	—	—	14	9
	Maximum	23	38	25	24	—	—	32	38
II	Patient frequency	6	15	10	7	—	—	17	55
	Mean severity score (Y_BOCS-SS)	22.50	22.67	26.50	23.29	—	—	24.59	24.02
	StdDev	5.50	5.22	5.38	6.24	—	—	5.70	5.54
	Minimum	17	16	17	12	—	—	16	12
	Maximum	32	35	36	29	—	—	35	36
III	Patient frequency	3	16	11	8	—	—	15	53
	Mean severity score (Y_BOCS-SS)	15.33	18.44	14.36	19.38	—	—	18.60	17.60
	StdDev	3.21	6.32	4.95	4.57	—	—	6.58	5.88
	Minimum	13	10	8	13	—	—	8	8
	Maximum	19	35	25	25	—	—	30	35
IV	Patient frequency	4	11	3	3	—	1	15	37
	Mean severity score (Y_BOCS-SS)	20.00	19.18	25.00	21.33	—	16.00	19.80	20.08
	StdDev	6.16	9.11	7.00	8.96	—	—	6.28	7.19
	Minimum	11	10	18	11	—	16	10	10
	Maximum	25	37	32	27	—	16	34	37
V	Patient frequency	3	7	8	6	2	—	7	33
	Mean severity score (Y_BOCS-SS)	18.00	20.00	22.50	23.00	28.00	—	24.29	22.36
	StdDev	6.00	6.81	7.73	5.33	1.41	—	6.32	6.47
	Minimum	12	10	15	13	27	—	12	10
	Maximum	24	29	39	27	29	—	33	39
VI	Patient frequency	3	7	4	3	—	—	8	25
	Mean severity score (Y_BOCS-SS)	20.00	21.29	22.25	25.33	—	—	20.00	21.36
	StdDev	11.53	5.99	4.35	8.33	—	—	4.93	6.18
	Minimum	9	14	18	16	—	—	14	9
	Maximum	32	33	28	32	—	—	29	33
Total patient frequency		24	74	44	32	2	1	84	261
Total Mean severity score (Y_BOCS-SS)		18.54	20.51	21.25	22.03	28.00	16.00	21.64	21.05
Total StdDev		6.59	6.76	6.93	5.64	1.41	—	5.98	6.42
Total Minimum		9	10	8	11	27	16	8	8
Total Maximum		32	38	39	32	29	16	35	39

Pectora roborant cultus recti

4.3.3.vi Comparison amongst clusters in terms of childhood trauma history

An investigation of the extent in which the six clusters differed from one another in terms of total childhood interpersonal trauma history (assessed with the CTQ) using Kruskal-Wallis one-way ANOVA on ranks suggested that the clusters were similar. Similarly, focussing on particular instances of childhood trauma, it was found that the clusters were more or less equal in terms of emotional, physical, or sexual abuse, as well as emotional or physical neglect. (Tables & figures [box plots] illustrating the comparison of medians of total childhood interpersonal trauma history and of particular instances of childhood trauma in the 6 clusters are available from the candidate.) It is clear (from some of the figures) that there were a few exceptions in terms of levels of reported interpersonal childhood trauma; for example, some of the patients included in Cluster I and Cluster II reported more sexual abuse and physical neglect, respectively, than average for that cluster.

4.4 Discussion

In this investigation, LCA was conducted in an iterative manner; 1- to 8- class solutions were tested on the data. The findings support the existence of six (6) classes / clusters of OCD cases who were not significantly different in terms of total OCD severity, and response to treatment with CBT or SRIs. The clusters were also not different in terms of their reported childhood interpersonal trauma history (with a few exceptions).

The first cluster was largest (58 cases) and was labelled '*Predominantly mental compulsions*'. Given the large number of cases included in this cluster, and the fact that mental compulsions also comprised the OC symptom that was reported most frequently by the total OCD sample (see Chapter 3), the strong associations found between Cluster I and

the OC symptoms of checking for mistakes, mental compulsions (including the repeating of special words, images, numbers, prayers, mental counting, list-making and reviewing of conversations) and re-reading / re-writing were not surprising. Interestingly, none of the patients included in this cluster had contamination fears (i.e. concern with dirt or germs) or related compulsions (i.e. excessive or ritualised hand-washing). Interestingly, Abramowitz *et al.* (2003) have found that mental compulsions were most prevalent among patients with intrusive, upsetting religious, violent or sexual thoughts. In this LCA study however, these types of symptoms were not included. In addition, in a previous study the presence of obsessions with a sexual / religious content was an unique factor related to poorer long term outcome (Alonso *et al.*, 2001); this is in contrast to the present findings that, compared to the other identified clusters, Cluster I had the largest number of patients (31 out of 36, 86%) reporting improvement with medication.

The findings suggest that Cluster II was strongly associated with a wide range of different OC symptoms, including obsessions with contamination and the obsessive need for symmetry / exactness, as well as related compulsions including washing, ordering / arranging, checking (for mistakes and doors/ locks, etc.), and other repeating rituals such as counting and re-reading/re-writing. The wide array of symptoms associated with Cluster II made selection of an appropriate label difficult; nevertheless, given that Cluster II was also associated with the highest OCD severity scores (on the YBOCS-SS) for both genders (24.0), it was labelled '*Maximal disorder*'. Compared to the average age of male patients in other clusters, the males in Cluster II were oldest, i.e. 38.1 years at the time of the interview.

Cluster III was labelled '*Minimal disorder*' as the patients in Cluster III had the lowest mean OCD severity score (17.6) and the lowest frequency of associated OC symptoms. Given the relatively weak associations with all of the OC symptoms analysed, it may be suggested

that this particular class of patients may have presented with symptoms other than the 9 included in the current LCA. The females included in this cluster had the highest age (39.2 years) compared to those in other clusters. Compared to the other clusters, Cluster III had the largest number of patients reporting improvement with CBT (i.e. 90%, or 26 out of 29 patients who had been treated with an adequate trial of CBT). Some studies have suggested that severity of OCD may predict pharmacotherapy outcome; for example, Alarcon *et al.* (1993) found that higher YBOCS-SS scores were associated with poorer response to medication. No consistent predictors of outcome have been identified for the psychotherapy of OCD yet. Indeed, there is a relative absence of documentation concerning the outcome of BT for OC symptoms other than washing and checking. It may be hypothesized though that the link between Cluster III and the comparatively best response to CBT may possibly be explained by the low OCD severity scores and not by the specific symptoms presented by patients included in Cluster II. More work is needed to investigate this issue further.

Cluster IV was *negatively* associated with checking, i.e. none of the patients included in Cluster IV reported checking for mistakes or very few reported checking of doors, locks etc. In addition, Cluster IV patients were mostly female (65%). There was a relatively strong positive association with counting compulsions. This cluster was labelled '*No checking compulsions*'. Although more work is needed to look at gender distribution of OC checkers, it has previously been suggested that *males* more often present with checking compulsions (Khanna and Mukherjee, 1992); this is consistent with the finding that this cluster characterized by "limited" or no checking consisted mostly of females.

Cluster V was similar to Cluster II in some respects, including symptomatology (including obsessions with contamination and related compulsions, and checking), and overall OCD

severity (Cluster V was associated with the second highest severity score on the YBOCS-SS after Cluster II, i.e. 22.4). In contrast, however to Cluster II, the patients included in Cluster V did not report obsessions with symmetry / exactness and ordering / arranging compulsions. Given the very strong positive association with checking (for mistakes) (100% of patients on Cluster V), Cluster V was labelled '*Checking compulsions*'. The "checking" subtype has been identified in a number of OCD FA studies, with some studies suggesting a strong association with male gender (e.g. more checking behaviour in boys (Zohar, 1999)). The findings in the present study also suggest the presence of more males (58%) than females (42%) in Cluster V; however this difference was not significant.

A very strong positive association with contamination fears (i.e. concern with dirt or germs) (96% of patients) and related compulsions (hand-washing) (100% of patients) was noted for Cluster VI. In contrast to the other clusters which also showed a positive association with these contamination-related symptoms, this cluster was not strongly associated with checking, or ordering / arranging. Therefore, the label chosen for this cluster was '*Pure Contamination compulsions / washing*'. Identification of a cluster of patients with mostly contamination fears and related compulsions was expected, given that this subgroup has been identified in all previous factor analyses. The gender distribution of Cluster VI was uneven as well, with males comprising 60% of this group. There is much stronger evidence in the literature for a link between washing and female gender (Bogetto *et al.*, 1999; Castle *et al.*, 1995; Geller *et al.*, 1998; Lensi *et al.*, 1996; Marks, 1987; Minichiello *et al.*, 1990; Rachman and Hodgson, 1980; Stern and Cobb, 1978). Very few findings to the contrary, e.g. increased contamination obsessions *in males* (Fischer *et al.*, 1997), exist.

4.5 Limitations

4.5.1 Latent class analysis

As noted before, LCA methodology was chosen for this investigation of OCD subtypes as it resolved many of the problems associated with FA (e.g. requiring all variables to be continuous, or assuming that underlying latent variables [factors] are measured on an interval or ratio scale). Nevertheless, the LCA technique also had limitations. In particular, LCA has primarily been applied in confirmatory applications involving a relatively small number of variables. Recent advances have suggested that LCA may also be applicable to larger exploratory settings (such as this OCD dataset), but this has not yet been tested comprehensively.

4.5.2 Content and number of identified clusters

Perhaps the most prominent concern relates to the clinical applicability of the LCA findings. It has previously been argued that (*pure*) symptoms are of key importance in defining groups of OCD patients (Leckman *et al.*, 1997). To an extent, the findings here similarly suggest that some groups or classes are characterized by "pure" symptoms, e.g. Cluster VI ('Pure contamination compulsions / washing'). On the other hand, one may argue that classes very often are rather characterized by *mixed* symptoms, e.g. Cluster II ('Maximal disorder' including a wide variety of OC symptoms), which certainly makes sense from a clinical point of view. Indeed, there is some evidence in support of the latter argument; in fact, it is well known that OCD patients mostly present with multiple symptoms at a particular point in time, and that these often change over time (Rettew *et al.*, 1992). Furthermore, in addition to Cluster II being characterized by a large variety of different OC symptoms (*mixed* clinical picture), it was also associated with the highest OCD severity. In summary, existing OCD literature and the findings here suggest that, not only does one need to investigate OCD phenotypes characterized by *pure* symptoms or predominantly one *type* of OC

symptom, but also those classes characterized by *mixed* or a wide array of different OC symptoms.

Arguably the consideration of *six* OCD subtypes or clusters of cases is also not very practical. Based on evidence from previous investigations, it may be argued that OCD may possibly be subtyped into fewer, more distinct subtypes, each with unique clinical characteristics and treatment outcomes; such data may be more useful in establishing etiology and perhaps prognosis in clinical practice.

4.5.3 Number of indicators / items included in the analysis

In addition, this dataset comprised 261 OCD cases and 45 variables; however, inclusion of more than 9 variables (indicators) into the LCA rendered "unstable" or unreliable output. Therefore it was chosen to include the 9 most frequently reported OC symptoms into the analyses assuming that these OC symptoms gave a good indication of the symptomatology characteristic of the present OCD sample. Clearly, this assumption may constitute a limitation with 9 symptoms perhaps being a very limited representation of OC symptomatology in general. In addition, as in FA, the identified classes / clusters are contingent upon the variables entered into the LCA, and this limited number of variables entered may have biased findings. In other words, other symptoms entered may have rendered a different solution. It was clear from the outset however, that all 45 YBOCS-CL items could not be included in the LCA if reliable output was to be obtained. In addition, exclusion of so many of the OC symptoms from the analysis is another limitation, given the fact that some of these symptoms (hoarding, for example) have been shown to constitute (aspects of) important possible OC dimensions in previous studies. Subsequently, given the importance of accurate representation of total OCD symptomatology when subtyping is based thereupon, it was attempted to remedy this situation, with implementation of another

clustering method using all of the 45 selected YBOCS-CL items (Ward's method; See Chapter 5).

In conclusion, the 6 identified clusters of OCD cases were labelled 'Predominantly mental compulsions', 'Maximal disorder', 'Minimal disorder', 'No checking compulsions', 'Checking compulsions', and 'Contamination compulsions / washing', respectively. These clusters did not differ significantly from each other in terms of their association with the clinical features that were investigated. Nevertheless, the clusters identified with LCA broadly resembled some of the current sub-classifications of OCD symptomatology suggested in the literature. More work is needed to address the limitations discussed here.

CHAPTER 5

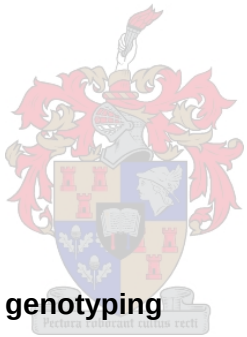
THE IDENTIFICATION OF OBSESSIVE-COMPULSIVE DISORDER SUBTYPES WITH CLUSTER ANALYSIS OF OBSESSIVE-COMPULSIVE SYMPTOMATOLOGY

Abstract

This study was an additional attempt to identify OCD subtypes based on their obsessive-compulsive symptomatology assessed with the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL). Cluster analysis (Ward's method) was applied to the data matrix, which consisted of the responses of 261 OCD patients to 45 selected YBOCS-CL items, to develop an empirically based typology for OCD. An optimal solution was achieved for six clusters, which were labeled: I) "Contamination fears / washing", II) "Hoarding / collecting", III) "Symmetry / ordering / counting / arranging / repeating", IV) "Sexual", V) "Somatic, religious and diverse" and VI) "Harm-related". Increased presentation of symptoms characteristic of each of the clusters was associated with specific demographic, clinical and, in some cases (i.e. Clusters IV, V and VI), genetic characteristics. The *L/L* (*met/met*) genotype of the catechol-O-methyltransferase (*COMT*) *Val158Met* polymorphism was associated with increased sexual, somatic, religious and diverse, and harm-related symptoms of OCD. Most clusters were significantly correlated with one another. The findings confirm the existence of OCD symptom clusters similar to those obtained in earlier studies. The high correlations amongst clusters, and the fact that clusters were not clearly differentiated by their associated demographic, clinical and genetic features, suggest that other approaches to optimally characterize the heterogeneity of OCD are still needed. However, subtyping OCD based on symptom structure may potentially assist efforts to identify more robust endophenotypes.

5.1 Introduction

Despite increased research interest in the identification of OCD subtypes and their associated features, the existing data are far from definitive and are still subject to revision. Therefore, the primary aim of this study was to categorize obsessive-compulsive (OC) symptomatology by means of cluster analysis (Ward's method) of the individual symptoms of the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL), in an attempt to remedy some of the limitations of the latent class analysis (LCA) of OC symptomatology manifested by 261 obsessive-compulsive disorder (OCD) cases that were presented in Chapter 4. Secondly, the associations between the OCD symptom subtypes (the identified clusters) and specific demographic, clinical and genetics variables were investigated.



5.2 Methodology

5.2.1 Subjects, interview and genotyping

This investigation made use of the same YBOCS-CL data obtained from the sample of 261 patients with OCD (described in Chapters 2 and 4). As a reminder to the reader, interviewing and genotyping procedures are described briefly:

Two hundred and sixty one patients with OCD (N=261), with ages ranging from 16 to 71, were included in the study (mean age: 34.1 years (SD: 12.9)). Of the 261 patients, 130 were female (mean age: 36.7 years (SD: 14.5)) and 131 male (mean age: 31.6 years (SD: 10.5)).

Demographic data, including current age, age at onset of the illness, gender and ethnicity, were obtained). In addition to the Structured Clinical Interview for Axis I Disorders (SCID-I/P), selected parts of the SCID-II/P (obsessive-compulsive, avoidant, schizotypal and borderline personality disorders, respectively) (First *et al.*, 1998), were used to examine lifetime comorbidity. The SCID-OCSD (Du Toit *et al.*, 2001) was implemented to assess comorbid OCD-related conditions not covered by the SCID-I.

The YBOCS-CL, the assessment measure of choice given its extensive use in OCD research, was used to assess current OC symptoms. As noted before, previous factor analysis studies based their work on the assumption that the YBOCS-CL is a comprehensive checklist of OC symptomatology rendering responses of continuous (or ordinal) nature (i.e. absent, present, principal or prominent). In contrast, the responses of the participants to the YBOCS-CL in this project were categorical and binary (present / absent). In other words, the OC symptoms were defined as binary '0; 1' - indicator measurements and therefore it was possible to display any combination of symptoms as a string of zeroes and ones. A 'zero' represented symptom absence and a 'one' the presence of a particular OC symptom. With this data collection, distinction was not made between symptoms considered "primary / principal" and "present" as was the case in some previous studies.

The presence/absence of tics (current and/or past, motor/vocal) was clinically assessed.

When an adequate trial of pharmacotherapy with a serotonin reuptake inhibitor (SRI) (i.e. at least 10 weeks on the medication with a minimum of 6 weeks on mid-range dose) or cognitive-behavioural therapy (CBT) (i.e. 8 or more sessions with an expert OCD/CBT psychotherapist) had been undertaken, responsivity to pharmacotherapy / psychotherapy

was assessed using the global improvement item of the Clinical Global Impression (CGI) scale (Guy, 1976).

The self-report Childhood Trauma Questionnaire (CTQ) was used to assess the nature and severity of possible childhood interpersonal trauma in the patients (Bernstein *et al.*, 1994). Sub-scales of the CTQ include measures of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Reliability and validity of the CTQ have been well researched and the scale appears to provide a useful measure of childhood trauma (Bernstein *et al.*, 1997).

The self-report Temperament and Character Inventory (TCI) (Cloninger *et al.*, 1994) was also used to measure behaviours associated with seven personality dimensions, namely novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence.

DNA extracted from venous blood (10-30 ml) in a Caucasian subset of OCD patients (N=204), was genotyped to look for polymorphisms in genes involved in monoamine function, and previously hypothesized to be relevant to OCD. The following (7) polymorphisms were examined: a 48 base pair (bp) variable number of tandem repeats (VNTR) in the third exon of dopamine receptor type 4 (*DRD4*) (Lichter *et al.*, 1993), a 40bp VNTR in the 3' untranslated region of the dopamine transporter (*DAT*) (Vandenbergh *et al.*, 1992), a 44bp insertion/deletion polymorphism in the promoter region of the serotonin transporter (*5-HTTLPR*) (Heils *et al.*, 1996) and restriction fragment length polymorphisms in the $5HT_{1D\beta}$ (*G861C*) (Sidenberg *et al.*, 1993), the serotonin receptor type 2A ($5HT_{2A}$) (*T102C*) (Warren *et al.*, 1993), tyrosine hydroxylase (*TH*) (Val81Met) (Ishiguro *et al.*, 1998), *COMT* (Val58Met) (Karayiorgou *et al.*, 1997) and *MAO-A* (*C1460T/EcoR*V) (Hotamisligil and

Breakefield, 1991) genes. Target genomic fragments, containing these polymorphisms, were amplified by means of the polymerase chain reaction (PCR) using published primer sequences and protocols (*5HT$_{1D\beta}$* (Hemmings *et al.*, 2003); *5HT$_{2A}$ T102C* (Warren *et al.*, 1993); *DAT* VNTR (Vandenbergh *et al.*, 1992) and *DRD4* VNTR (Lichter *et al.*, 1993)).

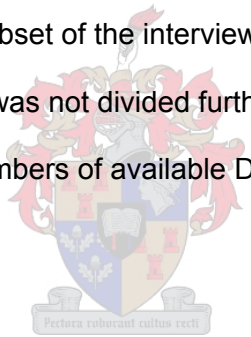
5.2.2 Cluster analysis of the YBOCS-CL items

Another *type* of cluster analysis (i.e. Ward's method – also appropriate for use with binary data (Ward, 1963)) of the nine most frequently occurring OC symptoms was implemented to compare these findings with the LCA-data. This particular analysis classified *variables* (current OC symptoms) compared to the previous attempt where OCD *cases* were classified (Chapter 4). Subsequently, all of the 45 YBOCS-CL items, each representing a single obsessive or compulsive symptom, were included in the cluster analysis to determine whether one could identify clearly discernable OCD subgroups or symptom subtypes based on this much larger set of indicators.

5.2.3 Data analysis

Selected YBOCS-CL items, each representing a current and single obsessive or compulsive symptom, were used for the cluster analyses. Selection of items followed the example of previous factor analytic studies (e.g. Baer, 1994; Summerfeldt *et al.*, 1999), where only ratings of *current* symptoms (i.e. present=1, or absent=0, with ratings of "past" symptoms=2 converted to "absent"=0) were included in the cluster analysis, since inaccuracies or bias in participants' recall of non-current symptoms may have influenced results. The YBOCS-CL also contains a number of 'other' and 'miscellaneous' OCD symptoms, which were excluded. (For detailed reasoning behind exclusions, please refer to Chapter 4).

For each respondent, cluster scores were obtained by the calculation of the mean scores for each cluster. The associations of the identified clusters of OC symptoms with demographic variables (age, gender), clinical variables (age of onset, OC symptom severity, level of insight, temperament, childhood trauma, treatment response) and genotypes were examined. An association study between OCD clusters and the selected polymorphisms was performed using the cluster scores as quantitative phenotypes. The association analyses were performed using Spearman correlations, one-way analysis of variance (ANOVA) and Mann-Whitney U-tests, as appropriate. Since the probability plots showed that the residuals were not normally distributed, and in some cases, the presence of heteroscedasticity, non-parametric tests were used to investigate the associations among the patient cluster scores and the selected variables. The present genetic investigations were conducted using a Caucasian subset of the interviewed OCD patients (N=204, males: N=107, females: N=97). This subset was not divided further (into e.g. Afrikaners / non-Afrikaners) given the relatively low numbers of available DNA-samples of OCD patients for genetic analyses.



5.3 Results

5.3.1 Cluster analysis of the *nine* most prevalent OC symptoms

At the 1.0 linkage distance level, cluster analysis of the nine most frequently occurring OC symptoms (YBOCS-CL items) obtained three clusters (Figure 1):

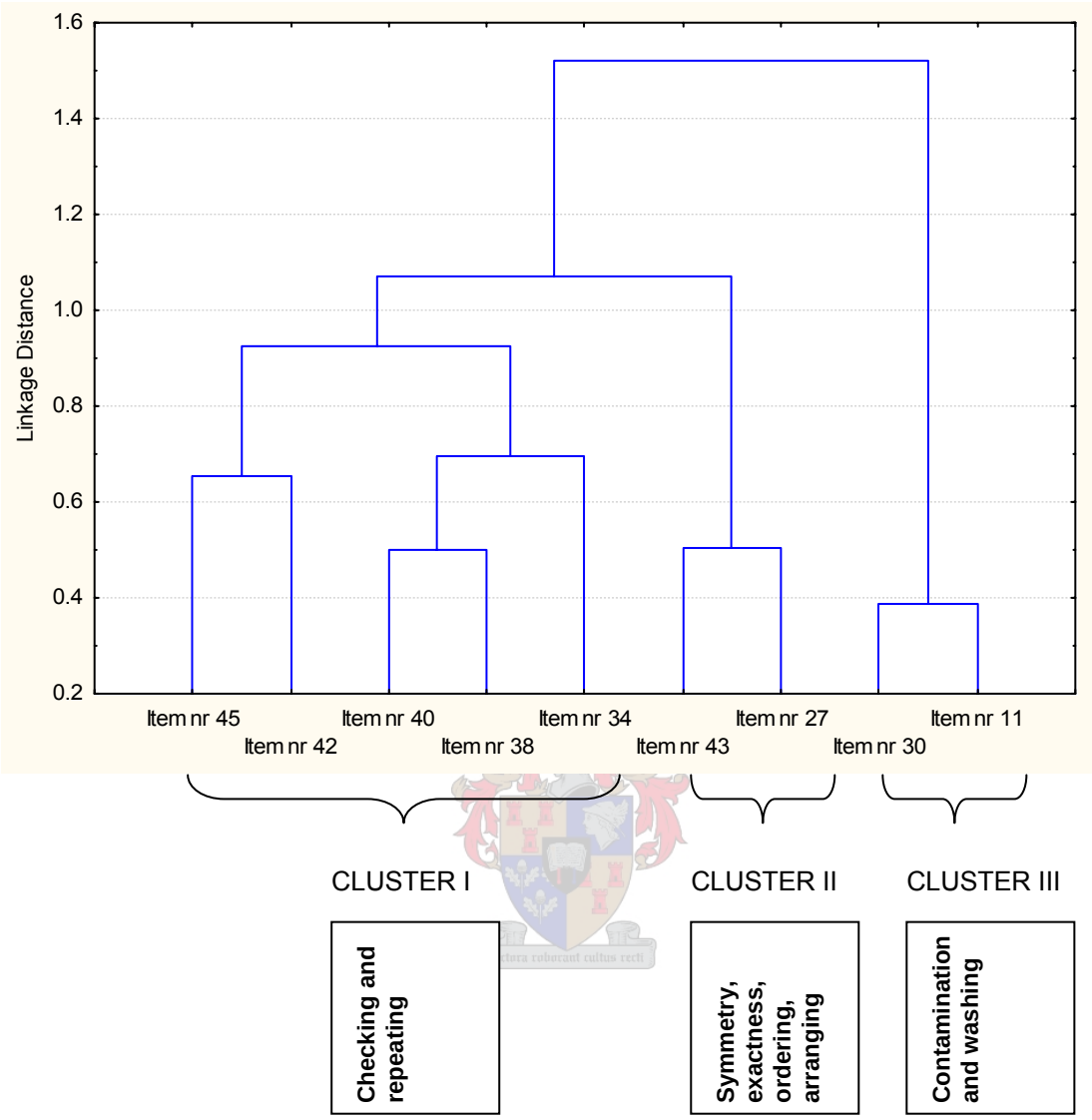
1.) Cluster I, subsequently termed “Checking and repeating”, included mental compulsions, counting, re-reading / re-writing, checking for mistakes, and checking locks, stove, appliances, etc.

2.) Based on the content of the two symptoms included in Cluster II, it was subsequently termed “Symmetry, exactness, ordering, arranging”.

3.) Cluster III also included two symptoms and based on their content was subsequently termed “Contamination and washing”.

(Figure 1 follows on the next page.)

FIGURE 1. **Cluster analysis (Ward's method) results: Tree Diagram for nine YBOCS-CL items***



CLUSTERS	YBOCS-CL item number	Item description*
I	45	Mental compulsions
	42	Counting compulsions
	40	Re-reading or re-writing
	38	Checking that did not make a mistake
	34	Checking locks, stove, appliances, etc.
II	43	Ordering / arranging compulsions
	27	Need for symmetry or exactness not accompanied by magical thinking
III	30	Excessive or ritualised hand washing
	11	Concern with dirt or germs

5.3.2 Cluster analysis of *45* YBOCS-CL items (OC symptoms)

Given the ease with which this programme managed to cluster the 9 indicators / items, it was decided to proceed with cluster analysis (Ward's Method, using the Statistica computer software package) of all of the 45 selected YBOCS-CL items. (The way in which these items were selected was described in detail in Chapters 3 and 4.)

At the 1.5 linkage distance level, cluster analysis of these 45 OC symptoms included in the YBOCS-CL rendered 6 clusters (Figure 2):

1.) Cluster I was termed "Contamination fears / washing", and included items referring to contamination or related fears or cleaning / washing rituals.

2.) Cluster II was termed "Hoarding / collecting", including both hoarding / collecting items of the YBOCS-CL.

3.) Cluster III included two "strands" of symptoms; firstly, symptoms related to obsessions with symmetry and order as well as ordering and arranging compulsions, and secondly, a number of "repetitive rituals", including mental compulsions (e.g. reviewing conversations), counting, 'repeating' compulsions (e.g. opening and closing the door, or getting up and sitting down repeatedly), re-reading / re-writing and checking (doors, locks, appliances, for mistakes, etc.). This cluster was subsequently termed "Symmetry / ordering / counting / arranging / repeating".

4.) Cluster IV was termed "Sexual" and included all of the YBOCS-CL sexually-related obsessive-compulsive symptoms (including 'forbidden or perverse sexual thoughts / images / impulses', and 'sexual behaviour towards others (aggressive)'.

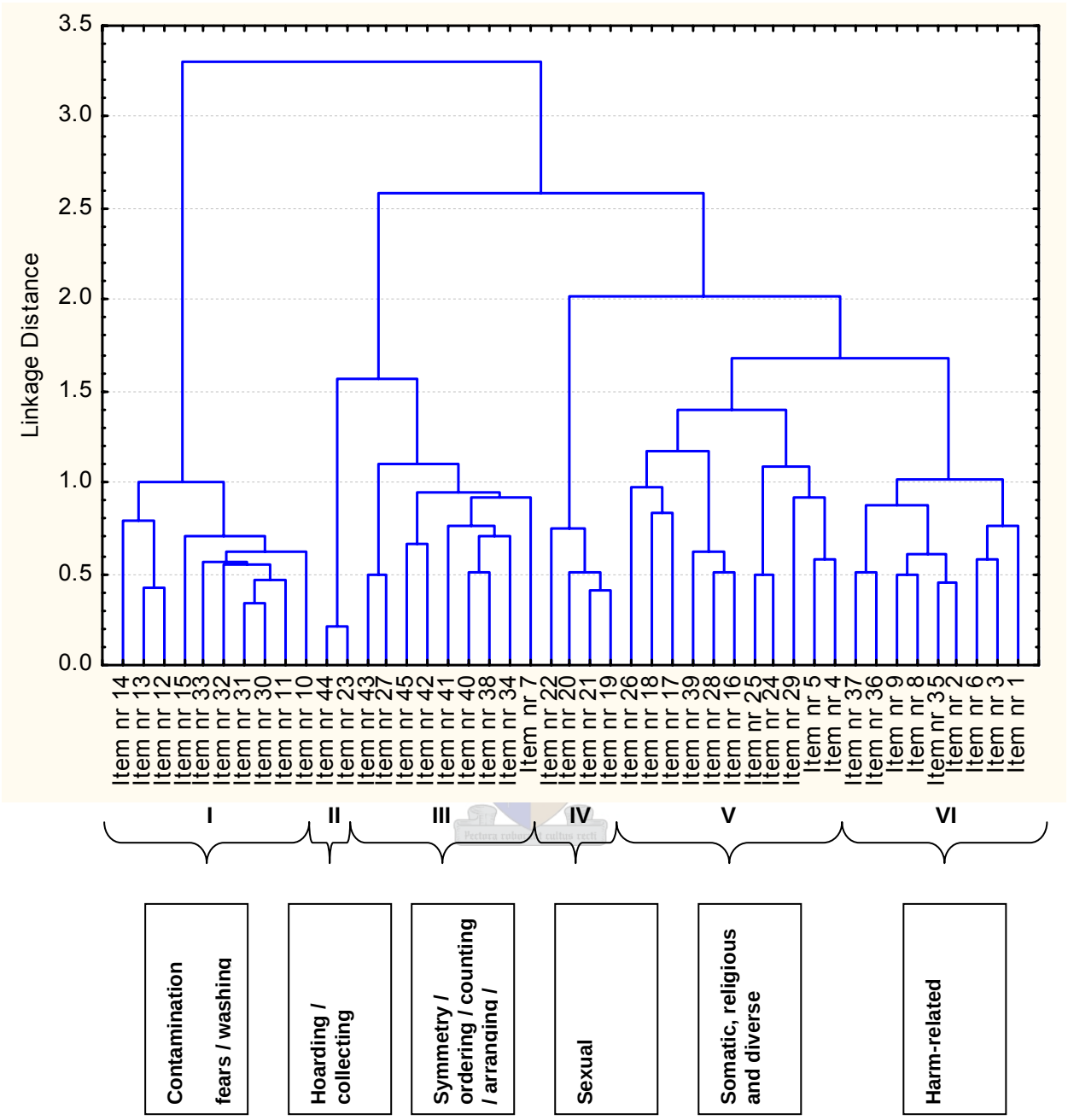
5.) Cluster V was termed "Somatic, religious and diverse" given the inclusion of a number of body-focused as well as religion-based symptoms together with a varying, apparently non-related, array of other obsessive-compulsive symptoms in this cluster. For example, in addition to concerns focused on bodily appearance or health (e.g. body dysmorphic fears, fears of illness / disease, fears of getting others

ill) and related (e.g. checking appearance) compulsions, other symptoms such as an obsessive fear of acting embarrassingly, and an obsession with symmetry and order accompanied by magical thinking, were also included in Cluster V.

6.) Cluster VI included most of the *aggressive or harm-related* obsessions and related compulsions of the YBOCS-CL (e.g. 'fear will harm self' and 'fear will harm others') and was subsequently termed "Harm-related".

(Figure 2 follows on the next page.)

FIGURE 2. Cluster analysis results: Tree Diagram for 45 YBOCS-CL items



CLUSTERS	YBOCS-CL item number	Item description*
CLUSTER I: Contamination fears / washing	14	Excessive concern with animals (e.g. insects)
	13	Excessive concern with household items (e.g. cleaners, solvents)
	12	Excessive concern with environmental contaminants (e.g. asbestos, radiation, toxic waste)
	15	Bothered by sticky substances or residues
	33	Other measures (than those in item 32) to prevent or remove contact with contaminants
	32	Compulsions involving cleaning of household items or other inanimate objects
	31	Excessive or ritualised showering, bathing, teeth brushing, grooming or toilet routine
	30	Excessive or ritualised handwashing
	11	Concern with dirt or germs
	10	Concerns or disgust with bodily waste or secretion (e.g. urine, faeces and saliva)
CLUSTER II: Hoarding / collecting	44	Hoarding / Collecting compulsions
	23	Hoarding / Saving obsessions
CLUSTER III: Symmetry / ordering / counting / arranging / checking / repeating	43	Ordering / Arranging compulsions
	27	Obsession with need for symmetry or exactness - Not accompanied by magical thinking
	45	Mental compulsions (e.g. special words, prayers, images, numbers repeated mentally or repeated in set manner to neutralise anxiety; mental reviewing e.g. reviewing of conversations)
	42	Counting compulsions
	41	Need to repeat routine activities (e.g. in / out door, up / down from chair, i.e. repeating rituals)
	40	Re-reading or re-writing
	38	Checking that I did not make a mistake
	34	Checking locks, stove, appliances, etc.
	7	Fear that I will steal things
CLUSTER IV: Sexual	22	(Obsession with) sexual behaviour toward others (aggressive)
	20	Content (of obsession) involves children or incest
	21	Content (of obsession) involves homosexuality
	19	Forbidden or perverse sexual thoughts / images / impulses
CLUSTER V: Somatic, religious and diverse	26	Obsession with need for symmetry or exactness - Accompanied by magical thinking (e.g. concerned that mother will have accident unless things are in the right place)
	18	No concern with consequences of contamination other than how it might feel
	17	Concerned that I will get others ill by spreading contamination (aggressive)
	39	Checking tied to somatic obsessions
	28	Concern with illness or disease
	16	Concerned that I will get ill because of contaminant
	25	Excessive concern with right / wrong, morality
	24	Concerned with sacrilege and blasphemy
	29	Excessive concern with a body part or an aspect of appearance (e.g. dysmorphophobia)
	5	Fear of doing something else embarrassing
	4	Fear of blurting out obscenities or insults
CLUSTER VI: Harm-related	37	Checking that nothing terrible did / will happen
	36	Checking that I did not / will not harm self
	9	Fear that I will be responsible for something else terrible happening (e.g. fire, burglary)
	8	Fear that I will harm others because of not being careful enough (e.g. hit/run MVA)
	35	Checking that I did not / will not harm others
	2	Fear that I might harm others
	6	Fear that I will act on unwanted impulses (e.g. to stab friend)
	3	Violent or horrific images
	1	Fear that I might harm myself

5.3.3 Clinical comparison data of the 6 identified clusters

The following significant results were found:

1.) Higher Cluster I-scores (i.e. “Contamination fears / washing”) were significantly associated with higher total OCD severity scores on the YBOCS-SS ($r = 0.29$; $p < 0.001$). An increase in Cluster I-scores was associated with comorbid specific phobia (Mann-Whitney U (MWU): $p = 0.01$), or anorexia nervosa (AN) (MWU: $p = 0.03$), and trichotillomania (TTM) (MWU: $p = 0.02$). Adult OCD patients (aged 18 years or older) with comorbid obsessive-compulsive personality disorder (OCPD) ($N = 100$; $p = 0.01$) or borderline personality disorder (BPD) ($N = 45$; $p = 0.01$) also presented with higher Cluster I-scores.

2.) Higher Cluster II-scores (i.e. “Hoarding / collecting”) were significantly associated with older age at the time of the interview ($r = 0.22$; $p < 0.001$). Significantly higher Cluster II-scores were found in patients with dysthymia (MWU: $p = 0.03$), generalized anxiety disorder (GAD) (MWU: $p = 0.01$), and hypochondriasis (MWU: $p = 0.01$). Adult OCD patients with comorbid OCPD ($N = 100$; $p < 0.001$) presented with higher Cluster II-scores.

3.) Higher Cluster III-scores (“Symmetry / ordering / counting / arranging / checking / repeating”) were significantly associated with younger age of OCD onset ($r = -0.15$; $p = 0.03$), and higher total OCD severity on the YBOCS-SS ($r = 0.30$; $p < 0.001$). OCD patients with higher Cluster III-scores showed lower cooperativeness on the TCI ($r = -0.23$; $p = 0.02$). Patients with any of the comorbid Axis I - disorders did not present with significantly higher Cluster III-scores or increased symmetry / ordering / counting / arranging / checking / repeating symptoms. In terms of personality disorders, patients with OCPD ($N = 100$; $p < 0.001$) or BPD ($N = 45$; $p = 001$) presented with higher Cluster III-scores.

4.) Patients with higher Cluster IV-scores ("Sexual") were significantly younger at the time of the interview ($r = -0.16$; $p = 0.01$). Male patients had higher scores on this cluster (MWU: $p = 0.001$). Higher scorers showed an association with good insight (into the excessiveness or senselessness of OC symptoms) (MWU: $p = 0.04$). Comorbidity with hypersexual disorder (MWU: $p = 0.002$) or tics (MWU: $p = 0.002$) was associated with higher Cluster IV-scores.

5.) Higher Cluster V-scores ("Somatic, religious and diverse") were associated with younger age at the time of the interview ($r = -0.15$; $p = 0.01$) and younger age of onset of OCD ($r = -0.19$; $p = 0.004$). There was a significant association with higher total OCD severity scores on the YBOCS-SS ($r = 0.13$; $p = 0.03$). OCD patients had significantly higher Cluster V-scores when comorbid with social anxiety disorder (SAD) (MWU: $p = 0.02$); specific phobia (MWU: $p = 0.02$), GAD (MWU: $p = 0.003$), body dysmorphic disorder (BDD) (MWU: $p < 0.01$), self-injury (MWU: $p = 0.04$) and hypersexual disorder (MWU: $p = 0.02$) (both 'Impulse Control Disorders, Not Otherwise Specified' (ICD NOS) in DSM-IV), respectively. Comorbidity with BPD ($N = 45$; $p < 0.01$) was associated with higher Cluster V-scores.

6.) Higher Cluster VI-scores ("Harm-related") were associated with younger age at the time of the interview ($r = -0.20$; $p = 0.001$), and younger age of OCD onset ($r = -0.25$; $p < 0.001$). Significantly higher Cluster VI-scores were evident in OCD patients with comorbid BDD (MWU: $p < 0.05$), IED (MWU: $p < 0.01$), self-injury (MWU: $p < 0.01$), hypersexual disorder (MWU: $p = 0.03$), or BPD ($N = 45$; MWU: $p = 0.001$).

None of the identified clusters were significantly associated with either treatment response (medication or CBT), scores on the CTQ dimensions of emotional / physical / sexual abuse or emotional / physical neglect specifically, or with scores on the TCI temperament dimensions of novelty seeking, harm avoidance, or reward dependence.

Most of the cluster scores of the different identified symptom clusters were highly correlated with one another (Table 1); in other words, an increase in, for example, Cluster VI-symptoms would suggest increased presentation of symptoms included in Clusters I to V. The highest correlations (i.e. r > 0.45) were found between Clusters V and VI (r = 0.0489) and Cluster V and I (r = 0.454). Cluster III were moderately correlated with Clusters I (r = 0.291), VI (r = 0.271), and II (r = 0.261), respectively. Lowest correlated (although still significantly) were Clusters I and VI (r = 0.138).

TABLE 1. Correlations (Spearman) amongst Clusters I – VI

		CLUSTER I	CLUSTER II	CLUSTER III	CLUSTER IV	CLUSTER V	CLUSTER VI
CLUSTER I: Contamination fears / washing	Spearman r	1	0.045	0.291**	-0.002	0.454**	0.138*
	p-value	---	NS	0.000	NS	0.000	0.026
CLUSTER II: Hoarding / collecting	Spearman r	0.045	1	0.261**	-0.016	0.159**	0.175*
	p-value	NS	---	0.000	NS	0.01	0.005
CLUSTER III: Symmetry / ordering / counting / arranging / checking / repeating	Spearman r	0.291**	0.261**	1	-0.023	0.218**	0.271**
	p-value	0.000	0.000	---	NS	0.000	0.000
CLUSTER IV: Sexual	Spearman r	0.002	-0.016	-0.023	1	0.200**	0.205**
	p-value	NS	NS	NS	---	0.001	0.001
CLUSTER V: Somatic, religious and diverse	Spearman r	0.454**	0.159**	0.218**	0.200**	1	0.489**
	p-value	0.000	0.01	0.000	0.000	---	0.000
CLUSTER VI: Harm-related	Spearman r	0.138*	0.175*	0.271**	0.205**	0.489**	1
	p-value	0.026	0.005	0.000	0.001	0.000	---

**. Correlation is significant at the 0.01 level

*. Correlation is significant at the 0.05 level

5.3.4 Molecular analyses: OC clusters with selected polymorphisms

The significant results of the association analysis (ANOVA) performed on the seven (7) polymorphisms and six cluster scores distributions are summarized in Tables 2 and 3. One of the 7 polymorphisms that were studied showed a significant association with some of the symptom clusters. In the Caucasian subset of the total interviewed sample, patients carrying the *L/L* (*met/met*) genotype of the *COMT Val158Met* polymorphism scored significantly higher on Cluster IV ("Sexual") ($p < 0.001$), Cluster V ("Somatic, religious and diverse") ($p = 0.004$) and Cluster VI ("Harm-related") ($p = 0.018$) than those with the *H/H (val/val)* or *H/L (val/met)* genotypes, respectively (Table 2). Allelic comparisons were performed using the Mann-Whitney U-test (Table 3). There were significant differences in the Cluster IV-, V- and VI- mean scores for the alleles of *COMT* for OCD patients. Patients carrying the low activity *L (met)* alleles were found to score significantly higher on Cluster IV (mean: 0.14 ± 0.26), Cluster V (mean: 0.23 ± 0.20) and Cluster VI (mean: 0.29 ± 0.29) respectively, than those carrying the high activity *H* (*val*) alleles (in Cluster IV: mean: 0.08 ± 0.20; Mann-Whitney U-test, $Z = -2.017$; $p = 0.04$; in Cluster V: mean: 0.17 ± 0.16; Mann-Whitney U-test, $Z = -2.731$; $p = 0.006$; and in Cluster VI: mean: 0.22 ± 0.26; Mann-Whitney U-test, $Z = -2.151$; $p = 0.03$).

(Tables 2 and 3 follow on the next page.)

TABLE 2. Analysis of variance for the three *COMT* genotypes (Caucasians)

Clusters	Group 1: 35 *val/val*	Group 2: 93 *val/met*	Group 3: 36 *met/met*	F	*p* value
(I) Contamination fears / washing	0.33 ± 0.34	0.29 ± 0.29	0.27 ± 0.31	0.40	NS
(II) Hoarding / collecting	0.24 ± 0.41	0.26 ± 0.41	0.32 ± 0.45	0.33	NS
(III) Symmetry / ordering / counting / arranging / repeating	0.40 ± 0.28	0.44 ± 0.27	0.43 ± 0.25	0.33	NS
(IV) Sexual*	0.11 ± 0.23	0.06 ± 0.17	0.24 ± 0.32	8.95	**<0.001**
(V) Somatic, religious and diverse**	0.15 ± 0.16	0.19 ± 0.17	0.29 ± 0.22	5.62	**0.004**
(VI) Harm-related***	0.21 ± 0.25	0.23 ± 0.26	0.37 ± 0.31	4.14	**0.018**

* Cluster IV: Group 1 vs 3: p = 0.032; group 2 vs group 3: p < 0.001

** Cluster V: Group 1 vs 3: p = 0.005; group 2 vs 3: p = 0.03

*** Cluster VI: Group 1 vs 3: p = 0.04; group 2 vs 3: p = 0.03

TABLE 3. Mann-Whitney U-test for alleles of the *COMT Val158Met* polymorphism

Clusters	*H (val) allele*	*L (met) allele*	Z-adjusted	*p*-level	N group H	N group L
(I) Contamination fears / washing	0.31 ± 0.31	0.28 ± 0.30	-0.697	0.49	163	165
(II) Hoarding / collecting	0.25 ± 0.41	0.29 ± 0.43	-0.690	0.49	163	165
(III) Symmetry / ordering / counting / arranging / repeating	0.42 ± 0.27	0.44 ± 0.26	-0.474	0.64	163	165
(IV) Sexual	0.08 ± 0.20	0.14 ± 0.26	-2.017	**0.04**	163	165
(V) Somatic, religious and diverse	0.17 ± 0.16	0.23 ± 0.20	-2.731	**0.006**	163	165
(VI) Harm-related	0.22 ± 0.26	0.29 ± 0.29	-2.151	**0.03**	163	165

5.4 Discussion

The cluster analysis of the nine most frequently reported OC symptoms in a sample of 261 OCD patients rendered a 3-cluster solution. This OCD symptom dimension solution was consistent with most findings from previous factor analysis (FA) studies (e.g. Leckman *et al.*, 1997), but differed to an extent from the OC symptom profile of the six clusters of cases that were identified with LCA (see Chapter 4). This is reasonable given that in the current chapter, cluster analyses of current OC *symptoms* (i.e. variables) were done compared to the previous investigation where OCD *cases* were categorized or grouped according to their symptoms, i.e. the one method carved out the specific OC symptoms from one another, the other method rendered groups in which patients had multiple OC symptoms.

The three clusters or symptom dimensions identified here comprised checking, obsessions with symmetry / exactness / ordering and arranging, as well as obsessive contamination fears and related compulsions – perhaps also a more useful or "neat" classification than the six cluster of cases solution rendered by the LCA of nine OC symptoms. The comparability of the cluster analysis of the nine OC symptoms compared to previous classification attempts (and also the omission of other important OC symptoms such as hoarding) encouraged subsequent cluster analyses of the 45 selected items of the YBOCS-CL.

Cluster analysis of the 45 selected items of the YBOCS-CL in this sample of OCD patients identified 6 separate clusters at the 1.5 linkage distance level. These clusters were labelled as follows:

I) "Contamination fears / washing";

II) "Hoarding / collecting";

III) "Symmetry / ordering / counting / arranging / checking / repeating";

IV) "Sexual";

V) "Somatic, religious and diverse" and

VI) "Harm-related".

A number of demographic and clinical features defined each cluster and will subsequently be discussed. In terms of genetics, the *L/L* (*met/met*) genotype of the *COMT Val158Met* polymorphism was associated with increased sexual, somatic, religious and diverse, and harm-related symptoms of OCD.

5.4.1 CLUSTER I: The *CONTAMINATION FEARS / WASHING* cluster

The cluster labelled "Contamination fears and washing" has emerged as a separate symptom cluster in all previous factor analysis studies. In this study, patients with increased Cluster I-symptomatology had significantly higher YBOCS-SS total severity scores. Subsequently, it may be argued that these OC symptoms (related to contamination / washing) reflect a more severe form or subtype of OCD. On the other hand, given the relatively high number of patients presenting with this symptom profile, this association may have been inflated artificially given the increased statistical power. The findings also suggest that OCD patients with comorbid specific phobia(-s), AN or TTM had more Cluster I - symptoms compared to those without these comorbid disorders. The significant phenomenological overlap between the symptoms of OCD and AN, and the frequent comorbidity of the two conditions, have been described in many studies (e.g. Fahy *et al.*, 1993; Hsu *et al.*, 1993). Similarly, existing comorbidity data have suggested some overlap between TTM and OCD (Stein *et al.*, 1995). However, whether patients with TTM and OCD present with increased Cluster I-symptoms in particular needs further investigation. The relationship with specific phobia, AN, TTM, OCPD, BPD and higher severity scores may suggest that these may all be severity related rather than related to the specific OC symptomatology characterizing Cluster I.

5.4.2 CLUSTER II: The *HOARDING / COLLECTING* cluster

Similar to most of the previous factor analysis studies, this study also rendered a separate hoarding / collecting symptom dimension. Hoarding may be defined as the acquisition of and failure to discard possessions of little use or value to others (Frost and Gross, 1993). Clinically significant hoarding results in living spaces being sufficiently cluttered as to preclude normal use and activities, and creates considerable distress or impairment in functioning (Frost and Hartl, 1996). Furthermore, hoarding may represent an important clinical subtype with different pathophysiology or neuroanatomy in patients with OCD (Damecour and Charron, 1998; Fontenelle *et al.*, 2004; Frost and Gross, 1993; Stein *et al.*, 1999; Winsberg *et al.*, 1999). Similar to previous studies, our findings suggested that patients with OCD who hoard obsessively are older than OCD patients who do not hoard (Frost *et al.*, 2000; Saxena *et al.*, 2002). The finding of an association between a number of Axis I-conditions (including mood and anxiety disorders (such as dysthymia and GAD), as well as hypochondriasis is consistent with data suggesting that OCD patients with hoarding often present with significant anxiety and depression (Frost *et al.*, 2000; Baer, 1994; Samuels *et al.*, 2002). Hoarding may be a symptom of both OCD and OCPD; indeed, in this symptom cluster there was also a significant association with OCPD, a finding corresponding with epidemiological and genetic reports (Clifford *et al.*, 1984; Lensi *et al.*, 1996).

5.4.3 CLUSTER III: The *SYMMETRY / ORDERING / COUNTING / ARRANGING / CHECKING / REPEATING* cluster

The third symptom cluster showed increased symptoms relating to concerns with symmetry, ordering, counting, arranging, checking and repeating. While knowledge of the different symptom subtypes of OCD has been expanding much in recent years, relatively little attention has been given to this set of symptoms. Radomsky and Rachman (2004) have

recently commented that this neglect is surprising given epidemiological evidence that ordering and arranging is one of the more common OCD presentations (Rasmussen and Eisen, 1992; Sasson *et al.*, 1997). Surprisingly, the findings here did not show an association between increased Cluster III-symptomatology and the presence of comorbid Axis I-disorders. However, increased comorbidity with OCPD and BPD was noted.

5.4.4 CLUSTER IV: The *SEXUAL* cluster

Cluster IV consisted of symptoms such as 'forbidden or perverse sexual thoughts / images / impulses', '(aggressive) sexual behaviour towards others' and 'sexual obsessions involving children / incest'. It was found that males with OCD tend to report more of these types of symptoms compared to women. In addition to the sexual symptomatology characterizing this cluster, an association with younger age at the time of the interview and comorbidity with tics, or hypersexual disorder (HD) was also suggested. This is consistent with a number of studies; for example, sexual symptoms (Bogetto *et al.*, 1999; Lensi *et al.*, 1996) as well as comorbid tics (Bogetto *et al.*, 1999; Holzer *et al.*, 1994; Leckman *et al.*, 1994; Pauls *et al.*, 1995) have previously been found to be more common in OCD males. Also, there may arguably be an association between tics, male gender, early age of onset, and disruptive behaviour disorders in younger OCD patients (Geller *et al.*, 2001). Of relevance here, for example, is the finding that intrusive violent or sexual images and thoughts were more likely to be seen in OCD patients with tics (George *et al.*, 1993). The question may be raised whether the association between increased sexual symptomatology and the presence of comorbid tics can be explained by the known link between male gender and both these factors. In terms of comorbidity, OCD patients with comorbid HD presented with increased (violent) sexual obsessions and/or compulsions. The findings also suggested that higher scorers on Cluster IV had good insight in the excessiveness or senselessness of their OC symptoms. Although a few researchers have posited a relationship between type

of OCD symptom and level of insight (Damecour and Charron, 1998; Matsunaga *et al.*, 2002), the available data on the association between insight and symptom subtypes are relatively limited and should be investigated further.

5.4.5 CLUSTER V: The *SOMATIC, RELIGIOUS AND DIVERSE* cluster

Cluster V, characterized by somatic, religious and diverse symptomatology, did not occur as an independent factor in previous factor analysis studies. However, most of the items included in this cluster had a "somatic" or "health-related" focus, which is consistent with the high incidence of these symptoms reported in epidemiological studies. Indeed, it has been suggested that 34% of OCD patients present with obsessions concerning bodily (somatic) symptoms (Rasmussen and Tsuang, 1986). As noted previously, OCD patients often have somatic concerns (Simeon *et al.*, 1995), including excessive or unfounded concerns about body defects, imagined defects in appearance, or concerns about illness (i.e. somatic obsessions / related compulsions). Increased comorbidity with BDD was therefore not surprising. The present findings did not, however, suggest an association between Cluster V - symptomatology and hypochondriasis. The findings did nevertheless suggest an association between increased somatic symptoms and GAD. Similarly, other studies have found a higher prevalence of GAD among OCD patients with health concerns (Abramowitz *et al.*, 1999). This is consistent with the findings (Starcevic *et al.*, 1992) that patients with GAD exhibit a high rate of hypochondriacal or illness-related symptoms. In addition, patients presenting with these types of symptoms were younger at the time of the interview and also reported a younger age of onset of OCD. Previous reports have suggested that OCD patients with early age of onset were characterized by increased severity of OC symptoms at baseline (Fontenelle *et al.*, 2003). Subsequently it may be argued that the link between Cluster V and increased OCD severity scores may be explained by the association with early onset or possibly with the specific symptomatology characteristic of Cluster V.

Also, the relationship with BDD, GAD, HD, self-injury, specific phobia, social anxiety disorder and BPD, and higher severity scores may suggest that these may all be severity related reather than related to the specific OC symptomatology characterizing Cluster V.

5.4.6 CLUSTER VI: The *HARM-RELATED* cluster

Cluster VI encompassed harm-related or aggressive fears and related compulsions. Patients that presented with increased harm-related fears and/or related compulsions in this study presented with OCD at an earlier age. The findings also suggest an association between this cluster and younger age at the time of the interview. Increased obsessional fear of violence or harm to the self / others with related rituals in patients with prominent Cluster I – symptomatology may provide explanations for the increased comorbidity of Cluster VI with BDD, IED and perhaps self-injury and BPD as well. All of these conditions involve a degree of *destructiveness*, whether aimed at the self or others.

5.4.7 Genetics findings

Genetic findings suggest that Caucasian patients carrying the *L/L* (*met/met*) genotype of the *COMT Val158Met* polymorphism had more sexual (Cluster IV -), somatic, religious and diverse (Cluster V -), and harm-related (Cluster VI -) symptomatology than those with the *H/H* or *H/L* genotype, respectively. Patients carrying the low activity *L (met)* alleles were found to score significantly higher on these clusters than those carrying the *H* (*val*) alleles. Here, a role for the dopaminergic system in the development of (some subtypes of) OCD has been suggested, given the involvement of *COMT* in the inactivation of catecholamines such as dopamine. Some previous studies of genes involved in monoaminergic neurotransmitter systems have also suggested an association between OCD and polymorphisms of *COMT* (Camarena *et al.*, 1998, 2002; Karayiorgou *et al.*, 1997, 1999). In particular, the low activity variant of the *COMT* gene has previously been associated with

OCD in males (Karayiorgou *et al.*, 1997). However, these findings have not been consistently replicated; for example, Alsobrook *et al.* (2002) observed a significant association of OCD with the *COMT L* allele in females, but not in males, while in a study of the Afrikaner population of South Africa, Niehaus *et al.* (2001) observed an association between the increased occurrence of OCD and the *H/L* genotype irrespective of gender. Whether *COMT* plays a role in the development of Cluster IV-symptomatology, or whether the link between *COMT (L alleles)* and increased Cluster IV-symptoms can be explained by the prominence of males with these symptoms, remains an important question. Focusing attention on the Karayiorgou - findings on *COMT* (Karayiorgou *et al*., 1997), it may be hypothesized that the dominance of males in Cluster IV may explain the link that was found between this cluster of symptoms with the low activity variant of *COMT.* Conversely, males and females did not differ with regards to the extent to which Cluster V-symptoms were presented, so that it may be argued that genetics, rather than gender, may have played a role in the nature of these symptoms.

Clearly, the existing data on genetics and specific OC symptom subtypes are limited. Existing data do however include findings such as those of Alsobrook *et al.* (1999), the first researchers to use the OC symptom dimensions in a family / genetic study. They have found that higher scores on their identified cluster characterized by aggressive / sexual / religious obsessions and related compulsions or factors characterized by symmetry / ordering were twice as likely to have first-degree family members with OCD compared to patients scoring low on these factors. Given the relatively varying nature of the symptoms characteristic of the identified Clusters IV, V and VI, it may be argued that the *COMT Val158Met* polymorphism is involved in the etiology of OCD in general (or perhaps of a significant number of symptom subtypes) rather than just with the development of a single specific OC symptom subtype. Furthermore, recent studies have shown that this functional

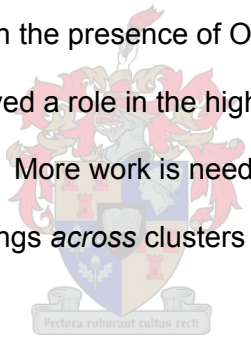
polymorphism may influence performance on tests of prefrontal cortex (PFC) (such as executive function and working memory) and prefrontal cortex physiologic activity (Callicott *et al.*, 2003; Diamond *et al.*, 2004; Egan *et al.*, 2001; Gallinat *et al.*, 2003; Goldberg *et al.*, 2003; Malhotra *et al.*, 2002; Mattay *et al.*, 2003). Interestingly, it has been suggested that symptoms of PFC dysfunction are characteristic of many psychiatric disorders such as OCD; for example, neuro-imaging studies have provided strong evidence that frontal-subcortical brain circuitry may mediate OCD symptomatology (Saxena *et al.*, 1998). Arguably, these findings support the involvement of the *COMT* genotype in specific cognitive dysfunctions, which in turn, may impact on the modulation of (some) OC symptoms. Clearly, the continued search for other vulnerability genes (and the possible interaction thereof with other factors such as cognitive load) for the development of specific OCD symptom subtypes should remain a priority.

As in Clusters I and II, this investigation did not find a relationship between Cluster III and the investigated dopaminergic (and serotonergic) polymorphisms, suggesting that variants in other genes in these systems should rather be explored.

5.5 Limitations and conclusions

In summary, in this study it was attempted to find *differential* associations in the identified clusters. However, in terms of the associations found between, for example, higher OCD severity scores and some of the identified symptom clusters (e.g. Clusters I), admittedly these may have been artefactual findings that have come up significant given the relative higher statistical power (due to higher N) in these clusters compared to others. Nevertheless, some of these associated factors may be of particular interest given existing or previously replicated data, e.g. early age of onset (characteristic of Clusters III, V and VI).

In addition, focusing on the comorbidity patterns of each of the clusters, it may be suggested that mood and anxiety comorbidity is lower in some clusters (e.g. Cluster III), while OCPD comorbidity is higher in others (e.g. Clusters I to III). However, again the argument could be raised that with large enough sample size, any cluster would be associated with significantly increased comorbidity (which in some respects may be indicative of severity). Furthermore, although there was significant phenomenological overlap between Cluster III – symptoms (i.e. symmetry / ordering / counting / arranging / checking / repeating) and OCPD, Clusters I, II and III have all shown increased comorbidity with OCPD, as was noted before. What this may suggest, is that comorbid OCPD is firstly highly prevalent in OCD in general (consistent with existing literature), but also that OCPD may be associated with specific OC symptoms such as symmetry or hoarding obsessions / compulsions. In addition, given the possible disability or impairment associated with the presence of OCPD, one may argue that comorbidity with OCPD may have played a role in the higher OCD severity scores associated with both Clusters I and III. More work is needed to explore these hypotheses. Clearly, analysis of the overlap in findings *across* clusters is indicated in addition to focusing on findings *within* clusters.



Briefly focusing on a cut-off or linkage distance level of 2.0 (rather than 1.5) in Figure 1 (illustrating our original cluster analysis results), *three* clusters - rather than six - remain. In this instance, Cluster I would remain separate, Clusters II and III, and Clusters IV, V and VI of the original cluster analysis would be grouped together into Cluster II and III, respectively. Using the 6-cluster labels (or combinations thereof), Cluster I would remain “Contamination fears / washing”, Cluster II would be labeled “Hoarding / symmetry / ordering / counting / arranging / checking / repeating” and “Sexual / somatic / religious / harm-related / diverse” would be an appropriate label for Cluster III. In fact, the significant OCPD comorbidity associated with increased Clusters II- and III- scores, and the association found between

the *L/L* (*met/met*) genotype of *COMT Val158Met* polymorphism and Clusters IV, V and VI of the 6-cluster solution, supports such a 3-cluster solution for the data. However, it may be argued that only *three* OC symptom clusters would not do justice to the heterogeneous phenomenology that is characteristic of OCD.

The limitations of the present data need to be addressed: Firstly, following the example of previous factor analysis studies, only 45 items of the YBOCS-CL were used in the cluster analysis. Ideally, this type of analysis should be performed on all reported symptoms without the restriction of an *a priori* limited pool of items. In addition, given the known and significant phenomenological overlap between OCD and the OC spectrum disorders (OCSD's), as well as the significant comorbidity with OCSD's in the clusters that were identified in this investigation, decisions about the inclusion of more of the symptoms characteristic of the putative OCSD's in OC symptoms checklists (e.g. the YBOCS-CL) need to be revisited. Furthermore, focus on *current* OC symptoms may be considered a limitation. However, it may be argued that the inaccuracies or bias in patients' recall of non-current (past) symptoms may influence results, as such justifying use of current symptoms in the analyses. In the same vein, it has been suggested that the results from data reduction techniques such as cluster or factor analysis using symptoms reported at a given time should be interpreted with caution given the fact that the majority of patients do not maintain their initial symptoms across time (Baer, 1994) and present with multiple types of symptoms (Calamari *et al.*, 1999; Khanna *et al.*, 1990; Leckman *et al.*, 1997). This was an exploratory study and we therefore did not correct for multiple testing. Subsequently, some of the significant associations may in fact have been artefactual or the result of error 1.

In conclusion, despite the limitations, the findings here have again substantiated the presence of clinical subtypes of OCD. In particular, a number of OCD symptom subtypes

has been identified and described in terms of their associated demographic, clinical and, in some cases, genetic features. These findings significantly overlap with published OCD subtyping data; for instance, the six clusters identified here, each with their typical OC symptom profile, were similar to the early factor analysis work presented by Leckman *et al.* (1997) (especially when the Clusters IV, V and VI identified here, are combined). The finding that all three of these symptom clusters were associated with the *L/L* (*met/met*) genotype of the *COMT Val158Met* polymorphism supports the combination of Clusters IV, V and VI. On the other hand, the associated features (e.g. comorbid disorders such as depression, high severity or poor insight) did not clearly or uniquely differentiate clusters from one another. In fact, there were many instances of overlap amongst clusters in this regard. However, some hints, e.g. lack of comorbidity in some clusters, or increased comorbidity with OCPD, may be worth following up in future. Furthermore, the clusters were highly correlated with one another; for example, the highest correlation found between Cluster V and VI suggesting significant overlap and arguably supporting combining these OC symptoms into one cluster, whereas others were correlated to a much lesser extent (e.g. Clusters I and VI) suggesting that these clusters should probably remain separate clusters. The high correlations amongst the different clusters nevertheless suggest that delineation of OCD into OC symptom clusters is not the best or only way to approach the heterogeneity characteristic of OCD. Nevertheless, our findings support the idea that subtyping OCD based on symptom structure is a useful approach given its potential to assist in efforts to advance the understanding of OCD and to identify more robust endophenotypes. Finally, the different possible OCD subtypes have not been fully delineated yet, and more work remains to be done to fully understand the complex heterogeneity of OCD patients – especially in larger samples.

CHAPTER 6

CLUSTER ANALYSIS OF OBSESSIVE-COMPULSIVE SPECTRUM DISORDERS IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER

Abstract

While the majority of patients with obsessive-compulsive disorder (OCD) suffer from at least one comorbid obsessive-compulsive spectrum disorder (OCSD) in their lifetime, there has been relatively little systematic investigation of the structure and implications of such comorbidity. Nevertheless, published data as well as Chapter 5 of this dissertation have suggested that OC symptom clusters may be associated with comorbidity with some of the OCSD's. Subsequently, it has been suggested that comorbidity with certain OCSD's in OCD may also serve to define important OCD subtypes, characterized by differing phenomenology and neurobiological mechanisms. In this chapter, existing literature on the comorbidity of OCD with different putative OCSD's was reviewed. In addition, a cluster analysis of OCSD's in patients with OCD suggested that comorbid OCSD's in OCD fall into three different clusters (reward dependence, impulsivity, somatic), which are defined by different clinical features. None of these clusters was associated with any particular genetic variant. The *clusters* of conditions are partially consistent with previous theoretical approaches taken towards classifying the OCSD's. In conclusion, the lack of genetic validation of these clusters in the present study may indicate the involvement of other, as yet untested, genes. Further genetic and cluster analyses of comorbid OCSD's in OCD may ultimately contribute to a better delineation of OCD endophenotypes.

6.1 Introduction

Chapter 5 of this dissertation raised the question about the way that the putative obsessive-compulsive spectrum disorders (OCSD's) "fit" with the standard OC symptomatology outlined in the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL). Until now, this issue has not received that much attention in the literature. It is clear, however, that the OCSD symptoms have significant phenomenological and neurobiological overlap with the features of obsessive-compulsive disorder (OCD) and should arguably therefore be considered for inclusion in attempts to identify a comprehensive and multidimensional model for OC symptom subtypes. As was suggested before, the *expansion* of the OCD symptom checklists such as the YBOCS-CL is on the cards. At this stage, the YBOCS-CL contains very few items that can be labelled as "OC spectrum symptoms", suggesting the need for an incorporation of the other possible spectrum items from a different scale specifically assessing the OCSD's, such as the SCID-OCSD (Du Toit *et al.*, 2001), into the YBOCS-CL. On the other hand, arguably the YBOCS-CL measures one *entity*, and the SCID-OCSD another, suggesting that the items should not be combined for classification purposes.

Comorbidity data (see Chapter 5) nevertheless suggest that OCSD's in OCD cannot be ignored. In fact, comorbidity of certain OCSD's in OCD may serve to define important OCD subtypes, characterized by differing phenomenology and neurobiological mechanisms. For example, patients with comorbid OCD and Tourette's disorder (TD) appear to be characterized by specific demographic features (they are more likely to be male) and clinical characteristics (they are less likely to respond to SSRI's) (McDougle *et al.*, 1993). While the majority of OCD patients suffer from at least one comorbid OCSD (Du Toit *et al.*, 2001), there has been relatively little systematic investigation of the structure and implications of such comorbidity. One approach may be to focus on the different dimensions of the OCD

spectrum, which perhaps correspond to differential involvement of various neurochemical systems and neuroanatomical circuits (McElroy *et al.*, 1994; Van Ameringen *et al.*, 2001). Indeed, while most of the literature focuses on the dimensional relationships across OCD and different OCSD's, the current chapter will focus on the comorbidity of OCSD's in OCD. It will be argued that a consideration of such comorbidity may well contribute to delineating the heterogeneity of OCD.

In this study it was aimed to delineate OCD subtypes using cluster analysis of OCSD's in patients with OCD. The association of these identified clusters with demographic variables (age, gender), clinical variables (age of onset, obsessive-compulsive symptom severity and dimensions, level of insight, temperament/character, treatment response) and monoaminergic genotypes was investigated.

6.2 Methods

6.2.1 Subjects and interview

This investigation made use of the SCID-OCSD (Du Toit *et al.*, 2001) to assess putative OCSD's. Complete SCID-OCSD data were recorded for a subset of the interviewed sample of 261 patients; i.e. SCID-OCSD data from two hundred and ten adult patients with OCD (N=210: 102 male; 108 female), with ages ranging between 18 and 75 years (35.7 ± 13.3) were included in the analyses. For a detailed description of the recruitment and interviewing procedures, please refer to Chapter 2.

6.2.2 Genotyping

DNA was extracted from venous blood (10-30 ml) in a Caucasian subset of OCD patients (N=171) and controls (N=168), including patients (N=77) and controls (N=144) from the genetically homogeneous Afrikaner population, and was genotyped for polymorphisms in genes involved in monoamine function, which had previously been hypothesized to be relevant to OCD (Hemmings *et al.*, 2003). (Please refer to Chapter 2 for more information on the the genotyping protocols and the polymorphisms that were investigated.)

6.2.3 Data analysis

Firstly, as the items of the SCID-OCSD were binary (present / absent), a cluster analysis (Ward's method), appropriate for use with binary data (Ward, 1963), was performed on the items (lifetime) of the SCID-OCSD for all OCD patients. OCSD's were selected on the basis of previous literature and comprised TD, pathological gambling, hypersexual disorder, kleptomania, compulsive shopping, trichotillomania (TTM), intermittent explosive disorder (IED), eating disorders (including bulimia and anorexia nervosa), self-injury (i.e. impulse control disorder not otherwise specified), body dysmorphic disorder (BDD) and hypochondriasis. For each respondent cluster scores were obtained by calculation of the mean score for each cluster. The associations of cluster scores with demographic variables (age, gender), clinical variables (age of onset, obsessive-compulsive symptom severity and dimensions, level of insight, temperament, treatment response) and genotypes were then examined, using Pearson correlation coefficients and one-way analysis of variance (ANOVA), where appropriate. Since the normal probability plots showed that the residuals were not normally distributed, a non-parametric bootstrap ANOVA for multiple comparisons was used (Efron and Tibshirani, 1993).

6.3 Results

6.3.1 Cluster analysis

At the 1.1 linkage distance level, three clusters were obtained (Figure 1).

1.) Cluster I, subsequently named “Reward deficiency”, included TTM, pathological gambling, hypersexual disorder and TD.

2.) Cluster II, subsequently named “Impulsivity”, included compulsive shopping, kleptomania, eating disorders (including anorexia and bulimia nervosa), self-injury and IED disorder.

3.) Cluster III, subsequently named “Somatic”, included BDD and hypochondriasis.

6.3.2 Comparison data

The following significant results were found:

1.) Cluster I scores (i.e. “reward deficiency”) were significantly associated with earlier onset of OCD ($r = -0.17$; $p = 0.02$), and the presence of tics ($t = -3.26$; $p = 0.001$). Cluster I scores were also significantly associated with harm-related ($r = 0.18$; $p = 0.01$) and sexual / religious obsessions and compulsions ($r = 0.21$, $p = 0.004$).

2.) Cluster II scores (i.e. “impulsivity”) were significantly associated with female gender ($t = -2.45$, $p = 0.02$), increased severity of OCD on the YBOCS ($r = 0.18$, $p = 0.01$), a history of childhood emotional abuse ($r = 0.22$, $p = 0.03$) and increased scores on the temperament trait of novelty seeking ($r = 0.35$, $p < 0.001$).

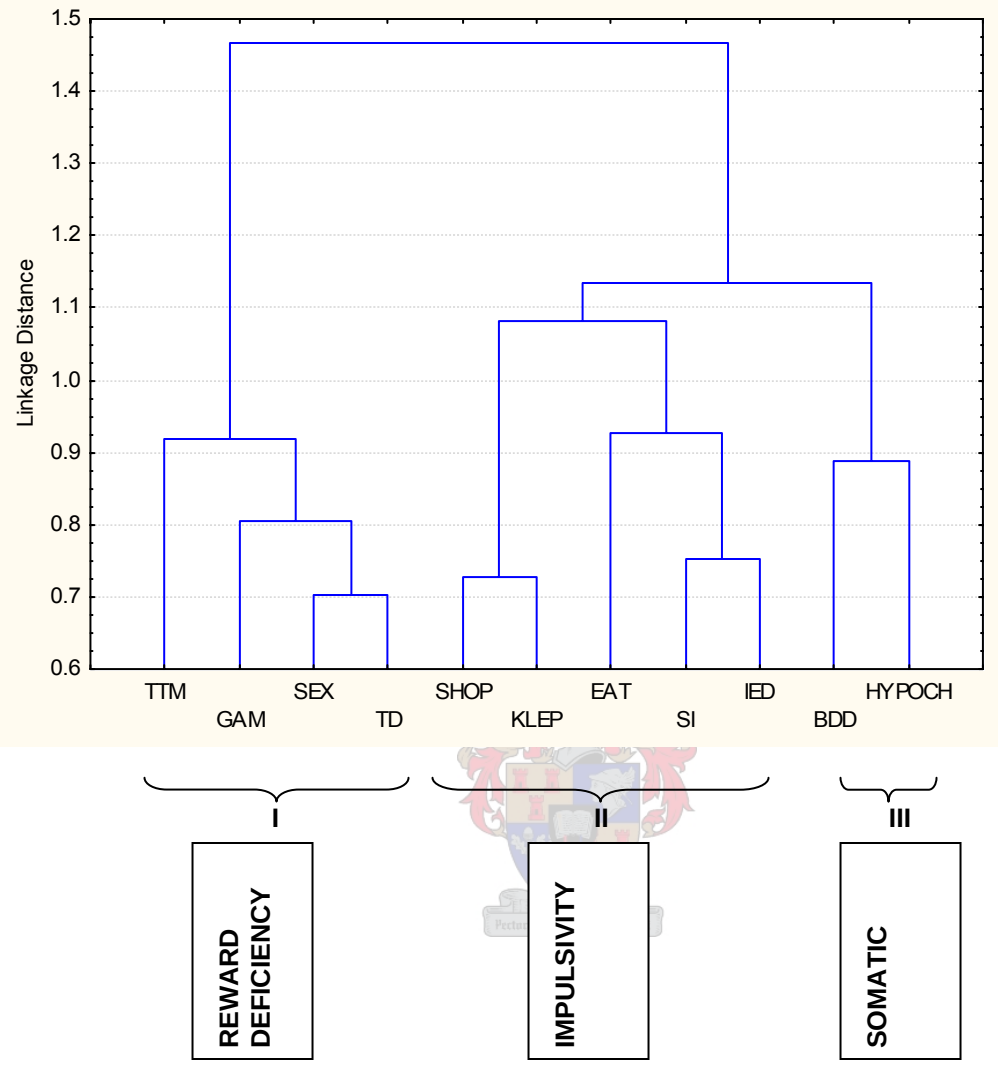
3.) Cluster III scores (i.e. “somatic”) were significantly associated with deficits in insight into the excessiveness or senselessness of obsessive-compulsive symptoms ($r = .22$; $p = 0.02$) and with somatic obsessions and compulsions ($r = 0.22$; $p = 0.002$).

The three identified clusters did not show significant associations with the other demographic and clinical variables (including treatment response) and there were no significant associations with the different genotypes.

(Figure 1 follows on the next page.)

.

FIGURE 1. Cluster analysis (Ward's method) results: Tree diagram



TTM = trichotillomania
GAM = pathological gambling
SEX = hypersexual disorder
TD = Tourette's disorder

SHOP = compulsive shopping
KLEP = kleptomania
EAT = eating disorders
SI = self-injury
IED = intermittent explosive disorder

BDD = body dysmorphic disorder
HYPOCH = hypochondriasis

6.4 Discussion

Cluster analysis of the OCSD's in this sample of OCD patients identified 3 separate clusters at the 1.1 linkage distance level. These clusters were labelled:

1) "Reward deficiency" (including TTM, pathological gambling, hypersexual disorder and TD),

2.) "Impulsivity" (including compulsive shopping, kleptomania, eating disorders, self-injury and IED) and

3.) "Somatic" (including BDD and hypochondriasis).

Each cluster was defined by different clinical features; none of these clusters were associated with any particular genetic variant.

6.4.1 The *REWARD DEFICIENCY* cluster

A substantial literature has documented the comorbidity between OCD and TD, and the finding that TTM, pathological gambling, and hypersexual disorder clustered together with TD is consistent with some previous evidence of comorbidity between these disorders. A number of authors have emphasized the involvement of the dopaminergic system in OCD patients with comorbid tics (McDougle *et al.*, 1994a; 1994b) and TD (Singer *et al.*, 1991). There is some evidence that pathological gambling (Hollander *et al.*, 2000), hypersexual disorder (Bergh *et al.*, 1997; Hollander *et al.*, 2000; Seedat *et al.*, 2000) and TTM (Stein and Hollander, 1992) (all clustered together with TD in Cluster I) may also be mediated by a dysfunctional dopaminergic system. Indeed Blum and colleagues (2000) have argued that a number of OCSD's is characterized by reward deficiency, pleasure seeking behaviour, and dopaminergic deficits – hence the use of the term "reward deficiency" to describe the cluster.

6.4.1.i Phenomenology

TD is characterized by motor and one or more verbal tics (described as sudden rapid repetitive non-rhythmic movements, gestures or utterances) beginning before the age of 18 years (APA, 1994), the performance of which is associated with a reduction in tension or relief. Similarly, the symptoms of TTM, hypersexual disorder (e.g. the excessive preoccupation with non-paraphilic sexually arousing fantasies, urges, or excessive sexual behaviours over time) and pathological gambling may also be seen as involving attempts at achieving gratification or reward.

Furthermore, the incidence of tics and tic disorders in OCD is high (37 – 59%) (Leonard *et al.*, 1992; Pitman *et al.*, 1987). Patients with a primary diagnosis of TD also often report OCD and OC symptoms (12 – 90%) (Como, 1995; Leckman *et al.*, 1994). Interestingly, tics share some phenomenological similarities with the compulsions of OCD (Como, 1995; Leckman *et al.*, 1994). On the other hand, tics may be distinguished from compulsions: In general, compulsions are typically quite complex and performed in response to an obsession or according to some rigidly applied rules. In contrast, although they may also be *complex*, tics are typically *less* complex than compulsions and not aimed at neutralizing the anxiety associated with the obsessions (APA, 1994).

There is a large body of evidence suggesting that OCD patients with tics and OCD patients without tics differ in a number of ways, with differences observed in the phenomenology, symptom profile, age of onset and gender ratio, and pharmacological treatment response (also see Chapter 1: Background) (Holzer *et al.*, 1994; Leckman *et al.*, 1994; McDougle *et al.*, 1993; Zohar *et al.*, 1997). For example, in a comparison of patients with OCD alone and patients with both OCD and TD (George *et al.*, 1993), the

former group (OCD alone) was more likely to have:

(1) contamination obsessions and compulsions,

(2) fear of not saying the right thing, and

(3) BDD,

while the latter group (OCD with TD) was more likely to have:

(1) an obsession with the need for symmetry accompanied by magical thinking,

(2) fear of doing something embarrassing or of blurting out an obscenity,

(3) intrusive violent or sexual images and thoughts,

(4) touching compulsions,

(5) blinking or staring rituals,

(6) self-injurious compulsions,

(7) hoarding, and

(8) counting.

Several other studies have found similar findings, e.g. adolescents with OCD and comorbid tics were more prone to aggressive and sexual images and obsessions than were adolescents without tics (Zohar *et al.*, 1997). In another study comparing adult OCD patients with those who had comorbid OCD and TD, findings differed somewhat from the previous, with obsessions involving *non*-violent images being significantly more common in the OCD/TD group; however, the rest of the findings of this study by Petter *et al.* (1998) overlaps significantly with others, i.e. excessive concern with appearance, need for symmetry, touching, blinking or staring, and counting compulsions in patients with OCD/TD.

Sensory phenomena may be another important phenotypic measure for grouping patients into an OCD-TD/tics subtype. Sensory phenomena include both bodily and

mental sensations: Bodily sensations refer to focal or generalized body sensations (usually tactile, muscular-skeletal/visceral, or both) occurring either before, or during, the patient's performance of the repetitive behaviours. Mental sensations on the other hand include urge only, energy release (i.e. mental energy build-up that needs to be discharged), incompleteness, and just-right perceptions. Evidence suggests that these bodily and mental sensations are more frequently found in patients with OCD and TD than in patients with OCD alone (Miguel *et al.*, 2000).

OCD patients with and without tics may also differ in terms of other clinical features. An OCD family study found that younger age of onset of OCD symptoms and possibly male gender in probands were associated with increased tic disorders in relatives (Leckman *et al.*, 2003). Similarly, an association of Cluster I scores was found with earlier onset OCD, as well as with harm-related and sexual / religious obsessions and compulsions, and these findings are consistent with previous data indicating that OCD with tics is characterized by early age of onset and by these symptom subtypes (Do Rosario-Campos *et al.*, 2001; Eichstedt and Arnold, 2001; Geller *et al.*, 1998; George *et al.*, 1993).

6.4.1.ii Neurobiology

Tic disorders tend to occur in a specific subgroup of OCD families, suggesting that presence of tic disorders is more likely to indicate a more familial OCD phenotype (Pauls *et al.*, 1995). Consistent with this hypothesis, family studies of OCD probands have revealed tics in at least 17% of adult patients and increased rates of tics in their first-degree relatives (Holzer *et al.*, 1994; Pauls *et al.*, 1995). Interestingly, it was suggested that tics are more useful than obsessions or compulsions in distinguishing relatives of

patients with OCD from relatives of control subjects.

In addition to genetic or familial transmission, OCD with comorbid tics may also both be seen after neuroimmunological insult. Regional cerebral blood flow patterns in individuals with OC behaviour in TD families are comparable to their relatives with TD, and differ from individuals with primary OCD, but with no family history of tic disorders (Moriarty *et al.*, 1997). This finding further supports the hypothesis that at least some forms of OCD are genetically related to TD.

Additional data supporting the existence of an OCD-TD/tic subtype focus on treatment response. However, despite evidence that treatment response differs between OCD patients with tics *versus* OCD patients without tics, there are inconsistencies in treatment data. A retrospective, case-controlled analysis by McDougle *et al.* (1993) found that the SSRI, fluvoxamine, alone was less effective in OCD patients with tics than in patients without tics. In a continuation of this study, the researchers (McDougle *et al.*, 1994a) found that treatment-refractory OCD patients with comorbid tic disorders (including TD) responded to haloperidol (a dopamine blocker) augmentation of fluvoxamine, whereas this strategy was of little benefit for patients without tics. Other studies have also suggested that augmentation of SRI's with dopamine blockers may be useful in treatment-refractory OCD (Mohr *et al.*, 2002).

The release of dopamine in the ventral striatum (nucleus accumbens) plays a crucial role in reward processing (Blum *et al.*, 2000), and dysfunction in such reward processing may be characteristic of the conditions included in this cluster of comorbid OCSD's. It can be speculated that the gratification / release symptoms that characterize this cluster of

disorders are mediated by dopaminergic dysfunction in ventral striatal circuits.

6.4.2 The *IMPULSIVITY* cluster

The second identified cluster included compulsive shopping, kleptomania, eating disorders, self-injury and IED, and as these conditions are associated with impaired impulse control, Cluster II was termed “impulsivity”. Comorbidity of impulse control disorders in OCD is consistent with previous work noting that many patients with OCD manifest impulsive behaviour or comorbid impulse control disorders (Hollander *et al.*, 1996; Hollander and Rosen, 2000; Manchanda *et al.*, 1979; McElroy *et al.*, 1994; Millar, 1983; Stein and Hollander, 1993a, 1993b; Stein *et al.*, 1994; Thornton and Russell, 1997; Winchel and Stanley, 1991).

The findings indicated that Cluster II was associated with increased novelty seeking, a temperament trait that is characterized by impulsivity and risk taking behaviour (Cloninger *et al.*, 1993). Indeed, although OCD has been associated with increased harm or risk avoidance, the role of impulsivity in OCD has received substantial theoretical and clinical interest (Oldham *et al.*, 1996). Much of this work has used aggressive and auto-aggressive (suicidal) behaviours as an index of impulsivity. For example, it has been suggested that at least a subset of OCD patients has difficulties controlling their anger (Hoehn-Saric and Barksdale, 1983; Manchanda *et al.*, 1979; Millar, 1983). Similarly, consistent with the hypothesis of significant impulsivity in OCD, an epidemiological study showed increased incidence of conduct problems in the childhood history of OCD patients (Hollander *et al.*, 1996).

Impulsivity is a characteristic feature of the OCSD’s in this cluster of conditions. For

example, kleptomania is classified in the DSM-IV as one of the impulse control disorders, and is characterized by repeated failure to resist impulses to steal objects not for personal use or financial gain. Compulsive shopping is also characterized by the presence of repetitive impulsive and excessive buying that leads to personal and familial distress, with impulsivity singled out as one of the main clinical features of this condition (Lejoyeux *et al.*, 1996). Furthermore, the literature has consistently found that OCD patients often present with comorbid eating disorders (Nagata *et al.*, 2000) as well as with self-injurious behaviours (Winchel and Stanley, 1991). Indeed eating disorders, essentially characterized by a severe disturbance in the person's perception of body shape and weight, may also have impulsive symptoms or 'multi-impulsivity' (Eddy and Walbroehl, 1998; Fessler, 2002; Nagata *et al.*, 2000). In addition, as previously discussed, in their comparison of OCD patients with and without comorbid putative OCSD's, Du Toit *et al.* (2001) found that one of the OCSD's with the highest prevalence rates was self-injury (i.e. impulse control disorder not otherwise specified). The compulsive self-injurious behaviours seen in these patients with OCD included pathological skin picking, trichotillomania, and onychophagia (nail biting).

Also included in this cluster is IED, a condition that is characterized by discrete episodes of aggressive impulses that result in serious assaultive acts towards other people and/or destruction of property (DSM-IV). Rather little research has been done on IED as defined by these DSM-IV criteria, or on the comorbidity between IED and OCD. The association between OCD and IED-type of behaviour is supported by early analyses that revealed that patients with obsessive-compulsive "neurosis" have impulsive "other-directed" symptoms, such as acting-out hostility (Manchanda *et al.*, 1979; Millar, 1983), arguably resembling aspects of IED.

The finding of an association between Cluster II scores and increased severity of OCD is consistent with previous data indicating a link between impulsivity and OCD severity (Stein *et al.*, 1994). In addition, the association of Cluster II scores with female gender and with emotional abuse is consistent with previous studies linking a subset of OCD patients, as well as eating disorders and self-injurious behaviours in women, to early traumatic experiences (Bogetto *et al.*, 1999; De Silva and Marks, 1999; Fallon *et al.*, 2000; Paul *et al.*, 2002; Yates, 2004).

6.4.2.i Phenomenology

In summary, OCD patients with any of the OCSD's included in Cluster II may present with significant impulsiveness or impulse control problems. Indeed, increasing data from comorbidity studies support the existence of an OCD-Impulsivity subtype. For example, an earlier analysis of this data set (Du Toit *et al.*, 2001) compared OCD patients with and without comorbid OCSD's, and found evidence for significant comorbidity between OCD and impulse control disorders, e.g. 10.6% of patients also presented with comorbid compulsive shopping and IED. The cluster analysis findings also positioned some of these impulse control disorders (including compulsive shopping, kleptomania and IED) in one cluster, supporting a common feature of impulsivity in these comorbid OCSD's in OCD patients.

It has been suggested that obsessive-compulsive and impulsive symptoms are qualitatively similar in that both involve difficulties delaying or inhibiting repetitive behaviours (Hollander and Wong, 1995). Indeed, there are significant similarities in the phenomenology between OCD and disorders of impulse control. For example, both OCD and the impulse control disorders are characterized by intrusive, irresistible urges

to commit an act that may or may not be seen as senseless. Also, many patients with either of these conditions frequently experience an increasing sense of tension associated with attempts to resist the behaviour, and temporary relief from anxiety following their engagement in the behaviour.

In addition, the cluster analysis findings suggest an association between the conditions included in this "impulsivity" cluster with female gender and with emotional abuse. This is consistent with previous work linking a subset of OCD patients, as well as eating disorders and self-injurious behaviours in women, to early traumatic experiences (Bogetto *et al.*, 1999; De Silva and Marks, 1999; Fallon *et al.*, 2000; Paul *et al.*, 2002).

6.4.2.ii Neurobiology

In addition to the phenomenological similarities, there are also some similarities in the neurobiology and treatment response between OCD and disorders of impulse control, suggesting that patients with the OCD-Impulsivity subtype may require treatment with medications proven useful for these conditions (e.g. SRI's). Interestingly, abnormalities in central serotonergic system function are reported in patients with impulsive aggressive behaviour as well as in patients with OCD, with many of the medications that are useful in the treatment of impulsivity and OCD respectively, acting on the serotonergic system. There are now several controlled studies of serotonergic medications in different impulse control disorders, including borderline personality disorder. Similarly, reductions in impulsivity and hostility have been noted after successful treatment of OCD symptoms with SRI's (Lopez-Ibor Jr, 1990).

In addition, medications that do not act on the serotonergic system may also prove to be

useful in disorders characterized by impulsivity. Arguably, the anticonvulsants, which are effective for controlling impulsivity in a number of these conditions, may also be useful in OCD patients with comorbid impulsivity. For example, Khanna has written about the use of carbamazepine in the treatment of OCD (Khanna, 1988). There has also been some interest in the use of valproate, gabapentin, lamotrigine and the mood-stabilizer lithium. Some studies have shown that antipsychotics have been effective in reducing hostility and suicidality in patients with a personality disorder (Klein, 1968; Montgomery and Montgomery, 1982; Soloff *et al.*, 1986). Similarly, antipsychotics have proven beneficial when added to an SRI in the treatment of OCD patients with symptoms of (amongst others) cluster B personality disorders (these may include impulsivity). No data on the effect of antipsychotics on specifically impulsivity in OCD patients could be found however.

6.4.3 The *SOMATIC* cluster

BDD, characterized by a preoccupation with imagined defects in appearance (APA, 1994), and hypochondriasis, a disorder characterized by repeated concerns about illness, were included in Cluster III which was termed “somatic”. Ruminations and rituals that concern health or appearance are the hallmark of somatic-related disorders included in this cluster, and may include a number of OCSD’s, e.g. BDD, hypochondriasis and perhaps olfactory reference syndrome (ORS) (ORS was not included in this cluster analysis however). There are other obsessive-compulsive related symptoms that can also be conceptualized as revolving around the body, the body functions or appearance, for example eating disorders, TTM, and self-injury; however, these conditions were included in other clusters.

The finding of an association between Cluster III and somatic obsessions and compulsions was therefore not surprising. Indeed, consistent with a somatic subtype of OCD, many OCD patients report somatic or body-focused concerns and rituals (Simeon *et al.*, 1995). In addition, somatic OCD symptoms are often seen in non-psychiatric healthcare settings, e.g. Dermatology clinics. For example, brief psychiatric screening of 92 patients attending a Dermatology clinic revealed that approximately one fifth scored positive either for OCD or for a clinically relevant spectrum disorder such as BDD (Fineberg and Roberts, 2001).

Somatic concerns in patients with BDD manifest as obsessive preoccupations with an imagined or minimal defect in physical appearance despite an objectively normal appearance (also described as “imagined ugliness”) (DSM-IV). BDD patients suffer from repetitive, persistent ideas or thoughts about these defects, with consequent compulsive, mostly body-focused, behaviours, including constant checking in mirrors, applying make-up to cover-up the “flaw”, excessive grooming (e.g. hair), and repeated reassurance seeking from others about their “defect” (Phillips, 1991). Body parts often involved in BDD concerns are the head or facial features (including nose, mouth, skin and hair), body size or symmetry and the sexual organs (penis, breasts) (Hollander *et al.*, 1993b).

Hypochondriasis is similarly characterized by excessive somatic concerns. In particular, patients with hypochondriasis have a preoccupation or excessive concern with the fear of having, or a belief that they have an illness (in the absence of objective proof), with subsequent reassurance seeking, compulsive checking behaviours and a relentless pursuit of medical care (DSM-IV). Again, patients with hypochondriacal concerns may present widely to general medical settings seeking medical assistance for their somatic

symptoms.

ORS is another putative OCD-related condition characterized by persistent preoccupations about body odour accompanied by shame, embarrassment, significant distress, avoidance behaviour and social isolation. Although ORS was not included in the cluster analysis described here, this condition may arguably be positioned together with other disorders with somatic concerns. ORS is not included in the DSM-IV or the International Classification of Diseases 10th Edition (ICD-10) as a separate category. Nevertheless, it has been argued that ORS represents a unique cluster of symptoms that can be delineated as a separate diagnostic entity (Lochner and Stein, 2003b). Patients with ORS describe excessive concerns with personal or body odour, a preoccupation with fear of causing offence to others, leading to excessive cleaning of the body or body parts, reassurance seeking and consequent significant functional impairment (Pryse-Phillips, 1971).

6.4.3.i Phenomenology

Similarities between OCD and BDD have been described in terms of clinical presentation, comorbidity rates, treatment response profiles, and other features. In particular, the two disorders have similar sex ratios, demographic characteristics, and illness severity (McKay *et al.*, 1997; Phillips *et al.*, 1998; Saxena *et al.*, 2001). In addition, the repetitive and intrusive nature of their body-focused concerns, together with rituals such as checking, also suggest significant overlap between OCD and BDD (Phillips, 1992; Saxena *et al.*, 2001). Some authors have suggested that "obsessive-compulsiveness" or obsessive or compulsive personality traits are a hallmark of BDD. BDD appears to be relatively common among patients with OCD, with rates of BDD

ranging from 8% to 38% among patients with OCD (Hollander and Phillips, 1993; Phillips, 1991; Phillips *et al.*, 1998; Pigott *et al.*, 1994; Simeon *et al.*, 1995). That BDD is related to OCD may also be supported by the finding of an elevated rate of BDD in family members of OCD patients compared to those of controls (Bienvenu *et al.*, 2000). Moreover, patients with body dysmorphic concerns frequently have poor insight; previous data have also suggested an association between health concerns and poor insight (Abramowitz *et al.*, 1999). Similarly, the data also suggest an association between the somatic cluster of conditions and poor insight.

In addition, some of the somatic symptoms presented by patients with OCD or BDD overlap with the somatic and health related concerns characteristic of hypochondriasis. Similar to OCD and BDD, patients with hypochondriasis may also have elaborate "checking" rituals involving their body resulting in at least temporary reduction in their anxiety levels. Consistent with the finding that hypochondriasis in included in the somatic cluster of conditions, it has been suggested that there is much overlap and relatively high prevalence of hypochondriasis in OCD (Bienvenu *et al.*, 2000; Jaisoorya *et al.*, 2003). Relatively few studies have systematically assessed the prevalence of comorbid hypochondriasis in OCD patients; nevertheless, Pigott *et al.* (1994) have found a lifetime prevalence rate of 23% for hypochondriasis in a sample of OCD patients. Recent work has also suggested that hypochondriasis occurred more frequently in OCD compared to controls (Bienvenu *et al.*, 2000; Jaisoorya *et al.*, 2003).

ORS symptoms meet DSM-IV criteria for obsessions and compulsions insofar as these are repetitive intrusive thoughts (about body odour and the offence that their body/body odour may cause to others), followed by ritualistic attempts to decrease anxiety (e.g.

excessive washing, asking for reassurance etc.). Also similar to some OCD and BDD patients, patients with ORS tend to change their clothes with more than the usual frequency, and often restrict their social and domestic excursions to an extent because of their obsessions and fears (Pryse-Phillips, 1971). In addition, in OCD, BDD, hypochondriasis and ORS, the fixity of and the resistance to the pathological thoughts vary to a large extent, and insight into the excessiveness or irrationality thereof may waver over time. The prevalence of comorbid ORS in OCD patients is unknown. Nevertheless, given the significant overlap between the somatic symptoms that are often characteristic of both disorders, it may be suggested that ORS may in some contexts even be considered as a variant of OCD or BDD. As such, one may argue that ORS symptoms should be considered for inclusion in OCD checklists such as the YBOCS-CL.

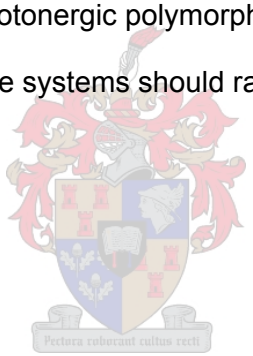
6.4.3.ii Neurobiology

A somatic subtype of OCD is validated by this cluster analysis, and there is evidence that both OCD and somatic OCD spectrum disorders respond to similar medications (Phillips and Najjar, 2003). In particular, in all of these disorders, a preferential response to treatment with anti-obsessional drugs, particularly SRI's and other agents that act by inhibiting the reuptake of serotonin, e.g. clomipramine, has been suggested. Until recently, approaches to treatment-resistant BDD in particular have received little investigation, but available data indicate that switching to another SRI and several SRI-augmentation strategies may be helpful (Phillips, 2002). In a family study conducted by Bienvenu *et al.* (2000), it was suggested that BDD may be co-transmitted with OCD, providing further evidence for a significant neurobiological overlap between these disorders.

For now, there is no evidence that OCD patients of the comorbid somatic subtype have a different or unique neurobiological profile or treatment response compared to other OCD subtypes. Nevertheless, it has been suggested that the group of OCD patients with poor insight may have a different treatment response than patients with better insight (Attiullah *et al.*, 2000), but the relationship between the degree of insight and outcome of therapy remains unclear (Kozak and Foa, 1994). Additional research is needed in order to address this issue.

6.4.4 Clusters and genetics

As noted previously, a relationship between any of the identified clusters and the investigated dopaminergic and serotonergic polymorphisms was not found, suggesting that variants in other genes in these systems should rather be explored.

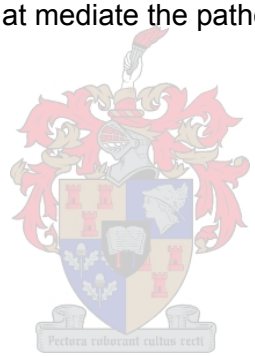


6.5 Conclusion

In conclusion, although aspects of the links discussed here have previously been described, to our knowledge this is the first cluster analysis based on a prospective comprehensive interview investigating a range of OCSD's. The data support the existence of OCD subtypes, partially similar to existing literature on possible OCD subtypes, based on comorbidity between OCD and OCSD's. The significant associations found between cluster scores and clinical variables suggest the value of delineating the dimensions in which OCSD's fall when comorbid with OCD: The TS/tics subtype of OCD (part of the reward deficiency cluster) has received particular attention. Nevertheless, the present data also suggest the existence of other subtypes including an

impulsivity subtype, and a somatic subtype. Several significant associations consistent with previous data were found between these subtypes and other clinical and demographic variables. A relationship between any of the identified clusters and the investigated dopaminergic and serotonergic polymorphisms was not found, suggesting that variants in other genes in these systems should rather be explored.

Mood and anxiety disorders are also highly comorbid with OCD, suggesting that future work on the structure of comorbid disorders in OCD should address the inclusion of these conditions. In addition, future work with larger samples, and additional variants in other genes, may ultimately show that examining comorbidity in OCD is helpful in delineating the endophenotypes that mediate the pathogenesis of this condition.



CHAPTER 7

GENERAL DISCUSSION AND CONCLUSION

The clinical presentation of obsessive-compulsive disorder (OCD) is remarkably diverse indeed. The variability in phenomenology has previously lead to the hypothesis that OCD is a heterogeneous type of psychiatric disorder and that the inconsistencies in clinical, natural history, treatment response and genetic study findings may be ascribed to this heterogeneity. Subsequently, it was suggested that OCD may be categorized into a number of subtypes, each associated with specific clinical and neurobiological features. Identification of *consistent* OCD phenotypes has the potential to further the understanding of OCD and may contribute to the identification of more robust endophenotypes.

The overall objective of the present study was to assemble, analyze and interpret original data in order to better previous efforts delineating valid and reliable OCD subtypes or dimensions and their associated features, with appropriate data classification and association study methods, in a large sample of South African OCD patients. The research reported here examined OCD from both a clinical and genetic perspective.

The analyses presented in this dissertation were based upon a comprehensive review of literature focused on the heterogeneity of OCD. The literature review provided an overview of the ways in which this neuropsychiatric disorder has been subtyped in an

attempt to integrate data on its symptomatology, psychobiology, genetics and treatment response to facilitate predictions about etiology and disease outcome. Until now, methods focused on OCD symptomatology and/or comorbidity (especially with obsessive-compulsive (OC) spectrum conditions) as classifying variables have been some of the most popular strategies for identifying OCD subtypes, and these foci have been receiving increased attention in recent years.

Presentation of the findings obtained with the Yale-Brown Obsessive-Compulsive Symptom Checklist (YBOCS-CL) established an important introduction to subsequent analyses of OC symptomatology and its associated features. Indeed, following the literature review of the heterogeneity of OCD, a review of available descriptive data on the YBOCS-CL was provided, with a discussion of the rationale for using this scale in the present investigations, and then, finally, provision of a profile of the OCD sample used based on their YBOCS-CL responses. This profile included for example, the frequencies in which the major OC symptom categories were reported, the mean number of symptoms reported by the patients and the frequency with which each individual item of the YBOCS-CL (i.e. symptom) was reported, as well as the association of each of these items / symptoms with specific demographic (gender, age, population) and clinical variables (total OCD severity and disability). The findings suggest that the present sample was not dissimilar to OCD samples used in other investigations. Thus, analyses and findings using this patient population and checklist arguably rendered information comparable and applicable to other OCD patients in similar contexts. This chapter also included comments on the content and comprehensiveness of the YBOCS-CL as an assessment tool of OC symptomatology.

The first subtyping attempt made use of latent class analysis (LCA), a special "type" of factor analysis appropriate for the categorical nature of the data rendered by the YBOCS-CL. The "best fit" comprised six (6) clusters of cases or OCD patient subtypes when the nine most frequently occurring obsessive-compulsive symptoms were included in the analysis. When additional indicators were used in LCA, the potential for computational instability increased. To gain insight into the cluster structure, the way in which clusters differ with respect to specific demographic variables (age, gender) and clinical variables (OC symptoms, total OCD severity, treatment response, childhood trauma history) was investigated. In summary, the LCA-findings support the existence of six clusters of OCD cases classified according to their OC symptomatology. Clusters I to VI were labelled 'Mental compulsions', 'Maximal disorder', 'Minimal disorder', 'No checking compulsions, 'Checking compulsions', and 'Pure contamination compulsions / washing', respectively. In contrast to factor analysis, in LCA or cluster analysis, patients are unambiguously assigned to groups that are created by maximizing between-group differences and minimizing within-group variability on the chosen set of measures. Here, each patient falls into only one class or cluster. Conversely, as noted before, in factor analysis, a subject may have loadings on all of the identified factors. Use of cluster analysis has gained ground in recent years, with some investigators suggesting that cluster analysis may be a superior method for identifying OCD subtypes. In a way, categorization of OCD patients into different groups and investigating their respective features go beyond the literature and thus add another dimension to the increasing efforts to fully delineate OCD subtypes. Some of the clusters identified with LCA broadly resembled some of the current sub-classifications of OCD suggested in the literature. It has previously been argued that *pure* symptoms are of key importance in defining groups of OCD patients. To an extent, the findings here similarly suggest that some

groups or classes are characterized by “pure” symptoms (e.g. ‘Pure contamination compulsions / washing’). On the other hand, it was argued that classes very often rather are characterized by *mixed* symptoms, e.g. Cluster II (‘Maximal disorder’ including a wide variety of OC symptoms). Indeed, there is some clinical evidence in support of the latter argument; in fact, it is well known that OCD patients mostly present with multiple symptoms that often change over time. It was concluded, based upon both the existing OCD literature and the findings here, that not only does one need to investigate OCD phenotypes characterized by *pure* symptoms or predominantly one *type* of OC symptom, but also those classes characterized by *mixed* or a wide array of different OC symptoms. As noted before, relatively few items were included in the LCA given the fact that, when using additional indicators in LCA, the potential for computational instability increased. Subsequently, given the importance of accurate and comprehensive representation of OCD symptoms when subtyping OCD based on patients’ reported symptomatology, it was attempted to remedy this situation with implementation of another clustering method. Cluster analysis (Ward’s method) of the same few items (the nine most frequently reported OC symptoms) in a sample of 261 OCD patients rendered a 3-cluster solution. This OCD symptom dimension solution was consistent with most findings from previous factor analysis studies, but differed to an extent from the six clusters of cases identified with LCA. This is reasonable given that these two methods actually render different types of data; the one cutting *across* symptoms and rendering groups in which patients had multiple OC symptoms (LCA), the other *cutting up* symptoms or carving out the specific OC symptoms from one another (cluster analysis). Importantly, each may be useful for different purposes. In particular, the three identified clusters or symptom dimensions comprised checking and repeating (i.e. *pure* compulsions), obsessions with symmetry / exactness / ordering and arranging, as well as obsessive contamination fears

and related compulsions (washing). The consistency of the cluster analysis of the nine OC symptoms compared to previous factor analyses encouraged subsequent cluster analyses of the 45 selected items of the YBOCS-CL. Cluster analysis of the 45 selected items of the YBOCS-CL in this sample of OCD patients identified 6 separate clusters; these clusters were labelled “Contamination fears / washing”, “Hoarding / collecting”, “Symmetry / ordering / counting / arranging / repeating”, “Sexual”, “Somatic, religious and diverse” and “Harm-related”. Each of the clusters was associated with specific demographic, clinical and, in some cases, genetic characteristics, which supported the presence of clinical subtypes of OCD. Notably, the genetics findings indicated the *L/L* (*met/met*) genotype of *COMT Val158Met* polymorphism plays a major role in the manifestation of sexual / somatic, religious and diverse / harm-related symptoms of OCD. This finding contributes to the relatively limited data on OC symptom subtypes and genetics. However, given the relatively varying nature of the symptoms characteristic of our three identified symptom clusters, it was argued that the *COMT Val158Met* polymorphism is involved in the etiology of OCD in general (or perhaps of a significant number of symptom subtypes) rather than just with the development of a single specific OC symptom subtype. Although each of the subtypes had a number of associated features, these associations did not clearly or uniquely differentiate clusters given the substantial overlap in this regard. Furthermore, the clusters were highly correlated with one another, suggesting that delineation of the OCD complex into symptom clusters is not the only or best way to approach the heterogeneity characteristic of OCD. The significant comorbidity with obsessive-compulsive spectrum disorders (OCSD’s) in each of the identified clusters highlighted the significant relationship of OCD with the OCSD’s. Indeed, although most efforts to subtype OCD thusfar gave prominence to classification built upon OC symptomatology, it was argued

that another important approach to subtyping would be to consider issues of comorbidity, especially with the OCSD's. A question was also raised about the way that the OCSD's "fit" with the standard OC symptomatology outlined in the YBOCS-CL. OCSD symptoms have significant phenomenological and neurobiological overlap with the features of OCD and should arguably therefore be considered for inclusion in attempts to identify a comprehensive and multidimensional model for OC symptom subtypes. At this stage, the YBOCS-CL contains very few items that can be labelled as "OC spectrum symptoms", suggesting the need for an incorporation of the other possible spectrum items from a different scale specifically assessing the OCSD's, such as the Structured Clinical Interview for the Diagnosis of putative OCSD's (SCID-OCSD), into the YBOCS-CL. Development of another version of the YBOCS-CL, the so-called Dimensional YBOCS (Personal communication with J.F. Leckman, Child Study Center, Yale University School of Medicine, New Haven, Connecticut, USA, Unpublished script), which incorporates a number of other symptoms characteristic of the OC spectrum, could be considered as an attempt to fill this void and thus may be an important contribution to the field of OCD research.

A description of the cluster analysis of comorbid OCSD's in patients with OCD followed, with findings suggesting that comorbidity of certain OCSD's in OCD may serve to define important OCD subtypes. This is the first cluster analysis based on a prospective comprehensive interview (the SCID-OCSD) investigating a range of OCSD's. The significant associations found between cluster scores and clinical variables suggest the value of delineating the dimensions in which OCSD's fall when comorbid with OCD. For example, the TS/tics subtype of OCD (part of the so-called "reward deficiency" cluster) has received particular attention. Nevertheless, the data also suggest the existence of

other subtypes including an impulsivity subtype, and a somatic subtype. Several significant associations consistent with previous data were found between these subtypes and other clinical and demographic variables. A significant relationship between the identified clusters and the investigated dopaminergic and serotonergic polymorphisms was not found, suggesting that variants in other genes in these systems should rather be explored. Given that mood and anxiety disorders often are comorbid with OCD, it was suggested that future work on the structure of comorbid disorders in OCD should address the inclusion of these conditions. In addition, future work with larger samples, and additional variants in other genes, may ultimately show that examining comorbidity in OCD is helpful in delineating the endophenotypes that mediate the pathogenesis of this condition.

In conclusion, the main finding of this study was that OCD is indeed a heterogeneous disorder that may be categorized into different symptom dimensions or subtypes. The identified OCD subtypes with their associated features were to a large extent consistent with previously published data. However, the findings here also suggested that there may be different ways of approaching the heterogeneity of OCD (e.g. focusing on OCD symptoms, as well as the spectrum of OCD-related disorders). In addition, in contrast to factor analysis, LCA provided a novel, appropriate and advantageous data analysis strategy for the data. Furthermore, to the candidate's knowledge, the attempt to classifiy OCD according to comorbid OCSD's was the first cluster analysis based on a prospective comprehensive interview investigating a range of OCSD's. As such, although the dimensional structure of OCD is still not entirely understood, the categorization of our OCD patients into different groups and the investigation of their respective clinical features and neurobiological underpinnings have gone beyond the

literature and thus add another dimension to the increasing efforts to fully delineate OCD subtypes.

ADDENDUM 1

REFERENCE LIST

1. Abramowitz, J. S., Brigidi, B. D., & Foa, E. B. (1999). Health concerns in patients with obsessive-compulsive disorder. J Anxiety Disord, 13, 529-539.

2. Abramowitz, J. S., Franklin, M. E., Schwartz, S. A., & Furr, J. M. (2003). Symptom presentation and outcome of cognitive-behavioral therapy for obsessive-compulsive disorder. J Consult Clin Psychol, 71, 1049-1057.

3. Ackerman, D. L., Greenland, S., & Bystritsky, A. (1998). Clinical characteristics of response to fluoxetine treatment of obsessive-compulsive disorder. J Clin Psychopharmacol, 18, 185-192.

4. Ackerman, D. L., Greenland, S., & Bystritsky, A. (1999). Side effects as predictors of drug response in obsessive-compulsive disorder. J Clin Psychopharmacol, 19, 459-465.

5. Alarcon, R. D., Libb, J. W., & Spitler, D. (1993). A predictive study of obsessive-compulsive disorder response to clomipramine. J Clin Psychopharmacol, 13, 210-213.

6. Albert, U., Maina, G., Ravizza, L., & Bogetto, F. (2002). An exploratory study on obsessive-compulsive disorder with and without a familial component: are there any phenomenological differences? Psychopathology, 35, 8-16.

7. Allen, A. J., Leonard, H. L., & Swedo, S. E. (1995). Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry, 34, 307-311.

8. Alonso, P., Menchon, J. M., Pifarre, J., Mataix-Cols, D., Torres, L., Salgado, P., & Vallejo, 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 Psychiatry, 62, 535-540.

9. Alsobrook II, J. P., Leckman, J. F., Goodman, W. K., Rasmussen, S. A., & Pauls, D. L. (1999). Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. Am J Med Genet, 88, 669-675.

10. Alsobrook II, J. P., Zohar, A. H., Leboyer, M., Chabane, N., Ebstein, R. P., & Pauls, D. L. (2002). Association between the COMT locus and obsessive-compulsive disorder in females but not males. Am J Med Genet, 114, 116-120.

11. Altamura, C., Paluello, M. M., Mundo, E., Medda, S., & Mannu, P. (2001). Clinical and subclinical body dysmorphic disorder. Eur Arch Psychiatry Clin Neurosci, 251, 105-108.

12. Altshuler, L. L., Hendrick, V., & Cohen, L. S. (1998). Course of mood and anxiety disorders during pregnancy and the postpartum period. J Clin Psychiatry, 59 Suppl 2, 29-33.

13. American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders. (4th ed.) Washington DC: American Psychiatric Association.

14. American Psychiatric Association: (2000). Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR). (4th ed.) Washington DC: American Psychiatric Press.

15. Attiullah, N., Eisen, J. L., & Rasmussen, S. A. (2000). Clinical features of obsessive-compulsive disorder. Psychiatr Clin North Am, 23, 469-491.

16. Baer, L. (1994). Factor analysis of symptom subtypes of obsessive-compulsive disorder and their relation to personality and tic disorders. J Clin Psychiatry, 55 Suppl, 18-23.

17. Baer, L. & Jenike, M. A. (1992). Personality disorders in obsessive-compulsive disorder.

Psychiatr Clin North Am, 15, 803-812.

18. Baer, L., Jenike, M. A., Black, D. W., Treece, C., Rosenfeld, R., & Greist, J. (1992). Effect of axis II diagnoses on treatment outcome with clomipramine in 55 patients with obsessive-compulsive disorder. Arch Gen Psychiatry, 49, 862-866.

19. Baer, L., Jenike, M. A., Ricciardi, J. N. 2nd, Holland, A. D., Seymour, R. J., Minichiello, W. E., Buttolph, M. L. (1990). Standardized assessment of personality disorders in obsessive-compulsive disorder. Arch Gen Psychiatry, 47, 826-830.

20. Baily, K. D. (1994). Typologies and taxonomies: an introduction to classification techniques. Thousand Oaks,CA: Sage Publications.

21. Ball, S. G., Baer, L., & Otto, M. W. (1996). Symptom subtypes of obsessive-compulsive disorder in behavioral treatment studies: a quantitative review. Behav Res Ther, 34, 47-51.

22. Barsky, A. J., Wyshak, G., & Klerman, G. L. (1992). Psychiatric comorbidity in DSM-III-R hypochondriasis. Arch Gen Psychiatry, 49, 101-108.

23. Bartholomew, D. J. & Knott, M. (1999). Latent variable models and factor analysis. (Second edition ed.) London: Arnold.

24. Basoglu, M., Lax, T., Kasvikis, Y., & Marks, I. (1988). Predictors of improvement in obsessive-compulsive disorder. J Anxiety Disord, 2, 299-317.

25. Baxter, L. R., Jr. (1994). Positron emission tomography studies of cerebral glucose metabolism in obsessive-compulsive disorder. J Clin Psychiatry, 55 Suppl, 54-59.

26. Bejerot, S., Schlette, P., Ekselius, L., Adolfsson, R., & von Knorring, L. (1998). Personality disorders and relationship to personality dimensions measured by the Temperament and Character Inventory in patients with obsessive-compulsive disorder. Acta

Psychiatr Scand, 98, 243-249.

27. Bellodi, L., Cavallini, M. C., Bertelli, S., Chiapparino, D., Riboldi, C., & Smeraldi, E. (2001). Morbidity risk for obsessive-compulsive spectrum disorders in first-degree relatives of patients with eating disorders. Am J Psychiatry, 158, 563-569.

28. Bellodi, L., Sciuto, G., Diaferia, G., Ronchi, P., & Smeraldi, E. (1992). Psychiatric disorders in the families of patients with obsessive-compulsive disorder. Psychiatry Res, 42, 111-120.

29. Bergh, C., Eklund, T., Sodersten, P., & Nordin, C. (1997). Altered dopamine function in pathological gambling. Psychol Med, 27, 473-475.

30. Bernstein, D. P., Ahluvalia, T., Pogge, D., & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry, 36, 340-348.

31. Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wentzel, K., Sapareto, E., Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry, 151, 1132-1136.

32. Berthier, M. L., Kulisevsky, J., Gironell, A., & Heras, J. A. (1996). Obsessive-compulsive disorder associated with brain lesions: clinical phenomenology, cognitive function, and anatomic correlates. Neurology, 47, 353-361.

33. Bienvenu, O. J., Samuels, J. F., Riddle, M. A., Hoehn-Saric, R., Liang, K. Y., Cullen, B. A., Grados, M. A., & Nestadt, G. (2000). The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. Biol Psychiatry, 48, 287-293.

34. Black, D. W., Monahan, P., Gable, J., Blum, N., Clancy, G., & Baker, P. (1998). Hoarding and

treatment response in 38 nondepressed subjects with obsessive-compulsive disorder. J Clin Psychiatry, 59, 420-425.

35. Black, D. W., Noyes, R., Jr., Goldstein, R. B., & Blum, N. (1992). A family study of obsessive-compulsive disorder. Arch Gen Psychiatry, 49, 362-368.

36. Black, D. W., Noyes, R., Jr., Pfohl, B., Goldstein, R. B., & Blum, N. (1993). Personality disorder in obsessive-compulsive volunteers, well comparison subjects, and their first-degree relatives. Am J Psychiatry, 150, 1226-1232.

37. Blum, K., Braverman, E. R., Holder, J. M., Lubar, J. F., Monastra, V. J., Miller, D., Lubar, J. O., Chen, T. J., & Comings, D. E. (2000). Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs, 32 Suppl, i-112.

38. Bogetto, F., Bellino, S., Vaschetto, P., & Ziero, S. (2000). Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. Psychiatry Res, 96, 91-98.

39. Bogetto, F., Venturello, S., Albert, U., Maina, G., & Ravizza, L. (1999). Gender-related clinical differences in obsessive-compulsive disorder. Eur Psychiatry, 14, 434-441.

40. Bolton, D., Raven, P., Madronal-Luque, R., & Marks, I. M. (2000). Neurological and neuropsychological signs in obsessive-compulsive disorder: interaction with behavioural treatment. Behav Res Ther, 38, 695-708.

41. Brody, A. L., Saxena, S., Schwartz, J. M., Stoessel, P. W., Maidment, K., Phelps, M. E., & Baxter, L. R., Jr. (1998). FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive-compulsive disorder. Psychiatry Res, 84, 1-6.

42. Brown, F. W. (1942). Heredity in the psychoneuroses. Proceedings of the Royal Society of

Medicine, 35, 785-790.

43. Buchanan, A. W., Meng, K. S., & Marks, I. M. (1996). What predicts improvement and compliance during the behavioral treatment of obsessive-compulsive disorder? Anxiety, 2, 22-27.

44. Calamari, J. E., Wiegartz, P. S., & Janeck, A. S. (1999). Obsessive-compulsive disorder subgroups: a symptom-based clustering approach. Behav Res Ther, 37, 113-125.

45. Calamari, J. E., Wiegartz, P. S., Riemann, B. C., Cohen, R. J., Greer, A., Jacobi, D. M., Jahn, S. C., & Carmin, C. (2004). Obsessive-compulsive disorder subtypes: an attempted replication and extension of a symptom-based taxonomy. Behav Res Ther, 42, 647-670.

46. Callicott, J. H., Egan, M. F., Mattay, V. S., Bertolino, A., Bone, A. D., Verchinksi, B., & Weinberger, D. R. (2003). Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry, 160, 709-719.

47. Camarena, B., Cruz, C., de la Fuente, J. R., & Nicolini, H. (1998). A higher frequency of a low activity-related allele of the MAO-A gene in females with obsessive-compulsive disorder. Psychiatr Genet, 8, 25-257.

48. Camarena, B., Rinetti, G., Cruz, C., Gomez, A., de, L. F., Jr., & Nicolini, H. (2001). Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive-compulsive disorder. Am J Med Genet, 105, 279-282.

49. Castle, D. J., Deale, A., & Marks, I. M. (1995). Gender differences in obsessive-compulsive disorder. Aust N Z J Psychiatry, 29, 114-117.

50. Catapano, F., Sperandeo, R., Perris, F., Lanzaro, M., & Maj, M. (2001). Insight and

resistance in patients with obsessive-compulsive disorder. Psychopathology, 34, 62-68.

51. Cattell, R. B. (1978). The scientific use of factor analysis. New York: Plenum Press.

52. Cavallini, M. C., Di Bella, D., Siliprandi, F., Malchiodi, F., & Bellodi, L. (2002). Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. Am J Med Genet, 114, 347-353.

53. Cavallini, M. C., Pasquale, L., Bellodi, L., & Smeraldi, E. (1999). Complex segregation analysis for obsessive-compulsive disorder and related disorders. Am J Med Genet, 88, 38-43.

54. Cheung, E. F. (2001). Obsessive-compulsive symptoms during treatment with clozapine in a patient with schizophrenia. Aust N Z J Psychiatry, 35, 695-696.

55. Christensen, H., Hadzi-Pavlovic, D., Andrews, G., & Mattick, R. (1987). Behavior therapy and tricyclic medication in the treatment of obsessive-compulsive disorder: a quantitative review. J Consult Clin Psychol, 55, 701-711.

56. Clark, D. A., Sugrim, I., & Bolton, D. (1982). Primary obsessional slowness: a nursing treatment programme with a 13-year-old male adolescent. Behav Res Ther, 20, 289-292.

57. Clifford, C. A., Murray, R. M., & Fulker, D. W. (1984). Genetic and environmental influences on obsessional traits and symptoms. Psychol Med, 14, 791-800.

58. Clomipramine Collaborative Group. (1991). Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry, 48, 730-738.

59. Cloninger, C. R., Przybeck, T. R., Svrakic, D. M., & Wetzel, R. D. (1994). The Temperament and Character Inventory: A guide to its development and use. Missouri: Center for

Psychobiology of Personality, Washington University, St. Louis.

60. Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. Arch Gen Psychiatry, 50, 975-990.

61. Como, P. G. (1995). Obsessive-compulsive disorder in Tourette's syndrome. Adv.Neurol, 65, 281-291.

62. Cummings, J. L. & Benson, D. F. (1988). Psychological dysfunction accompanying subcortical dementias. Annu Rev Med, 39, 53-61.

63. Damecour, C. L. & Charron, M. (1998). Hoarding: a symptom, not a syndrome. J Clin Psychiatry, 59, 267-272.

64. de Haan, L., Beuk, N., Hoogenboom, B., Dingemans, P., & Linszen, D. (2002). Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent-onset schizophrenia or related disorders. J Clin Psychiatry, 63, 104-107.

65. de Silva, P. & Marks, M. (1999). The role of traumatic experiences in the genesis of obsessive-compulsive disorder. Behav Res Ther, 37, 941-951.

66. Deltito, J. A. (1994). Valproate pretreatment for the difficult-to-treat patient with OCD. J Clin Psychiatry, 55, 500.

67. Demal, U., Lenz, G., Mayrhofer, A., Zapotoczky, H. G., & Zitterl, W. (1993). Obsessive-compulsive disorder and depression. A retrospective study on course and interaction. Psychopathology, 26, 145-150.

68. den Boer, J. A. (1997). Psychopharmacology of comorbid obsessive-compulsive disorder and depression. J Clin Psychiatry, 58 Suppl 8, 17-19.

69. Denys, D., de Geus, F., van Megen, H. J., & Westenberg, H. G. (2004). Symptom dimensions in obsessive-compulsive disorder: factor analysis on a clinician-rated scale and a self-report measure. Psychopathology, 37, 181-189.

70. DeVeaugh-Geiss, J., Moroz, G., Biederman, J., Cantwell, D., Fontaine, R., Greist, J. H., Reichler, R., Katz, R., & Landau, P. (1992). Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder--a multicenter trial. J Am Acad Child Adolesc Psychiatry, 31, 45-49.

71. Diamond, A., Briand, L., Fossella, J., & Gehlbach, L. (2004). Genetic and neurochemical modulation of prefrontal cognitive functions in children. Am J Psychiatry, 161, 125-132.

72. Diaz, S. F., Grush, L. R., Sichel, D. A., & Cohen, L. S. (1997). Obsessive-compulsive disorder in pregnancy and the puerperium. In Pato MT & Steketee G (Eds.), OCD across the life cycle. (pp. 97-112). Washington DC: American Psychiatric Press.

73. do Rosario-Campos, M. C., Leckman, J. F., Mercadante, M. T., Shavitt, R. G., Prado Hd, H. S., Sada, P., Zamignani, D., & Miguel, E. C. (2001). Adults with early-onset obsessive-compulsive disorder. Am J Psychiatry, 158, 1899-1903.

74. Dowling, F. G., Pato, M. T., & Pato, C. N. (1995). Comorbidity of obsessive-compulsive and psychotic symptoms: a review. Harv Rev Psychiatry, 3, 75-83.

75. du Toit, P. L., van Kradenburg, J., Niehaus, D., & Stein, D. J. (2001). Comparison of obsessive-compulsive disorder patients with and without comorbid putative obsessive-compulsive spectrum disorders using a structured clinical interview. Compr Psychiatry, 42, 291-300.

76. DuPont, R. L., Rice, D. P., Shiraki, S., & Rowland, C. R. Economic costs of obsessive-

compulsive disorder. Med Interface 8, 102-109. 1995. Abstract

77. Eddy, M. F. & Walbroehl, G. S. (1998). Recognition and treatment of obsessive-compulsive disorder. Am Fam.Physician, 57, 1623-1624.

78. Efron, B. & Tibshirani, R. (1993). An Introduction to the Bootstrap. London: Chapman and Hall.

79. Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A, 98, 6917-6922.

80. Eichstedt, J. A. & Arnold, S. L. (2001). Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? Clin Psychol Rev, 21, 137-157.

81. Eisen, J. L. & Rasmussen, S. A. (1993). Obsessive-compulsive disorder with psychotic features. J Clin Psychiatry, 54, 373-379.

82. Erzegovesi, S., Cavallini, M. C., Cavedini, P., Diaferia, G., Locatelli, M., & Bellodi, L. (2001). Clinical predictors of drug response in obsessive-compulsive disorder. J Clin Psychopharmacol, 21, 488-492.

83. Everitt, B. S. (1993). Cluster analysis. London: Edward Arnold.

84. Fahy, T. A., Osacar, A., & Marks, I. (1993). History of eating disorders in female patients with obsessive-compulsive disorder. International Journal of Eating Disorders, 14, 443.

85. Fallon, B. A., Qureshi, A. I., Laje, G., & Klein, B. (2000). Hypochondriasis and its relationship to obsessive-compulsive disorder. Psychiatr Clin North Am, 23, 605-616.

86. Feinstein, S. B., Fallon, B. A., Petkova, E., & Liebowitz, M. R. (2003). Item-by-item factor

analysis of the Yale-Brown obsessive-compulsive scale symptom checklist. J Neuropsychiatry Clin Neurosci, 15, 187-193.

87. Fessler, D. M. (2002). Pseudoparadoxical impulsivity in restrictive anorexia nervosa: a consequence of the logic of scarcity. Int J Eat.Disord., 31, 376-388.

88. Fineberg, N. & Roberts, A. (2001). Obsessive-compulsive disorder: A twenty-first century perspective. In N. Fineberg, D. Marazziti, & D. J. Stein (Eds.), Obsessive-compulsive disorder: A practical guide (pp. 1-13). London: Martin Dunitz Ltd.

89. First, M. B., Spitzer, R. L., Gobbon, M., & Williams, J. B. W. (1998). Structured clinical interview for DSM-IV Axis I disorders - Patient edition (SCID-I/P, Version 2.0, 8/98 revision). New York: New York State Psychiatric Institute, Biometrics Research Department.

90. Fischer, D. J., Himle, J. A., & Hanna, G. L. (1997). Age and gender effects on obsessive-compulsive symptoms in children and adults. Depress Anxiety, 4, 237-239.

91. Flament, M. F., Whitaker, A., Rapoport, J. L., Davies, M., Berg, C. Z., Kalikow, K., Sceery, W., & Shaffer, D. (1988). Obsessive-compulsive disorder in adolescence: an epidemiological study. J Am Acad Child Adolesc Psychiatry, 27, 764-771.

92. Foa, E. B. & Goldstein, A. (1978). Continuous exposure and complete response prevention in the treatment of obsessive-compulsive neurosis. Behav Ther, 9, 821-829.

93. Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & *et al.* (2002). The obsessive-compulsive inventory: Development and validation of a short version. Psychol Assess, 14, 485-496.

94. Foa, E. B., Kozak, M. J., Steketee, G. S., & McCarthy, P. R. (1992). Treatment of depressive and obsessive-compulsive symptoms in OCD by imipramine and behaviour therapy.

Br J Clin Psychol, 31, 279-292.

95. Fontenelle, L. F., Mendlowicz, M. V., Marques, C., Versiani, M. (2003). Early- and late-onset obsessive-compulsive disorder in adult patients: an exploratory clinical and therapeutic study. J Psychiatr Res, 37, 127-133.

96. Fontenelle, L. F., Mendlowicz, M. V., Soares, I. D., & Versiani, M. (2004). Patients with obsessive-compulsive disorder and hoarding symptoms: a distinctive clinical subtype? Compr Psychiatry, 45, 375-383.

97. Freud S: Inhibitions, symptoms and anxiety (1926). In Stanford Edition of the Complete Works of Sigmund Freud, Vol 20. Translated and edited by Strachey J. London, England, Hogarth Press, 1959, pp 77-175.

98. Frost, R. O. & Gross, R. C. (1993). The hoarding of possessions. Behav Res Ther, 31, 367-381.

99. Frost, R. O. & Hartl, T. L. (1996). A cognitive-behavioral model of compulsive hoarding. Behav Res Ther, 34, 341-350.

100. Frost, R. O., Krause, M. S., & Steketee, G. (1996). Hoarding and obsessive-compulsive symptoms. Behav Modif., 20, 116-132.

101. Frost, R. O., Steketee, G., Williams, L. F., & Warren, R. (2000). Mood, personality disorder symptoms and disability in obsessive-compulsive hoarders: a comparison with clinical and nonclinical controls. Behav Res Ther, 38, 1071-1081.

102. Galderisi, S., Mucci, A., Catapano, F., D'Amato, A. C., & Maj, M. (1995). Neuropsychological slowness in obsessive-compulsive patients. Is it confined to tests involving the fronto-subcortical systems? Br J Psychiatry, 167, 394-398.

103. Gallinat, J., Bajbouj, M., Sander, T., Schlattmann, P., Xu, K., Ferro, E. F., Goldman, D., &

Winterer, G. (2003). Association of the G1947A COMT (Val(108/158)Met) gene polymorphism with prefrontal P300 during information processing. Biol Psychiatry, 54, 40-48.

104. Ganesan, V., Kumar, T. C., & Khanna, S. (2001). Obsessive--compulsive disorder and psychosis. Can J Psychiatry, 46, 750-754.

105. Geller, D., Biederman, J., Jones, J., Park, K., Schwartz, S., Shapiro, S., & Coffey, B. (1998). Is juvenile obsessive-compulsive disorder a developmental subtype of the disorder? A review of the pediatric literature. J Am Acad Child Adolesc Psychiatry, 37, 420-427.

106. Geller, D. A., Biederman, J., Faraone, S., Agranat, A., Cradock, K., Hagermoser, L., Kim, G., Frazier, J., & Coffey, B. J. (2001). Developmental aspects of obsessive-compulsive disorder: findings in children, adolescents, and adults. J Nerv Ment Dis, 189, 471-477.

107. Geller, D. A., Biederman, J., Jones, J., Shapiro, S., Schwartz, S., & Park, K. S. (1998). Obsessive-compulsive disorder in children and adolescents: a review. Harv Rev Psychiatry, 5, 260-273.

108. George, M. S., Trimble, M. R., Ring, H. A., Sallee, F. R., & Robertson, M. M. (1993). Obsessions in obsessive-compulsive disorder with and without Gilles de la Tourette's syndrome. Am J Psychiatry, 150, 93-97.

109. Gershuny, B. S., Baer, L., Jenike, M. A., Minichiello, W. E., & Wilhelm, S. (2002). Comorbid posttraumatic stress disorder: impact on treatment outcome for obsessive-compulsive disorder. Am J Psychiatry, 159, 852-854.

110. Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B. S., Goldman, D., & Weinberger, D. R.(2003). Executive subprocesses in working

memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry, 60, 889-896.

111. Goodman, L. A. (1974). Exploratory latent structure analysis using both identifiable and unidentifiable models. Biometrika, 61, 215-231.

112. Goodman, W. K., McDougle, C. J., & Price, L. H. (1992). The role of serotonin and dopamine in the pathophysiology of obsessive-compulsive disorder. Int Clin Psychopharmacol, 7 Suppl 1, 35-38.

113. Goodman, W. K., McDougle, C. J., Price, L. H., Barr, L. C., Hills, O. F., Caplik, J. F., Charney, D. S., & Heninger, G. R. (1995). m-Chlorophenylpiperazine in patients with obsessive-compulsive disorder: absence of symptom exacerbation. Biol Psychiatry, 38, 138-149.

114. Goodman, W. K., McDougle, C. J., Price, L. H., Riddle, M. A., Pauls, D. L., & Leckman, J. F. (1990). Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive-compulsive disorder? J Clin Psychiatry, 51 Suppl, 36-43.

115. Goodman, W. K. & Price, L. H. (1992). Assessment of severity and change in obsessive-compulsive disorder. Psychiatr Clin North Am, 15, 861-869.

116. Goodman, W. K., Price, L. H., Rasmussen, S. A., Delgado, P. L., Heninger, G. R., & Charney, D. S. (1989a). Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Arch Gen Psychiatry, 46, 36-44.

117. Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989b). The Yale-Brown Obsessive-Compulsive Scale. II. Validity. Arch Gen Psychiatry, 46, 1012-1016.

118. Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C.

L., Heninger, G. R., & Charney, D. S. (1989c). The Yale-Brown Obsessive-Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry, 46, 1006-1011.

119. Gottesman, I. I. (1997). Twins: En route to QTLs for cognition. Science, 276, 1522-1523.

120. Gottesman, I. I. & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry, 160, 636-645.

121. Greenberg, B. D., Ziemann, U., Cora-Locatelli, G., Harmon, A., Murphy, D. L., Keel, J. C., & Wassermann, E. M. (2000). Altered cortical excitability in obsessive-compulsive disorder. Neurology, 54, 142-147.

122. Greist, J. H. (1996). New developments in behaviour therapy for obsessive-compulsive disorder. Int Clin Psychopharmacol, 11 Suppl 5, 63-73.

123. Greist, J. H. & Jefferson, J. W. (1998). Pharmacotherapy for obsessive-compulsive disorder. Br J Psychiatry Suppl 64-70.

124. Grimshaw, L. (1964). Obsessional disorder and neurological illness. J Neurol Neurosurg.Psychiatry, 27, 229.

125. Guy, W. (1976). ECDEU Assessment Manual for Psychopharmacology. Publication No. 76 - 338. Washington D.C.: Superintendent of Documents, U.S. Government Printing Office, U.S. Department of Health, Education, and Welfare.

126. Hantouche, E. G. & Lancrenon, S. (1996). [Modern typology of symptoms and obsessive-compulsive syndromes: results of a large French study of 615 patients] Typologie moderne des symptomes et des syndromes obsessionnels-compulsifs : resultats d'une large etude francaise chez 615 patients. Encephale, 22 Spec No 1, 9-21.

127. Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., & Lesch, K. P. (1996). Allelic variation of human serotonin transporter gene expression. J Neurochem., 66, 2621-2624.

128. Hemmings, S. M. J., Kinnear, C. J., Niehaus, D. J. H., Moolman-Smook, J. C., Knowles, J. A., Lochner, C., Corfield, V. A., & Stein, D. J. (2003). Investigating the role of dopaminergic and serotonergic candidate genes in obsessive-compulsive disorder. Eur Neuropsychopharmacol, 13, 93-98.

129. Hermesh, H., Shahar, A., & Munitz, H. (1987). Obsessive-compulsive disorder and borderline personality disorder. Am J Psychiatry, 144, 120-122.

130. Hodgson, R. J. & Rachman, S. (1977). Obsessional-compulsive complaints. Behav Res Ther, 15, 389-395.

131. Hoehn-Saric, R. & Barksdale, V. C. (1983). Impulsiveness in obsessive-compulsive patients. Br J Psychiatry, 143, 177-182.

132. Hollander, E. (1993). Introduction. In E.Hollander (Ed.), Obsessive-compulsive related disorders. (pp. 1-16). Washington DC: American Psychiatric Press.

133. Hollander, E., Buchalter, A. J., & DeCaria, C. M. (2000). Pathological gambling. Psychiatr Clin North Am, 23, 629-642.

134. Hollander, E., Cohen, L. J., DeCaria, C., Saoud, J. B., Stein, D. J., Cooper, T. B., Islam, N. N., Liebowitz, M. R., & Klein, D. F. (1993a). Timing of neuroendocrine responses and effect of m-CPP and fenfluramine plasma levels in OCD. Biol Psychiatry, 34, 407-413.

135. Hollander, E., Cohen, L. J., & Simeon, D. (1993b). Body dysmorphic disorder. Psychiatr Ann, 23, 359-364.

136. Hollander, E., De Caria, C., Stein, D., Simeon, D., Cohen, L., Hwang, M., & Islam, M. (1994). Behavioral response to m-CPP. Biol Psychiatry, 35, 426-427.

137. Hollander, E., DeCaria, C. M., Nitescu, A., Gully, R., Suckow, R. F., Cooper, T. B., Gorman, J. M., Klein, D. F., & Liebowitz, M. R. (1992). Serotonergic function in obsessive-compulsive disorder. Behavioral and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. Arch Gen Psychiatry, 49, 21-28.

138. Hollander, E., DeCaria, C. M., Sauoud, J., Klein, D. F., & Liebowitz, M. R. (1991). Neurological soft signs in obsessive-compulsive disorder. Arch Gen Psychiatry, 48, 278-279.

139. Hollander, E., Greenwald, S., Neville, D., Johnson, J., Hornig, C. D., & Weissman, M. M. (1996). Uncomplicated and comorbid obsessive-compulsive disorder in an epidemiologic sample. Depress Anxiety, 4, 111-119.

140. Hollander, E. & Phillips, K. (1993). Body image and experiences disorders. In American Psychiatric Press (Ed.), Obsessive-compulsive related disorders (pp. 17-48). Washington DC.

141. Hollander, E., Prohovnik, I., & Stein, D. J. (1995). Increased cerebral blood flow during m-CPP exacerbation of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci, 7, 485-490.

142. Hollander, E. & Rosen, J. (2000). Impulsivity. J Psychopharmacol, 14, S39-44.

143. Hollander, E. & Wong, C. M. (1995). Body dysmorphic disorder, pathological gambling, and sexual compulsions. J Clin Psychiatry, 56 Suppl 4, 7-12.

144. Holzer, J. C., Goodman, W. K., McDougle, C. J., Baer, L., Boyarsky, B. K., Leckman, J.

F., & Price, L. H. (1994). Obsessive-compulsive disorder with and without a chronic tic disorder. A comparison of symptoms in 70 patients. Br J Psychiatry, 164, 469-473.

145. Honjo, S., Hirano, C., Murase, S., Kaneko, T., Sugiyama, T., Ohtaka, K., Aoyama, T., Takei, Y., Inoko, K., & Wakabayashi, S. (1989). Obsessive-compulsive symptoms in childhood and adolescence. Acta Psychiatr Scand, 80, 83-91.

146. Hotamisligil, G. S. & Breakefield, X. O. (1991). Human monoamine oxidase A gene determines levels of enzyme activity. Am J Hum Genet, 49, 383-392.

147. Hsu, L. K., Kaye, W., & Weltzin, T. E. (1993). Are the eating disorders related to obsessive-compulsive disorder? International Journal of Eating Disorders, 14, 305-318.

148. Hugo, F., Van Heerden, B., Zungu-Dirwayi, N., & Stein, D. J. (1999). Functional brain imaging in obsessive-compulsive disorder secondary to neurological lesions. Depress Anxiety, 10, 129-136.

149. Hymas, N., Lees, A., Bolton, D., Epps, K., & Head, D. (1991). The neurology of obsessional slowness. Brain, 114, 2203-2233.

150. Insel, T. R., Hoover, C. F., & Murphy, D. L. (1983). Parents of patients with obsessive-compulsive disorder. Psychological Medicine, 13, 807-811.

151. Insel, T. R. (1992). Toward a neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry, 49, 739-744.

152. Ishiguro, H., Arinami, T., Saito, T., Akazawa, S., Enomoto, M., Mitushio, H., Fujishiro, H., Tada, K., Akimoto, Y., Mifune, H., Shiozuka, S., Hamaguchi, H., Toru, M., & Shibuya, H. (1998). Systematic search for variations in the tyrosine hydroxylase gene and their associations with schizophrenia, affective disorders, and alcoholism. Am J Med

Genet, 81, 388-396.

153. Jaisoorya, T. S., Janardhan Reddy, Y. C., & Srinath, S. (2003). The relationship of obsessive-compulsive disorder to putative spectrum disorders: results from an Indian study. Compr Psychiatry, 44, 317-323.

154. Jenike, M. A. (1992). Pharmacologic treatment of obsessive-compulsive disorders. Psychiatr Clin North Am, 15, 895-919.

155. Jenike, M. A., Baer, L., Minichiello, W. E., & *et al.* (1997). Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry, 154, 1261-1264.

156. Jenike, M. A., Baer, L., Minichiello, W. E., Schwartz, C. E., & Carey, R. J., Jr. (1986). Concomitant obsessive-compulsive disorder and schizotypal personality disorder. Am J Psychiatry, 143, 530-532.

157. Karayiorgou, M., Altemus, M., Galke, B. L., Goldman, D., Murphy, D. L., Ott, J., & Gogos, J. A. (1997). Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder. Proc Natl Acad Sci USA, 94, 4572-4575.

158. Karayiorgou, M., Sobin, C., Blundell, M. L., Galke, B. L., Malinova, L., Goldberg, P., Ott, J., & Gogos, J. A. (1999). Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive-compulsive disorder. Biol Psychiatry, 45, 1178-1189.

159. Karno, M., Golding, J. M., Sorenson, S. B., & Burnam, M. A. (1988). The epidemiology of obsessive-compulsive disorder in five US communities. Arch Gen Psychiatry, 45, 1094-1099.

160. Kasvikis, J. G., Tsakiris, F., Marks, I., & *et al.* (1986). Women with obsessive-compulsive disorder frequently report a past history of anorexia nervosa. Int J Eat Disord, 5, 1069-1075.

161. Kaufman, L. & Rousseeuw, P. J. (1990). Finding groups in data: An introduction to cluster analysis. New York: John Wiley and Sons, Inc.

162. Khanna, S. (1988). Carbamezapine in obsessive-compulsive disorder. Clin Neuropharmacol., 11, 478-481.

163. Khanna, S., Kaliaperumal, V. G., & Channabasavanna, S. M. (1990). Clusters of obsessive-compulsive phenomena in obsessive-compulsive disorder. Br J Psychiatry, 156, 51-54.

164. Khanna, S. & Mukherjee, D. (1992). Checkers and washers: valid subtypes of obsessive-compulsive disorder. Psychopathology, 25, 283-288.

165. Khullar, A., Chue, O., & Tibbo, P. (2001). Quetiapine and obsessive-compulsive symptoms (OCS): Case report and review of atypical antipsychotic-induced OCS. J Psychiatry Neurosci, 26, 55-59.

166. Kim, J.-O. & Mueller, C. W. (1978a). Factor analysis. Beverly Hills: CA: Sage.

167. Kim, J.-O. & Mueller, C. W. (1978b). Introduction to factor analysis. Beverly Hills: CA: Sage.

168. Klein, D. F. (1968). Psychiatric diagnosis and a typology of clinical drug effects. Psychopharmacologia, 13, 359-386.

169. Klein, D. F. (1990). Pharmacotherapy of obsessive-compulsive disorder. Encephale, 16, 331-334.

170. Kozak, M. J. & Foa, E. B. (1994). Obsessions, overvalued ideas, and delusions in obsessive-compulsive disorder. Behav Res Ther, 32, 343-353.

171. Kringlen, E. (1965). Obsessional neurotics: a long term follow up. Br J Psychiatry, 111, 709-722.

172. Kringlen, E. (1970). Natural history of obsessional neurosis. Semin Psychiatry, 2, 403-419.

173. Lazarsfeld, P. F. & Henry, N. W. (1968). Latent structure analysis. Boston: Houghton Mifflin.

174. Leckman, J. F. (1993). Tourette's Syndrome. In E.Hollander (Ed.), Obsessive-compulsive related disorders (pp. 113-137). Washington DC: American Psychiatric Press.

175. Leckman, J. F., Grice, D. E., Barr, L. C., de Vries, A. L., Martin, C., Cohen, D. J., McDougle, C. J., Goodman, W. K., & Rasmussen, S. A. (1994). Tic-related vs. non-tic-related obsessive-compulsive disorder. Anxiety, 1, 208-215.

176. Leckman, J. F., Grice, D. E., Boardman, J., Zhang, H., Vitale, A., Bondi, C., Alsobrook, J., Peterson, B. S., Cohen, D. J., Rasmussen, S. A., Goodman, W. K., McDougle, C. J., & Pauls, D. L. (1997). Symptoms of obsessive-compulsive disorder. Am J Psychiatry, 154, 911-917.

177. Leckman, J. F., Pauls, D. L., Zhang, H., Rosario-Campos, M. C., Katsovich, L., Kidd, K. K., Pakstis, A. J., Alsobrook, J. P., Robertson, M. M., McMahon, W. M., Walkup, J. T., van de Wetering, B. J., King, R. A., & Cohen, D. J. (2003). Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. Am J Med Genet, 116B, 60-68.

178. Leckman, J. F., Zhang, H., Alsobrook, J. P., & Pauls, D. L. (2001). Symptom dimensions

in obsessive-compulsive disorder: toward quantitative phenotypes. Am J Med Genet, 105, 28-30.

179. Lejoyeux, M., Ades, J., Tassain, V., & Solomon, J. (1996). Phenomenology and psychopathology of uncontrolled buying. Am J Psychiatry, 153, 1524-1529.

180. Lenane, M. C., Swedo, S. E., Leonard, H., Pauls, D. L., Sceery, W., & Rapoport, J. L. (1990). Psychiatric disorders in first degree relatives of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry, 29, 407-412.

181. Lennkh, C., Strnad, A., Bailer, U., Biener, D., Fodor, G., & de Zwaan, M. (1998). Comorbidity of obsessive-compulsive disorder in patients with eating disorders. Eat Weight Disord, 3, 37-41.

182. Lensi, P., Cassano, G. B., Correddu, G., Ravagli, S., Kunovac, J. L., & Akiskal, H. S. (1996). Obsessive-compulsive disorder. Familial-developmental history, symptomatology, comorbidity and course with special reference to gender-related differences. Br J Psychiatry, 169, 101-107.

183. Leonard, H. L., Lenane, M. C., Swedo, S. E., Rettew, D. C., Gershon, E. S., & Rapoport, J. L. (1992a). Tics and Tourette's disorder: a 2- to 7-year follow-up of 54 obsessive-compulsive children. Am J Psychiatry, 149, 1244-1251.

184. Leonard, H. L. & Swedo, S. E. (2001). Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Int J Neuropsychopharmacol, 4, 191-198.

185. Leonard, H. L., Swedo, S. E., Lenane, M. C., Rettew, D. C., Hamburger, S. D., Bartko, J. J., & Rapoport, J. L. (1993). A 2- to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. Arch Gen Psychiatry, 50, 429-439.

186. Leonard, H. L., Swedo, S. E., Rapoport, J. L., Koby, E. V., Lenane, M. C., Cheslow, D. L., & Hamburger, S. D. (1989). Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents. A double-blind crossover comparison. Arch Gen Psychiatry, 46, 1088-1092.

187. Leonard, H. L., Swedo, S. E., Rapoport, J. L., Rickler, K. C., Topol, D., Lee, S., & Rettew, D. (1992b). Tourette syndrome and obsessive-compulsive disorder. Adv.Neurol, 58, 83-93.

188. Lewis, A. (1936). Problems of obsessional illness. Proceedings of the Royal Society of Medicine, 29, 325-336.

189. Lichter, J. B., Barr, C. L., Kennedy, J. L., Van Tol, H. H., Kidd, K. K., & Livak, K. J. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Hum Mol Genet, 2, 767-773.

190. Lo, W. H. (1967). A follow-up study of obsessional neurotics in Hong Kong Chinese. Br J Psychiatry, 113, 823-832.

191. Lochner, C., Hemmings, S. M. J., Kinnear, C. J., Niehaus, D. J. H., Nel, D. G., Corfield, V. A., Moolman-Smook, J. C., Seedat, S., & Stein, D. J. (2005). Cluster analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder: Clinical and genetic correlates. Compr Psychiatry, 46, 14-19.

192. Lochner, C. & Stein, D. J. (2003a). Heterogeneity of Obsessive-Compulsive Disorder: A Literature Review. Harvard Review of Psychiatry, 11, 113-132.

193. Lochner, C. & Stein, D. J. (2003b). Olfactory reference syndrome: Diagnostic criteria and differential diagnosis. J Postgrad Med, 49, 328-331.

194. Lopez-Ibor, J. J., Jr. (1990). Impulse control in obsessive-compulsive disorder: a

biopsychopathological approach. Prog Neuropsychopharmacol Biol Psychiatry, 14, 709-718.

195. Maina, G., Albert, U., Bogetto, F., Vaschetto, P., & Ravizza, L. (1999). Recent life events and obsessive-compulsive disorder (OCD): the role of pregnancy/delivery. Psychiatry Res, 89, 49-58.

196. Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry, 159, 652-654.

197. Manchanda, R., Sethi, B. B., & Gupta, S. C. (1979). Hostility and guilt in obsessive-compulsive neurosis. Br J Psychiatry, 135, 52-54.

198. Marks, I. M. (1987). Fears, phobias and rituals: Panic, anxiety and their disorders. New York: Oxford University Press.

199. Marks, I. M., Lelliott, P., Basoglu, M., Noshirvani, H., Monteiro, W., Cohen, D., & Kasvikis, Y. (1988). Clomipramine, self-exposure and therapist-aided exposure for obsessive-compulsive rituals. Br J Psychiatry, 152, 522-534.

200. Mataix-Cols, D., Baer, L., Rauch, S. L., & Jenike, M. A. (2000). Relation of factor-analyzed symptom dimensions of obsessive-compulsive disorder to personality disorders. Acta Psychiatr Scand, 102, 199-202.

201. Mataix-Cols, D., Fullana, M. A., Alonso, P., Menchon, J. M., & Vallejo, J. (2004). Convergent and discriminant validity of the Yale-Brown Obsessive-Compulsie Scale Symptom Checklist. Psychother Psychosom, 73, 190-196.

202. Mataix-Cols, D., Marks, I. M., Greist, J. H., Kobak, K. A., & Baer, L. (2002). Obsessive-compuslive symptom dimensions as predictors of compliance with response to

behavior therapy: results from a controlled trial. Psychother Psychosom, 171, 255-262.

203. Mataix-Cols, D., Rauch, S. L., Baer, L., Eisen, J. L., Shera, D. M., Goodman, W. K., Rasmussen, S. A., & Jenike, M. A. (2002). Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. Am J Psychiatry, 159, 263-268.

204. Mataix-Cols, D., Rauch, S. L., Manzo, P. A., Jenike, M. A., & Baer, L. (1999). Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry, 156, 1409-1416.

205. Mataix-Cols, D., Rosario-Campos, M. C., & Leckman, J. F. (2005). A multidimensional model of obsessive-compulsive disorder. Am J Psychiatry, 162, 228-238.

206. Matsunaga, H., Kiriike, N., Matsui, T., Iwasaki, Y., Koshimune, K., Ohya, K., & Stein, D. J. (2001). A comparative study of clinical features between pure checkers and pure washers categorized using a lifetime symptom rating method. Psychiatry Res, 105, 221-229.

207. Matsunaga, H., Kiriike, N., Matsui, T., Miyata, A., Iwasaki, Y., Fujimoto, K., Kasai, S., & Kojima, M. (2000). Gender differences in social and interpersonal features and personality disorders among Japanese patients with obsessive-compulsive disorder. Compr Psychiatry, 41, 266-272.

208. Matsunaga, H., Kiriike, N., Matsui, T., Oya, K., Iwasaki, Y., Koshimune, K., Miyata, A., & Stein, D. J. (2002). Obsessive-compulsive disorder with poor insight. Compr Psychiatry, 43, 150-157.

209. Matsunaga, H., Kiriike, N., Miyata, A., Iwasaki, Y., Matsui, T., Nagata, T., Takei, Y., &

Yamagami, S. (1998). Personality disorders in patients with obsessive-compulsive disorder in Japan. Acta Psychiatr Scand, 98, 128-134.

210. Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F., Kolachana, B. S., Callicott, J. H., & Weinberger, D. R. (2003). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A, 100, 6186-6191.

211. Mavissakalian, M., Hamann, M. S., & Jones, B. (1990a). Correlates of DSM-III personality disorder in obsessive-compulsive disorder. Compr Psychiatry, 31, 481-489.

212. Mavissakalian, M., Hamann, M. S., & Jones, B. (1990b). DSM-III personality disorders in obsessive-compulsive disorder: changes with treatment. Compr Psychiatry, 31, 432-437.

213. McDougle, C. J., Epperson, C. N., Pelton, G. H., Wasylink, S., & Price, L. H. (2000). A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry, 57, 794-801.

214. McDougle, C. J., Goodman, W. K., Leckman, J. F., Barr, L. C., Heninger, G. R., & Price, L. H. (1993). The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharmacol, 13, 354-358.

216. McDougle, C. J., Goodman, W. K., Leckman, J. F., Lee, N. C., Heninger, G. R., & Price, L. H. (1994). Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry, 51, 302-308.

217. McDougle, C. J., Goodman, W. K., & Price, L. H. (1994). Dopamine antagonists in tic-related and psychotic spectrum obsessive-compulsive disorder. J Clin Psychiatry, 55

Suppl, 24-31.

218. McDougle, C. J., Goodman, W. K., Price, L. H., Delgado, P. L., Krystal, J. H., Charney, D. S., & Heninger, G. R. (1990). Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry, 147, 652-654.

219. McElroy, S. L., Phillips, K. A., & Keck, P. E., Jr. (1994). Obsessive-compulsive spectrum disorders. J Clin Psychiatry, 55 Suppl, 33-51.

220. McKay, D., Neziroglu, F., & Yaryura-Tobias, J. A. (1997). Comparison of clinical characteristics on obsessive-compulsive disorder. J Anxiety Disord, 11, 447-454.

221. McKeon, P. & Murray, R. (1987). Familial aspects of obsessive-compulsive neurosis. Br J Psychiatry, 151, 528-534.

222. Mendlowicz, M. V. & Stein, D. J. (2000). Quality of life in individuals with anxiety disorders. Am J Psychiatry, 157, 669-682.

223. Miguel, E. C., do Rosario-Campos, M. C., Prado, H. S., do, V. R., Rauch, S. L., Coffey, B. J., Baer, L., Savage, C. R., O'Sullivan, R. L., Jenike, M. A., & Leckman, J. F. (2000). Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. J Clin Psychiatry, 61, 150-156.

224. Miguel, E. C., Leckman, J. F., Rauch, S. L., do Rosario-Campos, M. C., Hounie, A. G., Mercadante, M. T., Chacon, P., & Pauls, D. L. (2005). Obsessive-compulsive disorder phenotypes: Implications for genetic studies. Mol Psychiatry, 10, 258-275.

225. Millar, D. G. (1983). Hostile emotion and obsessional neurosis. Psychol Med, 13, 813-819.

226. Minichiello, W. E., Baer, L., & Jenike, M. A. (1987). Schizotypal personality disorder: a poor prognostic indicator for behavior therapy in the treatment of obsessive-

compulsive disorder. J Anxiety Disord, 1, 273-276.

227. Minichiello, W. E., Baer, L., & Jenike, M. A. (1988). Behavior therapy for the treatment of obsessive-compulsive disorder: theory and practice. Compr Psychiatry, 29, 123-137.

228. Minichiello, W. E., Baer, L., Jenike, M. A., & Holland, A. (1990). Age of onset of major subtypes of obsessive-compulsive disorder. J Anxiety Disord, 4, 147-150.

229. Mogotsi, M., Kaminer, D., & Stein, D. J. (2000). Quality of life in the anxiety disorders. Harv Rev Psychiatry, 8, 273-282.

230. Mohr, N., Vythilingum, B., Emsley, R. A., & Stein, D. J. (2002). Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsive disorder. Int Clin Psychopharmacol, 17, 37-40.

231. Montgomery, S. A. & Montgomery, D. (1982). Pharmacological prevention of suicidal behaviour. J Affect Disord, 4, 291-298.

232. Moriarty, J., Eapen, V., Costa, D. C., Gacinovic, S., Trimble, M., Ell, P. J., & Robertson, M. M. (1997). HMPAO SPET does not distinguish obsessive-compulsive and tic syndromes in families multiply affected with Gilles de la Tourette's syndrome. Psychol Med, 27, 737-740.

233. Mundo, E., Bareggi, S. R., Pirola, R., & Bellodi, L. (1999). Effect of acute intravenous clomipramine and antiobsessional response to proserotonergic drugs: Is gender a predictive variable? Biol Psychiatry, 45, 290-294.

234. Murphy, T. K., Goodman, W. K., Fudge, M. W., Williams, R. C. Jr, Ayoub, E. M., Dalal, M., Lewis, M. H., & Zabriskie, J. B. (1997). B lymphocyte antigen D8/17: A peripheral marker for childhood-onset obsessive-compulsive disorder and Tourette's syndrome? Am J Psychiatry, 154, 402-407.

235. Murray, C. J. L. & Lopez, A. D. (1996). Global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. (Vols. 1) Harvard: World Health Organization.

236. Nagata, T., Kawarada, Y., Kiriike, N., & Iketani, T. (2000). Multi-impulsivity of Japanese patients with eating disorders: primary and secondary impulsivity. Psychiatry Res, 94, 239-250.

237. Nestadt, G., Addington, A., Samuels, J., Liang, K. Y., Bienvenu, O. J., Riddle, M., Grados, M., Hoehn-Saric, R., & Cullen, B. (2003). The identification of OCD-related subgroups based on comorbidity. Biol Psychiatry, 53, 914-920.

238. Nestadt, G., Lan, T., Samuels, J., Riddle, M., Bienvenu, O. J., III, Liang, K. Y., Hoehn-Saric, R., Cullen, B., Grados, M., Beaty, T. H., & Shugart, Y. Y. (2000a). Complex segregation analysis provides compelling evidence for a major gene underlying obsessive-compulsive disorder and for heterogeneity by sex. Am J Hum Genet, 67, 1611-1616.

239. Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O. J., III, Liang, K. Y., LaBuda, M., Walkup, J., Grados, M., & Hoehn-Saric, R. (2000b). A family study of obsessive-compulsive disorder. Arch Gen Psychiatry, 57, 358-363.

240. Nestadt, G., Samuels, J. F., Riddle, M. A., Bienvenu, O. J., Liang, K. Y., Grados, M. A., & Cullen, B. (2002). Obsessive-compulsive disorder: defining the phenotype. J Clin Psychiatry, 63 Suppl 6, 5-7.

241. Neziroglu, F., Anemone, R., & Yaryura-Tobias, J. A. (1992). Onset of obsessive-compulsive disorder in pregnancy. Am J Psychiatry, 149, 947-950.

242. Nicolini, H., Weissbecker, K., Mejia, J. M., & Sanchez, de C. (1993). Family study of

obsessive-compulsive disorder in a Mexican population. Arch Med Res, 24, 193-198.

243. Niehaus, D. J., Kinnear, C. J., Corfield, V. A., du Toit, P. L., van Kradenburg, J., Moolman-Smook, J. C., Weyers, J. B., Potgieter, A., Seedat, S., Emsley, R. A., Knowles, J. A., Brink, P. A., & Stein, D. J. (2001). Association between a catechol-o-methyltransferase polymorphism and obsessive-compulsive disorder in the Afrikaner population. J Affect.Disord, 65, 61-65.

244. Norman, R. M., Davies, F., Malla, A. K., Cortese, L., & Nicholson, I. R. (1996). Relationship of obsessive-compulsive symptomatology to anxiety, depression and schizotypy in a clinical population. Br J Clin Psychol, 35, 553-566.

245. Noshirvani, H. F., Kasvikis, Y., Marks, I. M., Tsakiris, F., & Monteiro, W. O. (1991). Gender-divergent aetiological factors in obsessive-compulsive disorder. Br J Psychiatry, 158, 260-263.

246. Oldham, J. M., Hollander, E., & Skodol, A. E. (1996). Impulsivity and compulsivity. Washington, DC: American Psychiatric Press.

247. Paul, T., Schroeter, K., Dahme, B., & Nutzinger, D. O. (2002). Self-injurious behavior in women with eating disorders. Am J Psychiatry, 159, 408-411.

248. Pauls, D. L., Alsobrook, J. P., Goodman, W., Rasmussen, S., & Leckman, J. F. (1995). A family study of obsessive-compulsive disorder. Am J Psychiatry, 152, 76-84.

249. Perse, T. L., Greist, J. H., Jefferson, J. W., Rosenfeld, R., & Dar, R. (1987). Fluvoxamine treatment of obsessive-compulsive disorder. Am J Psychiatry, 144, 1543-1548.

250. 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.

251. Petter, T., Richter, M. A., & Sandor, P. (1998). Clinical features distinguishing patients with Tourette's syndrome and obsessive-compulsive disorder from patients with obsessive-compulsive disorder without tics. J Clin Psychiatry, 59, 456-459.

252. Pfohl, B., Black, D. W., Noyes, R., Coryell, W. H., & Barreira, P. J. (1991). Axis I and axis II comorbidity findings: implications for validity. In J.M.Oldham (Ed.), Personality Disorders: New Perpectives on Diagnostic Validity. (Washington DC: American Psychiatric Press.

253. Phillips, K. A. (1991). Body dysmorphic disorder: the distress of imagined ugliness. Am J Psychiatry, 148, 1138-1149.

254. Phillips, K. A. (2002). Pharmacologic treatment of body dysmorphic disorder: review of the evidence and a recommended treatment approach. CNS Spectrum, 7, 453-460.

255. Phillips, K. A., Gunderson, C. G., Mallya, G., McElroy, S. L., & Carter, W. (1998). A comparison study of body dysmorphic disorder and obsessive-compulsive disorder. J Clin Psychiatry, 59, 568-575.

256. Phillips, K. A. & Najjar, F. (2003). An open-label study of citalopram in body dysmorphic disorder. J Clin Psychiatry, 64, 715-720.

257. Pigott, T. A., L'Heureux, F., Dubbert, B., Bernstein, S., & Murphy, D. L. (1994). Obsessive-compulsive disorder: comorbid conditions. J Clin Psychiatry, 55 Suppl, 15-27.

258. Pigott, T. A., Pato, M. T., Bernstein, S. E., Grover, G. N., Hill, J. L., Tolliver, T. J., & Murphy, D. L. (1990). Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results. Arch Gen Psychiatry, 47, 926-932.

259. Pitman, R. K. (1987). Pierre Janet on obsessive-compulsive disorder (1903). Review and commentary. Arch Gen Psychiatry, 44, 226-232.

260. Pitman, R. K. (1993). Posttraumatic obsessive-compulsive disorder: A case study. Compr Psychiatry, 34, 102-107.

261. Pitman, R. K., Green, R. C., Jenike, M. A., & Mesulam, M. M. (1987). Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. Am J Psychiatry, 144, 1166-1171.

262. Prichep, L. S., Mas, F., Hollander, E., Liebowitz, M., John, E. R., Almas, M., DeCaria, C. M., & Levine, R. H. (1993). Quantitative electroencephalographic subtyping of obsessive-compulsive disorder. Psychiatry Res, 50, 25-32.

263. Pryse-Phillips, W. (1971). An olfactory reference syndrome. Acta Psychiatr Scan, 47, 484-509.

264. Rachman, S. (1974). Primary obsessional slowness. Behav Res Ther, 12, 9-18.

265. Rachman, S. & Hodgson, R. (1980). Obsessions and compulsions. Englewood Cliffs: Prentice-Hall.

266. Radomsky, A. D. & Rachman, S. (2004). Symmetry, ordering and arranging compulsive disorder. Behav Res Ther, 42, 893-913.

267. Rapoport, J. L., Swedo, S. E., & Leonard, H. L. (1992). Childhood obsessive-compulsive disorder. J Clin Psychiatry, 53 Suppl, 11-16.

268. Rasmussen, S. A. (1994). Obsessive-compulsive spectrum disorders. J Clin Psychiatry, 55, 89-91.

269. Rasmussen, S. A. & Eisen, J. (1991). Phenomenology of OCD: Clinical subtypes,

heterogeneity and coexistence. In A.H.Zohar, T. R. Insel, & S. A. Rasmussen (Eds.), Psychobiology of OCD (pp. 13-43). New York: Springer-Verlag.

270. Rasmussen, S. A. & Eisen, J. L. (1988). Clinical and epidemiologic findings of significance to neuropharmacologic trials in OCD. Psychopharmacol Bull, 24, 466-470.

271. Rasmussen, S. A. & Eisen, J. L. (1992). The epidemiology and clinical features of obsessive-compulsive disorder. Psychiatr Clin North Am, 15, 743-758.

272. Rasmussen, S. A. & Tsuang, M. T. (1984). The epidemiology of obsessive-compulsive disorder. J Clin Psychiatry, 45, 450-457.

273. Rasmussen, S. A. & Tsuang, M. T. (1986). Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry, 143, 317-322.

274. Rauch, S. L. & Baxter, L. R. (1998). Neuroimaging in obsessive-compulsive disorder and related disorders. In M.A.Jenike, L. Baer, & W. E. Minichiello (Eds.), Obsessive-compulsive disorders: Practical management (3rd edition ed., St. Louis: Mosby.

275. Rauch, S. L. & Savage, C. R. (1997). Neuroimaging and neuropsychology of the striatum. Bridging basic science and clinical practice. Psychiatr Clin North Am, 20, 741-768.

276. Rauch, S. L., Savage, C. R., Alpert, N. M., Fischman, A. J., & Jenike, M. A. (1997). The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry, 42, 446-452.

277. Ravizza, L., Barzega, G., Bellino, S., Bogetto, F., & Maina, G. (1995). Predictors of drug treatment response in obsessive-compulsive disorder. J Clin Psychiatry, 56, 368-373.

278. Ravizza, L., Maina, G., & Bogetto, F. (1997). Episodic and chronic obsessive-compulsive

disorder. Depress Anxiety, 6, 154-158.

279. Rettew, D. C., Swedo, S. E., Leonard, H. L., Lenane, M. C., & Rapoport, J. L. (1992). Obsessions and compulsions across time in 79 children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry, 31, 1050-1056.

280. Richter, M. A., Summerfeldt, L. J., Antony, M. M., & Swinson, R. P. (2003). Obsessive-compulsive spectrum conditions in obsessive-compulsive disorder and other anxiety disorders. Depress.Anxiety., 18, 118-127.

281. Riddle, M. A., Scahill, L., King, R., Hardin, M. T., Towbin, K. E., Ort, S. I., Leckman, J. F., & Cohen, D. J. (1990). Obsessive-compulsive disorder in children and adolescents: phenomenology and family history. J Am Acad Child Adolesc Psychiatry, 29, 766-772.

282. Robinson, D., Wu, H., Munne, R. A., Ashtari, M., Alvir, J. M., Lerner, G., Koreen, A., Cole, K., & Bogerts, B. (1995). Reduced caudate nucleus volume in obsessive-compulsive disorder. Arch Gen Psychiatry, 52, 393-398.

283. Rocca, P., Ferrero, P., Gualerzi, A., Zanalda, E., Maina, G., Bergamasco, B., & Ravizza, L. (1991). Peripheral-type benzodiazepine receptors in anxiety disorders. Acta Psychiatr Scand, 84, 537-544.

284. Rosenberg, C. M. (1967). Familial aspects of obsessional neurosis. Br J Psychiatry, 113, 405-413.

285. Samuels, J., Bienvenu, O. J., III, Riddle, M. A., Cullen, B. A., Grados, M. A., Liang, K. Y., Hoehn-Saric, R., & Nestadt, G. (2002). Hoarding in obsessive-compulsive disorder: results from a case-control study. Behav Res Ther, 40, 517-528.

286. Sanavio, E. (1988). Obsessions and compulsions: the Padua Inventory. Behav Res Ther,

26, 169-177.

287. Sasson, Y., Zohar, J., Chopra, M., Lustig, M., Iancu, I., & Hendler, T. (1997). Epidemiology of obsessive-compulsive disorder: a world view. J Clin Psychiatry, 58 Suppl 12, 7-10.

288. Savage, C. R. (1997). Neuropsychology of subcortical dementias. Psychiatr Clin North Am, 20, 911-931.

289. Saxena, P. R., Maidment, K. M., Vapnik, T., Golden, G., Rishwain, T., Rosen, R. M., Tarlow, G., & Bystritsky, A. (2002). Obsessive-compulsive hoarding: symptom severity and response to multimodal treatment. J Clin Psychiatry, 63.

290. Saxena, S., Brody, A. L., Schwartz, J. M., & Baxter, L. R. (1998). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl 26-37.

291. Saxena, S. & Rauch, S. L. (2000). Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am, 23, 563-586.

292. Saxena, S., Winograd, A., Dunkin, J. J., Maidment, K., Rosen, R., Vapnik, T., Tarlow, G., & Bystritsky, A. (2001). A retrospective review of clinical characteristics and treatment response in body dysmorphic disorder versus obsessive-compulsive disorder. J Clin Psychiatry, 62, 67-72.

293. Schneier, F. R., Heckelman, L. R., Garfinkel, R., Campeas, R., Fallon, B. A., Gitow, A., Street, L., Del Bene, D., & Liebowitz, M. R. (1994). Functional impairment in social phobia. J Clin Psychiatry, 55, 322-331.

294. Seedat, S., Kesler, S., Niehaus, D. J., & Stein, D. J. (2000). Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with

dopaminergic agents. Depress Anxiety, 11, 185-186.

295. Sidenberg, D. G., Bassett, A. S., Demchyshyn, L., Niznik, H. B., Macciardi, F., Kamble, A. B., Honer, W. G., & Kennedy, J. L. (1993). New polymorphism for the human serotonin 1D receptor variant (5-HT1D beta) not linked to schizophrenia in five Canadian pedigrees. Hum Hered., 43, 315-318.

296. Simeon, D., Hollander, E., Stein, D. J., Cohen, L., & Aronowitz, B. (1995). Body dysmorphic disorder in the DSM-IV field trial for obsessive-compulsive disorder. Am J Psychiatry, 152, 1207-1209.

297. Singer, H. S., Hahn, I. H., & Moran, T. H. (1991). Abnormal dopamine uptake sites in postmortem striatum from patients with Tourette's syndrome. Ann Neurol, 30, 558-562.

298. Skoog, G. (1965). Onset of anancastic conditions. A clinical study. Acta Psychiatr Scand Suppl, 184, 1-82.

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

300. Sobin, C., Blundell, M. L., Weiller, F., Gavigan, C., Haiman, C., & Karayiorgou, M. (2000). Evidence of a schizotypy subtype in OCD. J Psychiatr Res, 34, 15-24.

301. Soloff, P. H., George, H., Nathan, R. S., Schulz, P. M., Ulrich, R. F., Perel, J. M. (1986). Progress in the pharmacotherapy of borderline personality disorders: A double-blind study of amitriptyline, haloperidol, and placebo. Arch Gen Psychiatry, 43, 691-697.

302. Starcevic, V., Uhlenhuth, E. H., Kellner, R., & Pathak, D. (1992). Patterns of comorbidity in panic disorder and agoraphobia. Psychiatry Res, 42, 171-183.

303. Stein, D. J. & Hollander, E. (1992). Low-dose pimozide augmentation of serotonin

reuptake blockers in the treatment of trichotillomania. J Clin Psychiatry, 53, 123-126.

304. Stein, D. J. & Hollander, E. (1993a). Impulsive aggression and obsessive-compulsive disorder. Psychiatr Annals, 23, 389-395.

305. Stein, D. J. & Hollander, E. (1993b). The spectrum of obsessive-compulsive related disorders. In Hollander E (Ed.), Obsessive-compulsive related disorders. Washington DC: American Psychiatric Press.

306. Stein, D. J., Hollander, E., Chan, S., DeCaria, C. M., Hilal, S., Liebowitz, M. R., & Klein, D. F. (1993). Computed tomography and neurological soft signs in obsessive-compulsive disorder. Psychiatry Res, 50, 143-150.

307. Stein, D. J., Hollander, E., Simeon, D., & Cohen, L. (1994). Impulsivity scores in patients with obsessive-compulsive disorder. J Nerv Ment Dis, 182, 240-241.

308. Stein, D. J., Hollander, E., Simeon, D., Cohen, L., Islam, M. N., & Aronowitz, B. (1994). Neurological soft signs in female trichotillomania patients, obsessive-compulsive disorder patients, and healthy control subjects. J Neuropsychiatry Clin Neurosci, 6, 184-187.

309. Stein, D. J., Roberts, M., Hollander, E., Rowland, C., & Serebro, P. (1996). Quality of life and pharmaco-economic aspects of obsessive-compulsive disorder. A South African survey. S.Afr.Med J, 86, 1579-1585.

310. Stein, D. J., Seedat, S., & Potocnik, F. (1999). Hoarding: a review. Isr.J Psychiatry Relat Sci, 36, 35-46.

311. Stein, D. J., Simeon, D., Cohen, L. J., & Hollander, E. (1995). Trichotillomania and obsessive-compulsive disorder. J Clin Psychiatry, 56 Suppl 4, 28-34.

312. Stein, D. J., Van Heerden, B., Wessels, C. J., van Kradenburg, J., Warwick, J., &

Wasserman, H. J. (1999). Single photon emission computed tomography of the brain with Tc-99m HMPAO during sumatriptan challenge in obsessive-compulsive disorder: investigating the functional role of the serotonin auto-receptor. Prog Neuropsychopharmacol Biol Psychiatry, 23, 1079-1099.

313. Steketee, G. (1990). Personality traits and disorders in obsessive-compulsives. J Anxiety Disord, 4, 351-364.

314. Stern, R. & Cobb, J. (1978). Phenomenology of obsessive-compulsive neurosis. Br J Psychiatry, 132, 233-239.

315. Stoll, A. L., Tohen, M., & Baldessarini, R. J. (1992). Increasing frequency of the diagnosis of obsessive-compulsive disorder. Am J Psychiatry, 149, 638-640.

316. Summerfeldt, L. J., Kloosterman, P. H., Antony, M. M., Richter, M. A., & Swinson, R. P. (2003). The relationship between miscellaneous symptoms and major symptom factors in obsessive-compulsive disorder. Behav Res Ther, In press.

317. Summerfeldt, L. J., Richter, M. A., Antony, M. M., & Swinson, R. P. (1999). Symptom structure in obsessive-compulsive disorder: A confirmatory factor-analytic study. Behav Res Ther, 37, 297-311.

318. Swedo, S. E. (1993). Is trichotillomania an obsessive-compulsive spectrum disorder? In The obsessive-compulsive related disorders. Edited by Hollander E. Washington, DC: American Psychiatric Press.

319. Swedo, S. E., Leonard, H., Mittleman, B. B., Allan, A. J., Rapoport, J. L., Dow, S. P., Kanter, M. E., Chapman, F., & Zabriskie, J. (1997). Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. Am J Psychiatry, 154, 110-

112.

320. Swedo, S. E. & Leonard, H. L. (1994). Childhood movement disorders and obsessive-compulsive disorder. J Clin Psychiatry, 55 Suppl, 32-37.

321. Swedo, S. E., Leonard, H. L., & Kiessling, L. S. (1994). Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics, 93, 323-326.

322. Swedo, S. E., Leonard, H. L., & Rapoport, J. L. (1992). Childhood-onset obsessive-compulsive disorder. Psychiatr Clin North Am, 15, 767-775.

323. Swedo, S. E. & Rapoport, J. L. (1989). Phenomenology and differential diagnosis of obsessive-compulsive disorder in children and adolescents. In J.L.Rapoport (Ed.), Obsessive-Compulsive Disorder in Children and Adolescents (pp. 13-32). Washington DC: American Psychiatric Press.

324. Swedo, S. E., Rapoport, J. L., Leonard, H., Lenane, M., & Cheslow, D. (1989). Obsessive-compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry, 46, 335-341.

325. Takeuchi, A., Nakagawa, A., Harai, H., Nakatani, E., Fujikawa, S., Yoshizato, C., & Yamagami, T. (1997). Primary obsessional slowness: Long-term findings. Behav Res Ther, 35, 445-449.

326. Taylor, S. (1998). Assessment of obsessive-compulsive disorder. In R.P.Swinson, M. M. Antony, S. Rachman, & M. A. Richter (Eds.), Obsessive-compulsive disorder: Theory, research, and treatment. (pp. 229-257). New York: Guilford Press.

327. Tek, C. & Ulug, B. (2001). Religiosity and religious obsessions in obsessive-compulsive disorder. Psychiatry Res, 104, 99-108.

328. Thienemann, M. & Koran, L. M. (1995). Do soft signs predict treatment outcome in

obsessive-compulsive disorder? J Neuropsychiatry Clin Neurosci, 7, 218-222.

329. Thomsen, P. H. (1995). Obsessive-compulsive disorder in children and adolescents: predictors in childhood for long-term phenomenological course. Acta Psychiatr Scand, 92, 255-259.

330. Thomsen, P. H. & Jensen, J. (1991). Latent class analysis of organic aspects of obsessive-compulsive disorder in children and adolescents. Acta Psychiatr Scand, 84, 391-395.

331. Thomsen, P. H. & Mikkelsen, H. U. (1993). Development of personality disorders in children and adolescents with obsessive-compulsive disorder. A 6- to 22-year follow-up study. Acta Psychiatr Scand, 87, 456-462.

332. Thomsen, P. H. & Mikkelsen, H. U. (1995). Course of obsessive-compulsive disorder in children and adolescents: a prospective follow-up study of 23 Danish cases. J Am Acad Child Adolesc Psychiatry, 34, 1432-1440.

333. Thoren, P., Asberg, M., Cronholm, B., Jornestedt, L., & Traskman, L. (1980). Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. Arch Gen Psychiatry, 37, 1281-1285.

334. Thornton, C. & Russell, J. (1997). Obsessive-compulsive comorbidity in the dieting disorders. Int J Eat.Disord, 21, 83-87.

335. Toro, J., Cervera, M., Osejo, E., & Salamero, M. (1992). Obsessive-compulsive disorder in childhood and adolescence: a clinical study. J Child Psychol Psychiatry, 33, 1025-1037.

336. Trumbull, D. W. (2001). Obsessive-compulsive symptomatology: a goal-directed response to anticipated traumatization? Psychiatry, 64, 309-318.

337. Tukel, R., Keser, V., Karali, N., Olgun, T., & Calikusu, C. (2001). Comparison of clinical characteristics in trichotillomania and obsessive-compulsive disorder. J Anxiety Disord, 15, 433-441.

338. Uebersax, J. (2000). A practical guide to local dependence in latent class models. http:ourworld.compuserve.com/homepages/jsuebersax/condep.htm.

339. Van Ameringen, M., Oakman, J. M., Mancini, C., & Farvolden, P. (2001). Obsessive-compulsive spectrum disorders: From serotonin to dopamine and back again. In Fineberg N, Marazziti D, & Stein DJ (Eds.), Obsessive-compulsive disorder: A practical guide (pp. 23-36). London: Martin Dunitz Ltd.

340. Van Oppen, P., Hoekstra, R. J., & Emmelkamp, P. M. (1995). The structure of obsessive-compulsive symptoms. Behav Res Ther, 33, 15-23.

341. Vandenbergh, D. J., Persico, A. M., Hawkins, A. L., Griffin, C. A., Li, X., Jabs, E. W., & Uhl, G. R. (1992). Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics, 14, 1104-1106.

342. Veale, D. (1993). Classification and treatment of obsessional slowness. Br J Psychiatry, 162, 198-203.

343. Vermunt, J. & Magidson, J. (2002). Latent Gold 3.0 upgrade manual. Belmont: Statistical Innovations.

344. Vermunt, J. K. & Magidson, J. (2002). Latent class cluster analysis. In J.A.Hagenaars & A. L. McCutcheon (Eds.), Advances in latent class analysis. Cambridge University Press.

345. Ward, J. H. (1963). Hierarchical grouping to optimize an objective function. J Am Stat Assoc, 58, 236-244.

346. Warren, J. T., Jr., Peacock, M. L., Rodriguez, L. C., & Fink, J. K. (1993). An MspI polymorphism in the hyman serotonin receptor gene (HTR2): Detection by DGGE and RFLP analysis. Hum Mol Genet, 2, 338.

347. Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Lee, C. K., Newman, S. C., Oakley-Browne, M. A., Rubio-Stipec, M., & Wickramaratne, P. J. (1994). The cross-national epidemiology of obsessive-compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry, 55 Suppl, 5-10.

348. - Welner, A., Reich, T., Robins, E., Fishman, R., & Van Doren, T. (1976). Obsessive-compulsive neurosis: record, follow-up, and family studies. I. Inpatient record study. Compr Psychiatry, 17, 527-539.

349. Wever, C. & Rey, J. M. (1997). Juvenile obsessive-compulsive disorder. Aust N Z J Psychiatry, 31, 105-113.

350. Williams, K. E. & Koran, L. M. (1997). Obsessive-compulsive disorder in pregnancy, the puerperium, and the premenstruum. J Clin Psychiatry, 58, 330-334.

351. Winchel, R. M. & Stanley, M. (1991). Self-injurious behavior: a review of the behavior and biology of self-mutilation. Am J Psychiatry, 148, 306-317.

352. Winsberg, M. E., Cassic, K. S., & Koran, L. M. (1999). Hoarding in obsessive-compulsive disorder: A report of 20 cases. J Clin Psychiatry, 60, 591-597.

353. Yaryura-Tobias, J. A., Anderson, M. C., & Neziroglu, F. A. (2000). Organicity in obsessive-compulsive disorder. Behav Modif., 24, 553-565.

354. Yates, T. M. (2004). The developmental psychopathology of self-injurious behavior: Compensatory regulation in posttraumatic adaptation. Clinical Psychology Review, 24, 35-74.

355. Zitterl, W., Lenz, G., Mairhofer, A., & Zapotoczky, H. G. (1990). Obsessive-compulsive disorder: course and interaction with depression. A review of the literature. Psychopathology, 23, 73-80.

356. Zohar, A. H. (1999). The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am, 8, 445-460.

357. Zohar, A. H., Pauls, D. L., Ratzoni, G., Apter, A., Dycian, A., Binder, M., King, R., Leckman, J. F., Kron, S., & Cohen, D. J. (1997). Obsessive-compulsive disorder with and without tics in an epidemiological sample of adolescents. Am J Psychiatry, 154, 274-276.

358. Zohar, J. & Insel, T. R. (1987). Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. Biol Psychiatry, 22, 667-687.

359. Zohar, J. & Insel, T. R. (1987). Drug treatment of obsessive-compulsive disorder. J Affect.Disord, 13, 193-202.

ADDENDUM 2

LIST OF TABLES

CHAPTER 1:	TABLE 1.	OCD classification studies using the YBOCS-CL
CHAPTER 3:	TABLE 1.	The major symptom categories with example items
	TABLE 2.	The 45 YBOCS-CL – items included in the current and subsequent analyses
	TABLE 3.	Frequencies in which the YBOCS-CL – items were reported (N=261) – in descending order
	TABLE 4.	Frequencies of the major symptom categories of the YBOCS-CL in 261 OCD patients
	TABLE 5.	Statistically significant associations between individual obsessive-compulsive symptoms and onset age
	TABLE 6.	Statistically significant associations between individual obsessive-compulsive symptoms and gender
	TABLE 7.	Statistically significant associations between individual obsessive-compulsive symptoms and population group
	TABLE 8.	Effect of presence / absence of each obsessive-compulsive symptom on the total mean OCD severity (YBOCS-SS) scores:
	TABLE 9.	Total OCD severity (YBOCS-SS) and disability (Disability Profile) scores in each of the major symptom categories
CHAPTER 4:	TABLE 1.	The two major classes of cluster analysis

TABLE 2. Marginal frequency table of the two most frequently occurring OC symptoms as assessed with the YBOCS-CL

TABLE 3. Joint frequency table of the two most frequently occurring OC symptoms as assessed with the YBOCS-CL

TABLE 4. Joint frequency table of the four most frequently occurring OC symptoms as assessed with the YBOCS-CL

TABLE 5. The YBOCS-CL item descriptions and numbers of the nine most prevalent OC symptoms and the frequency of occurrence of each in 261 OCD patients

TABLE 6. Graphical display of associations between the nine most prevalent symptoms

TABLE 7. Model fitting statistics for the nine indicators (OC symptoms) occurring most frequently

TABLE 8. Frequencies of patients with a Six-cluster solution vs a Four-cluster solution

TABLE 9. The distribution of the absence or presence of YBOCS-CL item nr 45 ‘Mental compulsions’ in the six clusters

TABLE 10. The distribution of the absence or presence of YBOCS-CL item nr 38 ‘Checking that did not make a mistake’ in the six clusters

TABLE 11. The distribution of the absence or presence of YBOCS-CL item nr 40 ‘Re-reading or re-writing’ in the six clusters

TABLE 12. The distribution of the absence or presence of YBOCS-CL item nr 11 ‘Concern with dirt or germs’ in the six clusters

TABLE 13. The distribution of the absence or presence of YBOCS-CL item nr 43 ‘Ordering / arranging compulsions’ in the six clusters

TABLE 14. The distribution of the absence or presence of YBOCS-CL item nr 34 ‘Checking locks, stove, appliances, etc.’ in the six clusters

TABLE 15. The distribution of the absence or presence of YBOCS-CL item nr 42 ‘Counting compulsions’ in the six clusters

TABLE 16. The distribution of the absence or presence of YBOCS-CL item nr 30 ‘Excessive or ritualised hand washing’ in the six clusters

TABLE 17. The distribution of the absence or presence of YBOCS-CL item nr 27 ‘Need for symmetry or exactness not accompanied by magical thinking’ in the six clusters

TABLE 18. The gender distribution within the six clusters

TABLE 19. The descriptive statistics of age with respect to gender within the six clusters

TABLE 20. The associations between the total OCD severity score and the genders within each of the clusters

TABLE 21. OCD severity scores of patients according to response to CBT in Clusters 1 – 6: All patients (N = 261)

TABLE 22. OCD severity scores of patients according to response to medication in Clusters 1 – 6: All patients (N = 261)

CHAPTER 5: TABLE 1. Correlations (Spearman) amongst Clusters I – VI

TABLE 2. Analysis of variance for the three COMT genotypes (Caucasians)

TABLE 3. Mann-Whitney U-test for alleles of the *COMT Val158Met* polymorphism

ADDENDUM 3

LIST OF FIGURES

CHAPTER 4: FIGURE 1. Stem-and-Leaf Diagram of the frequencies present in the 16 cells in the joint distribution of the four highest OC symptoms (items nr 11, 40, 38 and 45)

FIGURE 2. Stem-and-Leaf Diagram of the frequencies present in the 512 cells in the joint distribution of the nine most frequently occurring OC symptoms

CHAPTER 5: FIGURE 1. Cluster analysis (Ward's method) results: Tree Diagram for nine YBOCS-CL items*

FIGURE 2. Cluster analysis (Ward's method) results: Tree Diagram for 45 YBOCS-CL items

CHAPTER 6: FIGURE 1. Cluster analysis (Ward's method) results: Tree diagram

ADDENDUM 4

LIST OF PUBLICATIONS RESULTING FROM THIS DISSERTATION

1. Lochner C, Stein DJ. (2003). Heterogeneity of obsessive-compulsive disorder: A literature review. Harvard Review of Psychiatry, 11:113 - 132.

2. Lochner C, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA, Niehaus DJH, Stein DJ. (2004). Gender in obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: Clinical and genetic findings. European Neuropsychopharmacology, 14:437 - 445.

3. Lochner C, Niehaus DJH, Hemmings SMJ, Kinnear CJ, Corfield VA, Moolman-Smook JC, Seedat S, Stein DJ. (2005). Cluster analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder. Compr Psychiatry, 46:14 – 19.

ADDENDUM 5

LIST OF ABBREVIATIONS FREQUENTLY USED THROUGHOUT DISSERTATION:

• DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
• Obsessive-compulsive disorder	OCD
• Obsessive-compulsive spectrum disorder	OCSD
• Social anxiety disorder	SAD
• Tourette's disorder / syndrome	TD
• Trichotillomania	TTM
• Body dysmorphic disorder	BDD
• Stereotypic movement disorder	SMD
• Pathological gambling	PG
• Personality disorder	PD
• Obsessive-compulsive personality disorder	OCPD
• Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	PANDAS
• Serotonin reuptake inhibitor	SRI
• Cognitive Behavioural Therapy	CBT
• Structured Clinical Interview for AXIS I disorders – Patient Version	SCID-I/P
• Structured Clinical Interview for Obsessive-Compulsive Spectrum Disorders	SCID-OCSD
• Yale-Brown Obsessive-Compulsive	

Symptom Checklist	YBOCS-CL
• Yale-Brown Obsessive-Compulsive Symptoms Severity Scale	YBOCS-SS
• Disability Profile	DP
• Childhood Trauma Questionnaire	CTQ
• Temperament and Character Inventory	TCI
• Quality of Life	QOL
• Factor analysis	FA
• Cluster analysis	CA
• Latent class analysis	LCA

ADDENDUM 6

PUBLICATIONS

Peer-reviewed publications (in chronological order):

1.) Lochner C, Vythilingum B, Stein DJ. 2001. Olfactory reference syndrome: diagnostic criteria and differential diagnosis. Primary Care Psychiatry; 7 (2):55-59.

2.) Lochner C, Simeon D, Niehaus DJH, Stein DJ. 2001. Skin-picking and trichotillomania: A Phenomenological comparison. Depression & Anxiety; 15 (2):83-86.

3.) Lochner C, du Toit W, Zungu-Dirwayi N, van Kradenburg J, Marais A, Seedat S, Niehaus DJH, Stein DJ. 2001. Childhood interpersonal trauma in obsessive-compulsive disorder, trichotillomania, and controls. Depression and Anxiety; 15 (2):66-68.

4.) Lochner C, Stein DJ. 2001. Gender in obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: A literature review. Archives of Women's Mental Health; 4: 19-26.

5.) Hemmings SMJ, Kinnear CJ, Niehaus DJH, Moolman-Smook JC, Lochner C, Knowles JA, Corfield VA, Stein DJ. 2003. Investigating the role of dopaminergic and serotonergic candidate genes in obsessive-compulsive disorder. European Neuropsychopharmacology, 13: 93–98.

6.) Lochner C, Stein DJ. 2003. Heterogeneity of obsessive-compulsive disorder: A literature review. Harvard Review of Psychiatry, 11:113-132.

7.) Koen L, Oosthuizen PP, Niehaus DJH, Emsley RA, Muller JE, Stein DJ, Keyter N, Lochner C, Seedat, S. 2003. Prevalence of obsessive-compulsive disorder in first- and multi-episode male patients with schizophrenia-spectrum disorders. (Letter to the editor.) SAMJ, 93 (7): 517-518.

8.) Lochner C, Mogotsi M, du Toit PL, Kaminer D, Niehaus DJH, Stein DJ. 2003. Quality

of life in the anxiety disorders: a comparison of obsessive-compulsive disorder, panic disorder and social anxiety disorder. Psychopathology, 36 (5): 255-262.

9.) Lochner C & Stein DJ. 2003. Olfactory reference syndrome: Diagnostic criteria and differential diagnosis. Journal of Postgraduate medicine, 49 (4): 328-331.

10.) Hemmings SMJ, Kinnear CJ, Lochner C, Niehaus DJH, Knowles JA, Moolman-Smook JC, Corfield VA, Stein DJ. 2004. Early- versus late-onset obsessive-compulsive disorder: investigating genetic and clinical correlates. Psychiatry Research, 128 (2): 175-82.

11.) Lochner C, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA, Niehaus DJH, Stein DJ. 2004. Gender in obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: Clinical and genetic findings. Eur Neuropsychopharmacol. 2004 Oct;14 (5):437-445.

12.) Lochner C, Seedat S, Hemmings SMJ, Kinnear CJ, Corfield VA, Niehaus DJH, Moolman-Smook JC, Stein DJ. 2004. Dissociative experiences in obsessive-compulsive disorder and trichotillomania: Clinical and genetic findings. Compr Psychiatry, 45 (5): 384-391.

13.) Hemmings SMJ, Kinnear CJ, Lochner C, Niehaus DJH, Knowles JA, Moolman-Smook JC, Corfield VA, Stein DJ. Genetic correlates in TTM: A case-control association study in the South African Caucasian population. In press, J Affective Disorders, July 2003.

14.) Niehaus DJH, Oosthuizen P, Lochner C, Emsley RA, Jordaan E, Mbanga NI, Keyter N, Laurent C, Deleuze J-F, Stein DJ. 2004. A culture-bound syndrome "amafufunyana" and a culture-specific event "twasa": Differentiated by a family history of psychiatric disorders. Psychopathology, 37 (2):59 - 63. Epub 2004 Mar 31.

15.) Lochner C. 2004. Anxiety disorders, disability, and quality of life. Continued

Medication Education (CME) Journal, 22 (10): 574.

16.) Lochner C. 2004. Screening tools for anxiety in primary care. Continued Medication Education (CME) Journal, 22 (10): 575.

17.) Lochner C, Seedat S, Du Toit PL, Sandler R, Niehaus DJH, Stein DJ. 2005. Obsessive-compulsive disorder and trichotillomania: A phenomenological comparison. BMC Psychiatry, 5: 2.

18.) Lochner C, Hemmings SMJ, Kinnear CJ, Niehaus DJH, Nel DG, Corfield VA, Moolman-Smook JC, Seedat S, Stein DJ. 2005. Cluster analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder. Compr Psychiatry, 46 (1): 14-19.

CONFERENCE PROCEEDINGS

1.) Lochner C, Kruger L. 1999. Oral presentation: Women on Farms: Discourses of Distress. Psychology of Women Section Conference (BPA), Manchester Metropolitan University, UK.

2.) Lochner C, Kruger L. 1999. Oral presentation: Women on Farms: Discourses of Distress. 5th Annual SA: International Qualitative Methods Conference: Normality and Pathology, Wits University, South Africa.

3.) Lochner C. 2000. Oral presentation: The psychological treatment of anxiety disorders. Solvay CPD Program: Hosted by the Mental Health Information Centre of South Africa, Tygerberg Medical Campus.

4.) Lochner C, Simeon D, Niehaus DJH, Stein DJ. 2001. Oral presentation: Trichotillomania and skin-picking: a phenomenological comparison. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

5.) Lochner C, Mogotsi M, du Toit PL, Kaminer D, Niehaus DJH, Stein DJ. 2001. Oral presentation: Quality of life in the anxiety disorders: a comparison of obsessive-compulsive disorder and panic disorder. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

6.) Lochner C, Simeon D, Niehaus DJH, Stein DJ. 2001. Poster presentation: Trichotillomania and skin-picking: a phenomenological comparison. Psychopharmacology Conference, Spier Wine Estate, Stellenbosch.

7.) Lochner C, Mogotsi M, du Toit PL, Kaminer D, Niehaus DJH, Stein DJ. 2001. Poster presentation: Quality of life in the anxiety disorders: a comparison of obsessive-compulsive disorder, social anxiety disorder and panic disorder. Psychopharmacology Conference, Spier Wine Estate, Stellenbosch.

8.) Serebro P, Lochner C, Niehaus DJH. 2001. Poster presentation: Obsessive-Compulsive Disorder Association of South Africa (OCDSA). Psychopharmacology Conference, Spier Wine Estate, Stellenbosch.

9.) Lochner C, Stein DJ, Niehaus DJH, De Bruin GP. 2001. Poster presentation: Obsessive-compulsive disorder: Determination of possible relationship with specific personality dimensions. World Psychiatric Association Conference, Madrid, Spain.

10.) Hemmings SMJ, Kinear CJ, Niehaus DJH, Lochner C, Moolman-Smook HC, Brink PA, Corfield VA, Stein DJ. 2001. Poster presentation: Obsessive-compulsive disorder in the genetically homogeneous Afrikaner population - A case-control association study with polymorphisms in the serotonin and dopamine transporter genes. World Psychiatric Association Conference, Madrid, Spain.

11.) Lochner C. August 2002. Attendance and presentation of Genetics of obsessive-compulsive disorders research (MRC Unit on Anxiety and Stress Disorders) at start-up meeting of International Obsessive-Compulsive Foundation Genetics

Consortium in Philadelphia, USA.

12.) Lochner C, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Corfield VA, Niehaus DJH, Stein DJ. 2002. Oral presentation: Gender in obsessive-compulsive disorder: clinical and genetic findings. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

13.) Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Lochner C, Niehaus DJH, Corfield VA, Stein DJ. 2002. Poster presentation: Dissecting the genetic aetiology of obsessive-compulsive disorder (OCD): Early- vs late-onset OCD. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

14.) Koen L, Niehaus DJH, Lochner C, Daniels J, Kotze M, Warnich L, Stein DJ. 2002. Poster presentation: Pharmacogenetics: prospects for the future. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

15.) Niehaus DJH, Oosthuizen P, Lochner C, Emsley RA, Jordaan E, Mbanga NI, Keyter N, Laurent C, Deleuze J-F, Stein DJ. 2002. Poster presentation: The culture bound syndrome "amafufunyana" and a culture-specific event "twasa": Differentiated by a family history of psychiatric disorders. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

16.) Muller JE, Lochner C, Daniels JF, Niehaus DJH, Stein DJ. 2002. Poster presentation: Handwriting in obsessive-compulsive disorder, panic and social anxiety disorder. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

17.) Lochner C, Seedat S, Carey PD, Stein DJ. 2003. Poster presentation: Dissociative experiences in obsessive-compulsive disorder and trichotillomania: Role of childhood trauma. American Psychiatric Association (APA), San Francisko, USA.

18.) Lochner C, Niehaus DJH, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC,

Corfield VA, Seedat S, Stein DJ. 2003. Oral presentation: Factor analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder: Clinical and genetic correlates. Prize winner for best presentation. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch.

19.) Lochner C, Seedat S, Carey PD, Stein DJ. 2003. Poster presentation: Dissociative experiences in obsessive-compulsive disorder and trichotillomania: Role of childhood trauma. Academic Year Day, Faculty of Health Sciences, University of Stellenbosch. Prize winner for oral and poster presentation of good quality (Category: Neurosciences).

20.) Lochner C, Niehaus DJH, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Corfield VA, Seedat S, Stein DJ. 2003. Poster presentation: Factor analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder: Clinical and genetic correlates. Psychopharmacology Conference 2003, Spier Wine Estate, Stellenbosch.

21.) Lochner C, Seedat S, Carey PD, Stein DJ. 2003. Poster presentation: Dissociative experiences in obsessive-compulsive disorder and trichotillomania: Role of childhood trauma. Psychopharmacology Conference 2003, Spier Wine Estate, Stellenbosch.

22.) Lochner C, Seedat S, Du Toit PL, Sandler R, Niehaus DJH, Stein DJ. 2004. Poster presentation: Obsessive-compulsive disorder and trichotillomania: A phenomenological comparison. Anxiety Disorders Association of America (ADAA), Miami, Florida.

23.) Lochner C, Hemmings SMJ, Kinnear CJ, Niehaus DJH, Nel DG, Corfield VA, Moolman-Smook JC, Seedat S, Stein DJ. 2005. Cluster analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder:

Clinical and genetics correlates. Collegium Internationale Neuro-Psychopharmacologicum (CINP), Paris, France.

24.) Lochner C, Hemmings SMJ, Kinnear CJ, Moolman-Smook JC, Seedat S, Nel DG, Stein DJ. 2005. Cluster analysis of obsessive-compulsive symptomatology: Identifying obsessive-compulsive subtypes. Collegium Internationale Neuro-Psychopharmacologicum (CINP) (Psychiatry Division), Cape Town.

25.) Lochner C. May 2005. Attendance and presentation of Genetics of obsessive-compulsive disorders research (MRC Unit on Anxiety and Stress Disorders) at most recent meeting of International Obsessive-Compulsive Foundation Genetics Consortium in Boston, USA.

AWARDS

1.) Rafaelson Fellowship Award, for outstanding young investigators in neuropsychopharmacology research, by Collegium Internationale Neuropsychopharmicologicum (CINP).

2.) Lundbeck International Neuroscience Foundation (LINF) Sponsorship Award for Young Scientists 2004.