CHAPTER 12

# Discussion & Summary

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This thesis describes the study of genetic and environmental influences on individual differences in Obsessive-Compulsive Symptoms (OCS) across a large part of the lifespan. In this last chapter, the findings that have resulted from this project are summarised, discussed and some directions for future studies are considered.

## PART I. INTRODUCTION TO OCD, OCS AND TWIN STUDIES

**Chapter 2** provided a brief overview of Obsessive-Compulsive Disorder (OCD). OCD is a complex psychiatric disorder characterized by obsessions and/or compulsions. Obsessive-compulsive disorder has a relatively high prevalence of roughly 1% and is a highly disabling disease. The disorder is associated with shame, which causes long delays in accessing treatment. Differences between people in the liability to develop OCD are caused by a combination of genetic and environmental factors. Effective treatments exist, either pharmacotherapy or cognitive behavior therapy. In **chapter 3**, all known published twin studies on OCD/OCS have been described and over 70 years of twin research of OCD/OCS was presented. Four different approaches to twin studies of OCD/OCS were recognized. These approaches include (1) case-studies of twins with OCD from the old literature, (2) twin studies of OCD using *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, (3) twin studies of OCD using a dimensional approach, comparing resemblances in monozygotic and dizygotic twins, and (4) twin studies of OCD using a dimensional approach, analyzing the data with Structural Equation Modeling. It was concluded that only the studies using the last method have convincingly shown that obsessive-compulsive symptoms are heritable with genetic influences in children in the range of 45% to 65%. In adults, studies are suggestive for a genetic influence on obsessive-compulsive symptoms, ranging from 27% to 47%, but a large twin study using a biometrical approach with continuous data is still needed to provide conclusive evidence, including a closer look at sex-differences, issues of phenotypic assortment and cultural transmission in genetic architectures. That is exactly what I have done in this thesis.

## PART II. HERITABILITY, ASSORTATIVE MATING AND CULTURAL TRANSMISSION OF OCS

In **chapter 4** the genetic and environmental influences on OC symptoms were investigated in a large population based twin-family study. The OC scale of the YASR, based on the CBCL-OCS, developed by the group of Hudziak (Nelson *et al.*, 2001; Hudziak *et al.*, 2006) was used. The YASR-OCS contains the same 8 items as the CBCL-OCS, except that items are worded in the first person. At the best cut-off point of 7, the sensitivity and specificity of the YASR-OCS was 82.4% and 69.7% respectively, when compared to clinical controls, with a Cronbach's $\alpha$ coefficient of .69. YASR-OCS data were available in 5893 mono -and dizygotic twins, and 1304 additional siblings. There was no evidence for a special twin environment as familial resemblance was the same for DZ twins and non-twin siblings. The same genetic risk factors for OC behavior were expressed in men and women. Depending on the choice of fit-index we found small (heritability of 39% for men and 50% for women) or no sex-differences (heritability of 47% for both men and women) in heritability. The remaining variance in OC liability was due to non-shared environment. Thus, in the largest study to date, we found that OC symptoms showed a moderate heritability with no qualitative and, at most, small quantitative differences in genetic architecture.

The **fifth chapter** explored the existence and causes of marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample of around 1400 twin-spouse and over 850 parent pairs. Resemblance between spouses can be due to phenotypic assortment, social homogamy or marital interaction. Phenotypic assortment means that partner selection is based directly on the partner's phenotype; there is a preference for a phenotype like one's own, resulting in marital resemblance. Social homogamy refers to the tendency for individuals to have partners with similar social background, e.g. coming from the same religious background. Under social homogamy partner selection takes place within social strata, which are correlated with the phenotype under study. Marital interaction or shared influences after marriage refers to a process of mutual influences between spouses living together. In addition to the process of initial assortment, spouses may become more similar the longer they are married due to mutual influence between spouses or by sharing the same pathological factors. A significant degree of assortment, if it is due to phenotypic assortment, has consequences for the genetic architecture of a population. We found small but significant within-trait corre-

lations between .1 and .2 for spouse similarity in obsessive, anxious and depressive behavior as measured by the YASR-OCS, YASR anxious-depressed subscale and the STAI. Cross-trait correlations were also significant but lower. There was no correlation between length of relationship and marital resemblance, indicating that resemblance between spouses does not increase as a function of duration of marriage. Marital correlations were small, which makes it difficult to distinguish between social homogamy and phenotypic assortment, but as shared environmental influences explaining individual differences in OC symptoms have hardly been found in adults, it seems likely that phenotypic assortment is the main process. It is unlikely that correlations of this size will have a large impact on genetic studies. The purpose of **chapter 6** was to examine the role of genetic and environmental factors to variation in OC symptoms using an extended twin design, including 4408 twins, 1309 siblings, and 2305 parents. This design allows us to test for genetic and environmental factors, while taking phenotypic assortment and cultural transmission, the influence of the parental phenotype on shared environmental factors of the children, into account. The 12-item Padua Inventory Revised Abbreviated was used to measure OC symptoms. We found that both additive genetic and non-shared environmental factors contributed significantly to the variance of OC symptoms in men and women. In males, shared environmental influences played a relative large role (27%) with a small role for genetic factors (1%). Significant influence of cultural transmission was only found for men, but was minimal (<1%). Non-shared factors explained 71% of the variance of OC symptoms. For women, the heritability was estimated at 37% and non-shared environment explained 63% of the total variance in individual differences in OC symptoms. No evidence for a special twin environment was seen, cultural transmission, from parent to son, was small, suggesting that the effect of the shared environment in men mainly has a non-parental origin and is primarily due to within generational influences.

We concluded from part I that a large twin study on OC symptoms was lacking. Part II fills up this gap with two large twin studies using two different OC questionnaires. One may conclude that OC symptoms are heritable in women, independent of the measurement instrument , with roughly a heritability of 40-45%. For men, we found an similar heritability using the YASR-OCS, but also an influence of shared environment when OC was assessed with the Padua-ABBR. The results of the YASR-OCS for both men and women are in line with the results found in children and adolescents, so it seems that the shared environmental influences found for the Padua-ABBR are the exception. The Padua showed also low heritabilities in the Jonnal *et al.* study (2000) and has low correlations with for example the YBOCS (Denys *et al.*, 2004). The largest differences between YASR-OC and Padua-OC were seen for the DZM-correlations, which are quite high for Padua-OC in comparison with the DZM-correlations in the YASR-OCS study. The MZM correlations of the Padua-ABBR are in the same range as in the YASR-OCS study (chapter 4). Future research must establish whether the shared influences in men for the Padua-ABBR is a coincidental finding or that it was "real" shared environment (C). Earlier, C had not been detected in twin studies of OC symptoms, except in children at the age of 12 years (chapter 7). Furthermore, when YASR-OCS and Padua-ABBR data were used together in longitudinal analyses, no significant shared environmental factors were found (chapter 9).

Another focus of Part I was testing of several assumptions of twin studies like the absence of assortative mating or gene-environment correlation induced by simultaneous cultural and genetic transmission. Assortative mating exists for OC symptoms, but it is small, so that the bias in estimates for A, C and E is minimal. Gene-environmental correlations induced by genetic and cultural transmission were significant only for men, but explained only a small part of the variation in OC symptoms. Consistent with earlier findings (e.g. Jonnal *et al.*, 2000) no evidence was found for a special twin-environment (chapters four and five).

One assumption which was not tested in this thesis is whether OCD reflects the extreme of a normal distribution, while OC symptoms represent a milder form of the latter. There is indirect evidence that this is the case, but it is not explicitly tested yet, for example by fitting item-response models, as van den Oord *et al.* (2003) did for depression. The indirect evidence lies in the fact that family studies (Pauls *et al.*, 1995, Nestadt *et al.*, 2000) show that family members of OC patients have fewer OC symptoms than the proband with OCD, but more than controls and their families. However, without directly proving this assumption, one should be careful with conclusions that extend findings in the general population to a specific disease.

*Part II* of this thesis (Heritability, assortative mating and cultural transmission of OCS) has important clinical consequences. It is not long ago that parents of patients with psychiatric disorders, such as schizophrenia, were blamed for the disease of their offspring. Twin studies can be particularly effective in disentangling myths from facts, thus providing a tool for health care workers to inform patients and their families on the etiology of the disease, which often is mainly caused by genetic factors and individual experiences, instead of adverse family environment. Thus our research on OC symptoms might provide an opportunity to relieve

the feelings of guilt and shame that patients and their families meet.

The results from *part II* have enabled us to answer some advanced genetic epidemiological questions, with respect to sex differences in genetic architecture of OC symptoms, and influences of phenotypic assortment, marital interaction, cultural transmission and social homogamy. However, several questions need to be addressed in future research. As OCD is not a discrete diagnostic entity with sharp external boundaries (Denys, 2004), potential research questions include: Are the genetic risk factors specific to OC symptoms or shared with other psychiatric disorders? To what extent are the effects of these genetic risk factors mediated through intermediate phenotypes such as personality or neuropsychological processes? Do genetic risk factors moderate the effect of environmental risk factors on disease liability, e.g., genetic control of sensitivity to the environment? Are these moderating effects of genes on specific environmental risk factors conditional on age? And if so, what are specific age periods that make persons particularly vulnerable for gene x environment interaction? How can environmental and genetic risk factors be better characterized? We hope to answer some of these questions in the following years using data of the Netherlands Twin Register.

## PART III. GENETIC AND ENVIRONMENTAL INFLUENCES ON OCS OVER TIME

The objective of **chapter 7** was to assess genetic and environmental contributions underlying stability in childhood obsessive-compulsive symptoms. The use of both maternal and paternal ratings is unique. An advantage of a design in which multiple raters assess the behavior of genetically related subjects (i.e., twins) is that a distinction can be made between variance that is explained by a common perception of the parents (i.e., common phenotype) and variance that is explained by a unique perception of each parent on the behavior of their child (i.e. unique or rater specific phenotype). The common perception is not confounded by rater bias or measurement error (Hewitt *et al.*, 1992). The unique phenotype leaves room for specific views of a certain rater, but may include both rater bias and measurement error.

Maternal and paternal ratings on the 8-item Obsessive Compulsive Scale of the Child Behavior Checklist (CBCL-OCS) in Dutch mono- and dizygotic twin pairs from 8083 families were collected longitudinally, at ages 7, 10, and 12 years.

OC behavior assessed by the CBCL-OCS showed a moderate stability with phenotypic correlations of around .50 for boys and for girls. Stability of OC behavior was influenced mainly by genetic factors, but environmental factors shared by children growing up in the same family and by non-shared environmental factors also played a substantial role. Stability for OCS was lower when data were analyzed using cut-points, than when quantitative definitions were used.

**Chapter 8** described a cross-sectional study of genetic and environmental contributions to self-report obsessive-compulsive symptoms, the 8-item Obsessive-Compulsive Scale of the Youth Self Report (YSR-OCS), in Dutch adolescents at ages 12, 14, and 16 years. At age 12 no difference in prevalence was found for OC symptoms in boys and girls. At age 14 and 16, the prevalence was higher in girls. At all ages, genetic factors contributed significantly to OCS variation; 27% at age 12, 57% at age 14 and 54% at age 16. There were no sex-differences in heritability. Only at the age of 12, environmental factors shared by children from the same family explained part (16%) of the individual differences in OC symptom scores. At ages 14 and 16 years no contribution was observed of shared environment.

**Chapter 9** presented the first estimates of genetic and environmental contributions underlying stability in adult obsessive-compulsive behavior. The YASR-OCS was obtained from a group of mono -and dizygotic twins in 1991, 1995 and 1997 and the Padua Inventory Revised Abbreviated (PI-R ABBR) in 2002 with a mean age in 1991 of roughly 18 years till a mean age of 33 in 2002. Stability over time of obsessive-compulsive (OC) symptoms was examined and analyzed as a function of genetic and environmental components.

Heritability of OC behavior was around 40% at each time-point, independent of the instrument used. OC behavior was moderately stable with correlations between .39 and .61 for subsequent time-points. Variance in stability of OC behavior is influenced for 70% by additive genetic factors. Genetic correlations over time of roughly .8 were found for both men and women between the first three time-points with somewhat lower correlations of .6 between the first three time-points and the last time-point. Although the PI-R ABBR introduced new genetic influence, it seems in general that the same genes play a role in OC behavior over time. This implies that OC data of different ages can be pooled together in gene-finding studies.

*Part III* has focused on heritability of OC symptoms over time and underscored the justification of a lifetime approach to behavior and disease. The same 8 items regarding OC behavior were assessed in children, adolescents and adults. The longitudinal study in children simultaneously analysed ratings of OC symptoms of both fathers and mothers, trying to get a reliable measure. The study clearly shows that genetic factors are

indeed important in stability of OC symptoms, but that shared and non-shared environmental factors also play a role. This mix of factors is absent in adults, for whom we found that genetic factors explain the majority of the covariance of OC symptoms between time-points. The longitudinal study of OC symptoms in adults has used a simplex model, which can disentangle stable genetic factors from new genetic factors. In general, stable genetic influences seem to be responsible for the stability of OC symptoms. Interestingly, for stability in children, environmental factors are more important than in adults. This may indicate that how earlier treatment starts, the better environmental factors can be influenced.

The study in adolescents showed three cross-sectional analyses at three different ages in adolescence. The finding of shared environmental at the age of 12 is striking, as it is found independent of the rater, in this case mother, father and self reports. However, in general we found stable heritabilities of around 55% from childhood to adolescence, with only a small decline to roughly 45% in adults. Stability in OC symptoms in children is caused by the same genes over time. This seems also the case for adults. We do not yet know if the genetic factors that are expressed in children are the same as in adults. Therefore, the results of this part of the thesis raise important questions. For example: what is the stability of OC behavior in adolescence and are the genetic factors the same over time in adolescence? Are the genes responsible for OC symptoms in childhood the same as in adolescence, or even in adulthood? As the children are growing older and the sample is growing larger, we hope to publish longitudinal research on OC symptoms from childhood till adulthood, to solve these questions.

The longitudinal study in adults, using two different questionnaires to detect OC symptoms, raises the question if these two measurements measure the same trait, as genetic innovations were seen for the PI-R ABBR. The items of the YASR-OCS measure the existence of OC symptoms in general, while the PI-R ABBR measures more specific OC symptoms. Interestingly, this study also puts the findings of shared environment in men in chapter 6 in perspective. In this study we not only model the cross-sectional covariance between twins, but also the cross-twin cross-time correlations. Note that the same data (without the parents) were used for time-point 2002 as in chapter 6. Used in a longitudinal design with different OC questionnaires, shared environment could easily be dropped. As a consequence, the estimation of genetic factors in men is quite higher than in chapter 6.

The longitudinal study in adults also emphasizes the need to use more measurements at once, to capture all the information and not missing important aspects of the phenotype. It is notable that the well-known clinician administered Y-BOCS (Goodman *et al.*, 1989) and the self report PI-(R) (Sanavio, 1988; Van Oppen *et al.*, 1995) contain different symptom dimensions and have a correlation of only .27 (Denys *et al.*, 2004). This means that in clinical practice it is recommended to use both questionnaires to capture the entire spectrum of symptoms. For research, the ideal situation within the large scale of twin studies would be to have a relative compact self report scale, still capturing all the information, including the several important symptom dimensions within OCD. It would be worthwhile to have an internationally accepted short screener, developed in such a way that the scale is normally distributed, preventing statistical complications. The recently developed DY-BOCS (Rosario-Campos *et al.*, 2006) is too long and time consuming to use in a large-scale epidemiological studies. The 18-item OCI-R (Foa *et al.,* 2002) is promising with a recent study indicate that the subscales of the OCI-R are valid measures of symptom dimensions of OCD (Huppert *et al.,* 2007).

## PART IV. ENVIRONMENTAL FACTORS AND SYMPTOM DIMENSIONS IN OCS

**Chapter 10** focused on environmental factors that protect or exacerbate obsessive-compulsive behavior using a special twin design of discordant and concordant monozygotic twins. Since the PI-R ABBR was used to select the MZ pairs for the study, the use of the Padua Inventory Revised ABBR was evaluated. To investigate whether the PI-R ABBR can accurately screen for OCD, and to establish cut-points of OC behavior, Receiver Operating Characteristic (ROC) analyses were carried out. At the best cut point of 16, the sensitivity was .74 with a specificity of .72, when compared to clinical controls. Cronbachs' $\alpha$ of the scale was .73. From the 2002 wave of data collection in the NTR, we selected 25 monozygotic (MZ) twin pairs who were discordant (high-low) on the PI-R ABBR, 17 MZ twin pairs concordant high and 34 MZ pairs concordant low. Within-discordant MZ pair comparisons were used to investigate environmental factors unique to the individual, whereas between-concordant pair comparisons were used to study environmental factors shared by both twins of a pair.

The high scoring MZ twins of the discordant group reported more life events, especially sexual abuse, than lower scoring twins. The between-pair comparisons showed lower birth weight in the discordant MZ pairs than in the concordant MZ pairs. The discordant pairs revealed lowest birth weight compared to the concordant pairs. Further, the concordant high scoring twins tended to report in fewer instances to have a religious background, and tended to be less active in church. Finally, the concordant high scoring twins as well as their

partners and fathers had the lowest educational level when compared to the other groups. Longitudinal data on OC symptoms, anxiety and depressive symptoms in the concordant and discordant groups revealed an earlier age at onset of OC and related symptoms in the concordant high group (from 1991 on) than in the discordant group (mostly from 1997 on), confirming previous reports of an association of early-onset OC symptoms with higher genetic load. Parent scores of OC symptoms and anxious-depression suggested intermediate genetic load in the discordant group.

**Chapter 11** described the first attempt to estimate a heritability of obsessive-compulsive symptom dimensions. As recent research has shown that Obsessive-Compulsive Symptoms differ remarkably between patients and can be divided into several symptom dimensions, the objective was to examine to what extent these symptom dimensions are heritable. We studied a population sample of 1383 female twins from the Virginia Twin Registry. OCS was measured by a questionnaire with 20 items from the Padua Inventory. After factor analysis, three reliable OC symptom dimensions were retained: Rumination, Contamination, and Checking. These OC dimensions were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

The multivariate common pathway model provided the best description of the data. All symptom dimensions share variation with a latent common factor, i.e., OC behavior. Variation in this common factor was explained by both genes (36%) and environmental factors (64%). Only the Contamination dimension was influenced by specific genes and seemed to be a relatively independent dimension. The results suggest that a broad OC behavioral phenotype exists, influenced by both genes and non-shared environment. In addition, we found evidence for specific genetic and environmental factors underlying the Contamination dimension.

In *Part IV* we focused both on the environmental factors which play a role in Obsessive Compulsive symptoms and on symptom dimensions within OC symptoms.

The discordant MZ twin design is intriguing. Why is there a difference in a trait, while we know that the genome sequence is in general the same within a MZ twin pair? That this last conclusion is not always the case proves a recent publication of Bruder *et al.* (2008). They found clear differences in copy-number variation (CNV) between monozygotic twins, indicating that subtle differences exist between the genome of MZ twins. However, in general the discordant MZ twin design, with variants like comparing high-scoring and low-scoring twins, is especially suitable to unravel environmental causes to symptoms or diseases for example by changing gene-expression. We found a general risk factor like sexual abuse, but also a possible protective factor like a higher level of education. In addition to the small sample size, we were confronted in this study with a major problem which many studies face: How does one measure environmental factors in a precise and reliable manner? Although genetic factors play a role in many disorders and traits, the role of environmental factors and, more specifically, the interaction between both is in many cases at least as important. I predict that we will refocus on environment in the next decade, following large groups over time, while precisely registering environment, for example by computerized diaries. This type of research in combination with genetic data like for example gene expression profiles could give us further clues in unravelling the causes of OCS/OCD. At this moment, there is paucity within the OCD literature of statistical sound studies of environmental factors in OC phenomenology.

In addition to the study of chapter ten, we recently conducted an fMRI study with a subgroup of the MZ twin pairs discordant for OC symptoms described in chapter ten (den Braber *et al.*, 2008). Using a Tower of London planning paradigm twins with OCS showed significantly decreased brain activation during planning in dorsolateral prefrontal cortex, thalamus pulvinar, and inferior parietal cortex. These findings are consistent with the hypothesis of disturbed cortico-striato-thalamo-cortical (CSTC) circuitry underlying OCS and show the power and possibilities of the discordant twin design.

The study in collaboration with the group of Kendler focused on the fact that OCD is a heterogeneous disease with many faces. A general obsessionality factor exists influenced by genetic and environmental factors. However, besides a general factor there is evidence for specific genes and environment for the contamination dimension. Speculating on these results, it would imply that common genes and environment will make you obsessed, but that specific genes and environment determine which kind of symptoms you will have. The results are intriguing, but, more research is needed. In an ideal situation, data of a large group of male and female twins, who filled in two complete OC symptom measurements (for example a self report version of the Y-BOCS and the Padua Inventory), would be analysed in the same manner as described in our study to answer questions like: Which dimensions have specific genes and environment? Are there any sex differences? Is there any difference in heritabilities of specific symptom dimensions? When we are able to follow this group of twins in a longitudinal way, we also can answer questions like: Are dimensions stable over time? Are there sex-differences in stability? Is stability caused by genes or environment?

*Part IV* showed two studies with different approaches: a categorical one and a more continuous approach. Each approach has its merits and both show additional value, although within the psychiatric discipline, research, especially in the clinical field, seems to stick to category-based DSM-IV approaches. It would be a good step forward if researchers also underscore the value of the more continuous approaches and facilitate publishing of this type of research. On the other hand, thus taking a more categorical viewpoint, it would be a step forward if we could start a twin register with psychiatric patients in the Netherlands. At the moment, I don't know of any psychiatrist who asks his patient if he or she has a twin brother or sister. A clinical database of "psychiatric" twin pairs could provide us with an overwhelming source of information. We would be able to have a closer look at environmental factors and to estimate heritabilities of diagnoses. A twin register like this can only be started with cooperation of all researchers in this field and with enough funds, but it is an idea well worth trying. If we don't ask patients if they are twins, the remark of Lewis (1935) in the introduction of this thesis will remain true: it is a pity that twins are so rare.

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