Lewis could not imagine in 1935, that twin research would achieve such popularity nowadays. It still took more than 70 year after Lewis’ remark to present a thesis that is completely focused on the genetic and environmental influences on Obsessive-Compulsive Symptoms (OCS) using extended twin designs.

See Editorial page 10
OBSSESSION
The genetic and environmental architecture of obsessive-compulsive symptoms

Daniël Sebastiaan van Grootheest
Obsession

The genetic and environmental architecture of obsessive-compulsive symptoms

VRIJE UNIVERSITEIT

OBSESSION

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
on gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Psychologie en Pedagogiek
op donderdag 18 september 2008 om 10.45 uur
in de aula van de universiteit,
De Boelelaan 1105

donderdag 18 september 2008

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Acknowledgments

The research in this dissertation was supported by ZonMw, grant number 920-03-268 and NWO, grant number 400-03-330. The data-collection was supported by “Genetic basis of anxiety and depression” (NWO grant 904-61-090); “Database Twin register” (NWO grant 575-25-006); “Spinozapremie” (NWO/SPI 56-464-14192); CNCR (Centre Neurogenetics Cognition Research); Center for Medical Systems Biology: Multifactorial Diseases: Common Determinants, Unifying Technologies (NWO Genomics); “Twin-family database for behavior genetics and genomics studies” (NWO grant 480-04-004).

We thank all the participating twins and their families.

Publication of this thesis was financially supported by ZonMw.

Graphic design: Roman E. Jans (www.romanontwerp.nl)
Printed: Gildeprint Enschede

ISBN: 978 90 8659 237 1
©D.S.van Grootheest 2008 (ds.van.grootheest@psy.vu.nl)
# TABLE OF CONTENTS

1. **Aims and outline** 9

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

2. Obsessive-compulsive symptoms and disease: an overview 13
3. Twin studies on obsessive-compulsive disorder: a review 21

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

4. Genetic and environmental influences on obsessive-compulsive symptoms in adults: a population based twin-family study 31
5. Marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample 41
6. Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents 51

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

7. Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior 59
8. Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at age 12, 14 and 16 71
9. Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register 79

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

10. Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins 91
11. Heritability of obsessive-compulsive symptom dimensions 107

## CONCLUSION

12. Summary and discussion 117

   Samenvatting 125
   List of publications 131
   Dankwoord 133
   Curriculum Vitae 134
CHAPTER 1
Aims and outline

van Grootheest, D. S.
Aims and outline

Dr. FE Pilkington has kindly let me see the record of another pair of probably identical twins who show striking similarity in their respective obsessional illnesses. But two or three pairs tell very little; it is a pity that twins are so rare” by Aubrey Lewis (1933)

Lewis could not imagine in 1935, that twin research would achieve such popularity nowadays. It still took more than 70 year after Lewis’ remark to present a thesis that is completely focused on the genetic and environmental influences on Obsessive-Compulsive Symptoms (OCS) using extended twin designs.

In 2005, Kendler described four paradigms of psychiatric genetics, which are shown in table 1. Paradigm one, basic genetic epidemiology, has the goal to estimate the proportion of liability in a given population due to genetic and environmental differences between individuals. In case of genetic factors, this proportion is called heritability. Given a significant heritability, the goal of advanced genetic epidemiology, paradigm two, is to explore the nature and mode of action of these genetic risk factors, answering potential questions like: Do these genetic risk factors affect disease similarly in males and females? Do the actions of these risk factors change as a function of the developmental stage of the individual? Does the level of heritability for a disorder differ across populations? Paradigm three and four focus on gene finding and molecular genetics.

This thesis focuses on paradigms one and two within OCS using different assessment instruments in large twin samples. Two large samples came from the Netherlands Twin Register; one consisting of young twins (Bartels et al., 2007) and a second sample consisting of adult twins and their family members (Boomsma et al., 2006). Participants in both samples provided longitudinal data on OCS. The third sample came from the Virginia twin registry. The overall aim of this thesis is to explore the genetic and environmental architecture of OCS symptoms in the general population.

In Part I of this thesis we start with an overview and background of OCS and Obsessive-Compulsive Disorder (OCD) (chapter 2). Part II continues with a review on all published twin studies on OCD and OCS symptoms, starting with the first known published case of a MZ twin pair in 1929 (chapter 3). In Part II of this thesis, heritability, assortative mating, and genetic and cultural transmission of OCS were examined. Chapter 4 investigates the heritability of OCS, in a large sample of twins and sibs. Because of the large sample size we were able to take a closer look into the issue of sex-differences in the heritability of OCS. OCS was assessed with the VASR-OCS, a newly developed scale based on the 8 items of the CBCL-OCS in children (Nelson et al., 2001; Hudziak et al., 2006). Chapter 5 evaluates causes of marital resemblance on OCS, and on two correlated traits, i.e. depressive and anxious symptoms in a population based twin-family sample. Resemblance between spouses can be due to assortative mating, and genetic and cultural transmission of OCS. Chapter 6 investigates the heritability of OCS, using the PI-R Abbreviated, a scale including 12 items of the Padua Inventory Revised (Van Oppen et al., 1995). Data were derived from a large sample of twins, sibs and parents, and provided the opportunity to estimate genetic and environmental influences on OCS and the possible influence of cultural transmission, while controlling for assortative mating.

Part III is dedicated to genetic and environmental influences over time from child to adulthood. In chapter 7, longitudinal analyses in twin children are presented using both mother and father ratings in a combined multivariate multi-rater design. This chapter focuses on stability of OCS and examined the genetic and environmental influences on this stability. Chapter 8 shows the results of cross sectional analyses at three different ages in a group of adolescents. Chapter 9 focuses on longitudinal analyses in adults using 4 time-points and two different measurements.

Part IV of this thesis deals with the identification of environmental risk factors for OCS using a special twin design and offers in the second part a closer look at the heritability of symptom dimensions. In chapter 10, data from discordant and concordant monozygotic twins were used to investigate environmental factors that protect against or exacerbate obsessive-compulsive symptoms. Chapter 11 shows results of a co-operation with the Virginia twin register and investigates the heritability of symptom dimensions in a sample of American female twins. Finally, chapter 12 summarizes and discusses the main findings of this thesis and evaluates directions for future research into the genetic epidemiology of OCS symptoms.

References


Table 1. Four major paradigms of psychiatric genetics

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Samples studied</th>
<th>Methods of inquiry</th>
<th>Scientific goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Basic genetic epidemiology</td>
<td>Family, twin and adoption studies</td>
<td>Statistical</td>
<td>To quantify the degree of familial aggregation and/or heritability</td>
</tr>
<tr>
<td>2. Advanced genetic epidemiology</td>
<td>Family, twin and adoption studies</td>
<td>Statistical</td>
<td>To explore the nature and mode of action of genetic risk factors</td>
</tr>
<tr>
<td>3. Gene finding</td>
<td>High-density families, trios, case-control samples</td>
<td>Statistical</td>
<td>To determine the genetic location and identity of susceptibility genes</td>
</tr>
<tr>
<td>4. Molecular genetics</td>
<td>Individuals</td>
<td>Statistical</td>
<td>To identify critical DNA variants and trace the biological pathways from DNA to disorder</td>
</tr>
</tbody>
</table>

Adapted from Kendler (2005)
CHAPTER 2

Obsessive-compulsive symptoms and disease: an overview

This chapter is based on:


Obsessive-compulsive symptoms and disease: an overview


ABSTRACT
The chapter provides a brief overview of the latest research on symptoms, epidemiology, neuro-anatomy, genetic and environmental factors, and management 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.

Obsessive-compulsive disorder (OCD) is a complex and heterogeneous psychiatric disorder characterized by obsessions and compulsions (also known as ‘rituals’). Obsessions are unwanted ideas, images or impulses which repeatedly enter an individual’s mind. Although recognized to be self-generated they are experienced as ‘egodystonic’ (out of character and distressing). Compulsions are repetitive behaviors or mental acts which are often intended to neutralize anxiety provoked by the obsessions (Figure 1). These rituals are often driven by rules that must be applied rigidly. In order to qualify for the diagnosis, the symptoms must be disabling.

Figure 1.

The OCD cycle. Obsessions are intrusive thoughts (ideas, images or impulses) which repeatedly enter an individual’s mind against his/her will. These generate significant levels of anxiety and are difficult to dismiss. Compulsions or rituals are repetitive acts that are performed in an attempt to reduce the anxiety caused by the obsessions, but the relief is only temporary. Later in the course of OCD, rituals can become more automatic and increase, rather than reduce, the anxiety. (Adapted from Mataix-Cols et al. (1999))

SYMPTOMS
Although the core features of obsessions and compulsions appear to be remarkably consistent throughout the life span, in both sexes and in different cultures and races, the detailed content of these symptoms is varied. Two patients with OCD may present with completely non-overlapping symptom profiles. However, more commonly, patients experience multiple types of obsessions and compulsions. The most common types of obsessions and compulsions are listed in Table 1. These symptoms tend to group in predictable ways. Indeed, multiple factor and cluster-analytical studies (Leckman et al., 2007) have identified at least 4 relatively independent and temporally stable symptom dimensions: 1) contamination obsessions and washing/cleaning compulsions, 2) aggressive, sexual and religious obsessions and related compulsions (often checking), 3) obsessions concerning a need for symmetry or order, and 4) hoarding and collecting obsessions and compulsions (Figure 2).

Figure 2.

Schematic representation of the major symptom dimensions of OCD. Most studies consistently identified four symptom dimensions (continuous lines), while some others identified a fifth dimension consisting of sexual and religious obsessions (dashed line) but more research is needed to determine its validity. Note the overlap between these dimensions as mono-symptomatic patients are very rare.

Table 1. Most common types of obsessions and compulsions in a large sample of patients with OCD (n = 554)

<table>
<thead>
<tr>
<th>Obsessions</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contamination</td>
<td>208</td>
<td>59</td>
</tr>
<tr>
<td>Aggressive</td>
<td>246</td>
<td>69</td>
</tr>
<tr>
<td>Sexual</td>
<td>68</td>
<td>19</td>
</tr>
<tr>
<td>Religious</td>
<td>95</td>
<td>27</td>
</tr>
<tr>
<td>Symmetry</td>
<td>159</td>
<td>45</td>
</tr>
<tr>
<td>Hoarding</td>
<td>103</td>
<td>22</td>
</tr>
<tr>
<td>Obsessions</td>
<td>77</td>
<td>22</td>
</tr>
<tr>
<td>Compulsions</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Cleaning</td>
<td>212</td>
<td>60</td>
</tr>
<tr>
<td>Checking</td>
<td>253</td>
<td>72</td>
</tr>
<tr>
<td>Ordering</td>
<td>121</td>
<td>34</td>
</tr>
<tr>
<td>Repeating</td>
<td>176</td>
<td>50</td>
</tr>
<tr>
<td>Counting</td>
<td>125</td>
<td>35</td>
</tr>
<tr>
<td>Hoarding</td>
<td>73</td>
<td>21</td>
</tr>
</tbody>
</table>

Adapted from Mataix-Cols et al. (1999)

Aggressive and sexual obsessions in OCD must be differentiated from violent thoughts occurring in other disorders, such as urges to hurt people in psychopathy or abuse children in pedophilia. People with OCD fear that they might commit an offence but do not carry out the feared act and spend an excessive amount of time and energy resisting and controlling their behavior to avoid the risk of harm.

OCD often occurs together with other complicating conditions, such as depression or other anxiety disorders (Pigott et al., 1994). Screening for, and treating these co-morbidities is an important part of the management of the disorder (see Table 1). The majority of people with OCD of all ages understand the senseless nature of their repetitive, unwanted behaviors and intrusive, recurrent thoughts.

This may lead to shame, reluctance to seek help, and poor recognition by health professionals. People with OCD have long delays in accessing effective treatments, with delays of 14 years on average, although younger patients who had access to treatment sooner. Individuals with OCD frequently present to non-psychiatrists for treatment (Table 3) and psychiatric symptoms go undetected. There is need for greater awareness of OCD in a range of non-psychiatric health care settings, and clinicians need to be confident about recognizing it.

EPIDEMIOLOGY
OCD can occur throughout the lifespan, with children as young as 6 or 7 presenting with the characteristic impairing symptoms. At the other end of the age range, cases may present for the first time in old age. The majority of adults report the onset in childhood or adolescence. OCD can result in significant disability and the World Health Organization rates it as one of the top-twenty most disabling diseases. If untreated, OCD generally persists (Skoog & Skoog, 1999), yet there are effective, evidence-based psychological and pharmacological treatments. Recent epidemiological studies report prevalence rates of about 1% in adults and in 0.35% of 5-15 year old children (Crino et al., 2005; Heyman et al., 2001), although earlier studies have suggested rates as high as 1-3% in adults (Karno et al., 1988) and 1-2% in children and adolescents.

Table 2. Conditions commonly occurring with OCD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency of OCD association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>50-60%</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>22%</td>
</tr>
<tr>
<td>Social phobia</td>
<td>18%</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>17%</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>14%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>12%</td>
</tr>
<tr>
<td>Tourette’s Disorder</td>
<td>7%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>14%</td>
</tr>
</tbody>
</table>

Adapted from Pigott et al (2006)

Table 3. Non-psychiatrists likely to see patients with OCD

<table>
<thead>
<tr>
<th>Professional</th>
<th>Reason for consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioner</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>Chapped hands, eczema</td>
</tr>
<tr>
<td>Cosmetic surgeon</td>
<td>Compulsive hair pulling</td>
</tr>
<tr>
<td>Oncologist</td>
<td>Concerns about appearance</td>
</tr>
<tr>
<td>Genito-urinary specialist</td>
<td>Fear of cancer</td>
</tr>
<tr>
<td>Neurologist</td>
<td>Fear of HIV/AIDS</td>
</tr>
<tr>
<td>Obstetrician</td>
<td>OCD associated with Tourette’s Disorder</td>
</tr>
<tr>
<td>Gynaecologist</td>
<td>OCD during pregnancy or puerperium</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>Fear of contamination, vaginal discomfort from douching</td>
</tr>
</tbody>
</table>

Adapted from Mataix-Cols et al. (1999)
The causes of OCD are unknown but, like in most complex psychiatric disorders, are likely to stem from a combination of genetic, neurobiological, cognitive-behavioral and environmental factors.

**THE FUNCTIONAL NEUROANATOMY OF OCD**

Current neurobiological theories of OCD suggest that specific frontal-subcortical circuits are involved in the symptoms and cognitive deficits associated with the disorder. These theories arose from various sources of evidence: the presence of OCD symptoms in some neurological conditions (Tourette’s Syndrome, Huntington’s Disease, Sydenham’s Chorea) and other basal ganglia disorders (Laplane et al., 1989), the emergence of OCD-like behaviors in patients with focal brain injury and the fact that surgical interventions that interrupt these frontal-subcortical circuits improve both mood and OCD symptoms. However, the strongest support for these models comes from the advent of modern neuroimaging techniques, which provided a direct window into the OCD brain in vivo. Currently, the most widely accepted neuroanatomical model of OCD proposes the involvement of a direct and an indirect cortico-striato-thalamic pathway (Cummings, 1993; Saxena & Rauch, 2000). In the direct pathway, an excitatory glutamatergic signal projects to the striatum, sending an inhibitory GABA-ergic signal to the internal part of the globus pallidus. This results in a decreased inhibition (disinhibition) of the thalamus and thus an increased excitatory effect on the prefrontal cortex (Figure 3). In the indirect pathway, the striatum projects an inhibitory signal to the external part of the globus pallidus, sending an excitatory signal to the internal part of the globus pallidus. The net effect is an increased inhibition of the thalamus and decreased excitation on the prefrontal cortex. It is hypothesized that the direct pathway functions as a self-reinforcing positive feedback loop and contributes to the initiation and continuation of behaviors, whereas the indirect pathway provides a mechanism of negative feedback which is important for the inhibition of behaviors and in switching between habits and mental flexibility. The balance between the direct and indirect cortico-striatal circuits might mediate the symptoms of OCD: an excess tone in the direct relative to the indirect cortico-striatal circuit is hypothesized to result in enhanced activation of the orbitofrontal cortex, ventral striatum and medial-dorsal thalamus. Based on the positive therapeutic effects of selective serotonin reuptake inhibitors on OCD symptomatology and the inhibitory effect of serotonin on dopamine, it is suggested that failure of the serotonergic system results in decreased compensation of the dopaminergic influence on the frontal-striatal circuits. Dopamine (D) has a dual role on the balance between the direct and indirect fronto-striatal pathways. In the human brain, the D2 receptor is prominent in the ventromedial (relative to dorsolateral) prefrontal cortex and ventral (relative to dorsal) striatum (Hurd et al., 2001). Functionally, this dopaminergic differentiation implies a stronger D2 influence on the direct pathway of the ventromedial-frontal-striatal circuit and a stronger D1 influence on the indirect pathway of the dorsolateral-frontal-striatal circuit, resulting in a hyperactivated ventral and an inhibited dorsal fronto-striatal system (see Figure 3). This corresponds with the results of functional neuroimaging studies in OCD, showing increased activation of limbic and ventral fronto-striatal regions at rest and in response to disease-relevant event information (Rumjes et al., 2005) and decreased responsiveness of dorsal fronto-striatal regions during executive performance (van den Heuvel et al., 2005).

**INFLUENCE OF GENES AND ENVIRONMENT ON OCD**

The influence of genetic factors in OCD has been suggested since the earliest descriptions of the disorder and a number of study designs have been employed to determine what extent OCD is heritable. First, family studies have convincingly shown that OCD runs in families, that is, that first-degree relatives of OCD patients have an elevated risk of having OCD. This genetic contribution appears to contribute to genetic or environmental factors. For this purpose adoption or twin studies are needed. Adoption studies have established that a high concordance rate for OCD is present in monozygotic twins but not in dizygotic twins, indicating a genetic contribution. However, adoption studies have since been supplemented by genome-wide association studies (GWAS) which were the first to study a direct relationship between the genes and the disorder. An extensive overview of twin studies on OCD can be found in chapter 2.

Genetic linkage analysis provides a powerful approach to elucidate the underlying genetic factors in inherited disorders. Linkage studies are designed to determine whether a behavioral phenotype or a psychiatric disorder or a dimensional trait, is genetically linked to a specific region of the genome. Two independent studies have conducted focusing on glutamatergic transmission. Two independent studies have found an association between the GLIP1A1 gene and OCD (Stewart et al., 2006; Dickel et al., 2009). Linkage studies have been conducted focusing on glutamatergic transmission. Two independent studies have found an association between the GLIP1A1 gene and OCD (Stewart et al., 2006; Dickel et al., 2009). Linkage studies have been conducted focusing on glutamatergic transmission. Two independent studies have found an association between the GLIP1A1 gene and OCD (Stewart et al., 2006; Dickel et al., 2009).

**MANAGEMENT OF OCD**

Multiple randomized controlled trials (RCTs) have established the efficacy of both a form of psychotherapy called cognitive behavior therapy (CBT) and certain medications which inhibit the synaptic reuptake of serotonin, i.e. the tricyclic antidepressant clomipramine and the more highly selective serotonin reuptake inhibitors (SSRIs) (van Balkom et al., 1994). There is no evidence to support the efficacy of psychodynamic psychotherapy in OCD and its use is therefore not recommended. In both adults and children, the specific CBT technique most strongly associated with good outcome in CBT studies is exposure and response prevention.
Some centers offer neuropsychology (circuitry or anterior capsulotomy) for severe, treatment-resistant OCD but, for obvious reasons, these treatments have not been evaluated in controlled trials and remain controversial.

REFERENCES


CHAPTER 3
Twin studies on obsessive-compulsive disorder: a review

ABSTRACT
Genetic factors have historically been thought of as important in the development of obsessive-compulsive disorder (OCD). For the estimation of the relative importance of genetic and environmental factors, twin studies are an obvious approach. Twin studies of OCD have a long history, starting back in 1929. In this review, over 70 years of twin research of OCD is presented using four different approaches that represent the steps in the twin research of OCD from past to present. These steps 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 is concluded that only the studies using the last method have convincingly shown that, in children, obsessive-compulsive symptoms are heritable with genetic influences 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 part remains unexplained. Twin studies with continuous data is still needed to provide conclusive evidence. Strategies for future twin studies of OCD are discussed. The one hand and / or repetitive ritualized behavior or mental acts (compulsions) on the other hand (American Psychiatric Association, 1994). Compulsions are usually performed to relieve the anxiety and / or distress caused by the obsessions. The most frequent types of obsessions are fear of contamination, pathological doubt, somatic obsessions, need for symmetry, and sexual and aggressive obsessions. Well-known compulsions are checking, washing, counting, symmetry/precision and hoarding. Obsessive-compulsive (OC) symptoms are remarkably diverse and the clinical presentation can vary both within and across patients over time (Leckman et al., 1997). Nowadays, many studies have provided strong evidence that OCD is not a unitary nosological entity, as suggested from the current concept of Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision; TR; American Psychiatric Association, 1994), but a clinically heterogeneous disorder (Miguel et al., 2005). Patients experience a chronic or episodic course with exacerbations that can substantially impair social, occupational and academic functioning (Nestadt et al., 1997). The lifetime prevalence of OCD is estimated to be 0.7 and 2.5% (Horwath & Weissman, 2000). Family studies of OCD have suggested that OCD is familial (Grados et al., 2003), which is not synonymous with heritable. Genetic epidemiological methods to study the relative roles played by genes and environment in the etiology of OCD include twin and adoption studies. Adoption studies are generally rare and to our knowledge, no such studies have been published on OCD. Twin studies are based on the fact that monozygotic (MZ) twins are genetically identical, whilst dizygotic (DZ) twins share on average 50% of their segregating genes, which is similar to any nontwin siblings. If MZ twins resemble each other more than DZ twins, this is indicative for the importance of genetic influences on the trait under consideration. The influence of genetic factors has been suggested from the earliest descriptions of the disorder up until the present (Pauls & Alsobrook, 1999), but the twin studies literature on OCD has never been reviewed extensively, apart from some attention in book chapters (Billett et al., 1998; Macdonald et al., 1991). In this review, whether twin studies on OCD indeed suggest that OCD is a heritable disorder is addressed by giving an overview of all reported twin studies of OCD in the literature. We begin with case studies from the old literature and end with more recent twin studies using a model fitting approach. Finally, we draw conclusions about the heritability of OCD and discuss new strategies for future twin studies on OCD.

CASE STUDIES OF TWINS WITH OCD IN THE OLD LITERATURE, 1929 – 1965
In 1929, Lange published the first cases of twins with OCD in an article on the pathology of twins in psychiatry (Lange, 1929). This paper marked the beginning of twin studies on OCD. An overview of all published case studies of twins with OCD in the old literature, published between 1929 and 1965, is presented in Table 1. Most studies of this era have failed to distinguish between OC neurosis and mixed neurosis, and showed a tendency to confuse OC neurosis with OC personality or obsessive traits (Hoak & Schnurr, 1980). The history of OCD can partly explain this observation. In 1876, Westphal considered genetics to represent the most prominent etiological factor in OCD (Westphal, 1876). OCD was at that time a clearly defined psychiatric disorder, thought to be caused by organic factors such as a dysfunction of the autonomic nervous system. Lange emphasized on the ideas Freud (1896), this based on the idea of OCD changed and by the second half of the twentieth century OCD was (1) separated into obsessive neurotic and obsessive personality disorder, (2) considered to be on a continuum, ranging from ‘normal’ neurotic behavior, through personality disorder to neurosis, which warranted psychotherapy, (3) thought to be largely caused by early traumatic experiences or environmental factors, (4) and governed by psychoanalytic theories (Denys, 2004). Clear definitions of obsessive neurosis or obsessive personality disorder did not exist and this is reflected in the different diagnostic information provided by the case studies. Most studies provide insuffi- cient clinical data to verify a diagnosis of OCD, severely hampering judgment on whether the subjects would meet current standardized diagnostic criteria (Billett et al., 1998). Moreover, comparison of the case studies is difficult due to differences in diagnostic criteria between studies. Furthermore, there seemed to be a tendency to publish MZ and concordant twins, introducing reporting bias. This bias is caused by collecting twins in an unsystematic way, which tends to favor MZ and concordant pairs (Clifford et al., 1984). Another problem with case studies was mentioned by Lewis (1985) who wrote that ‘a striking concordance in one or two pairs of MZ twins proves nothing: one needs a series and control group of fraternal twins’. It is interesting however that Woodruff and Pitts (1964) regarded even one set of MZ, twins concordant for obsessive neurosis as important, stating that it was statistically improbable for MZ twins to be concordant in the absence of common determinants. This conclusion was based on their frequency-cited calculation of the prevalence of OCD of 0.05% in the general population (Woodruff & Pitts, 1964). They wrote that one in 132 living persons are MZ twins and calculated that the chance of finding a pair of MZ adult twins where both had OCD would be one in 600 million if the disorder would arise independently in each twin and was not due to some combination of shared genetic or environmental factors. The twin rule of pathology, that is any heritable disease will be more common in identical twins than in nonidentical twins, was already formulated in 1924 (Siemens). But around 1960 the debate continued as to which conclusions could be drawn from the finding of a marked increased concordance of MZ compared to DZ twins in schizophrenia (Parker, 1964). Besides the conclusion that a genetic predisposition could exist, an exclusive environmental basis for this consistent finding was also proposed (Jackson, 1960). This environmental basis could be caused by close identification or by confusion of ego identity, which was suggested to oc- cur in MZ twins (Jackson, 1960). Rosenthal (1960) had already shown that the second factor could not be held responsible, as twins in general would then be expected.
to have a higher incidence of schizophrenia than the general population, which is not the case. Parker (1964) described two MZ twins discordant for OCD, attempting to illustrate with these cases that marked identification can still occur without both twins developing symptoms of neurotic illness, throwing doubt on the validity of this purely environmental theory.

A further limitation of the old literature is the lack of a procedural blind to obtain diagnostic information or establish diagnoses. Knowledge of an index case’s status while evaluating the co-twin or vice versa is an unacceptable source of bias (Pauls & Alsobrook, 1999). Finally, in many cases the method of zygosity determination is unclear or there is lack of information to definitively establish monozygosity. With these limitations in mind, no conclusion about the heritability of OCD can be drawn from this literature.

TWIN STUDIES OF OCD MEETING DSM CRITERIA

The development of the DSM-III (3rd ed.; American Psychiatric Association, 1980) meant a new step forward in psychiatric research. Disorders in DSM-III have been defined in terms of syndromes, that is, symptoms that are observed in clinical populations to covary together in individuals. The major advantage of adopting a descriptive classification was its improved reliability over prior classification systems using nonop

tionalized definitions of disorders. From the outset, however, it was recognized that the primary strength of this descriptive approach was its ability to improve communication among clinicians and researchers, not its established validity (Kuper et al., 2002).

Table 2 shows several case studies and four larg

et epidemiological twin studies on OCD, meeting DSM-III or DSM-III-R (3rd ed.; rev.; American Psychiatric Association, 1987) criteria. The standardization of the diagnosis and higher reliability of the zygosity determination diminish some limitations of the case studies described above. Although case studies of twins with OCD can hardly solve the question about heritability, they can inspire researchers by generating new hypotheses, which can be a starting point for subsequent research. For example, McKeon et al. (1984) described four cases of OCD neurotic head injury, one from a discordant MZ twin pair. The twin is a 23-year-old Ugandan immigrant who started having OC symptoms after he was knocked down by a car and had been unconscious for 10 days. His rituals involved repeated checking of his clothing, brushing his teeth for more than an hour at a time and taking excessive precautions to avoid contamination in the bathroom. His early development had been normal and closely similar to that of his co-twin, who had no period in his development exhibiting OC symptoms. However, following the head injury, the twins’ behaviors diverged such that the brother developed OC symptoms. The authors conclude that head injury is a probable contributor to the development of OC neurons in some cases.

Four epidemiologic studies were published that will be described more extensively. Carey and Gottesman (1981) screened 30 MZ and 15 DZ twin pairs recruited from the Maudsley Twin Register, which represents a consecutive series of patients who were admitted to the Maudsley or Bethlem hospitals between 1948 and 1979. All probands reported unequivocal obsessive symptom

toms according to DSM-III criteria. The diagnosis may have been secondary to another diagnosis, so the results apply more in general to OCD traits than to OCD as a distinct diagnosis. Several writers have commented that the observed behavior may have been secondary to another disorder.

Concordance rates for ‘obsessive symptoms or features with no following diagnosis’ were 87% for MZ pairs and 47% for DZ pairs. Concordance rates for an ‘episode of psychiatric or GP treatment involving obsessional symptoms’ were 33% for MZ pairs and 7% (one twin pair) for DZ pairs.

Torgersen (1983) investigated genetic factors in the determination of six anxiety disorders in a study of 32 MZ and 53 DZ adult same-sex twin pairs from Norway. The sample consisted of twins born between 1910 and 1955 who were admitted for the treatment of neurotic or borderline psychotic disorder prior to 1977. Each twin was diagnosed according to DSM-III criteria. Of the 85 probands, 12 twins, 3 MZ and 9 DZ, had an OCD, but no co-twins with OCD were found. Although no twins were found to be concordant for any of the other DSM anxiety disorders either, the authors examined concordance rates in the larger context of an ‘anxiety spectrum’ (Pauls & Alsobrook, 1999). When the sexes were combined, the concordance for anxiety disorders in the proband group labeled ‘all anxiety disorders without General Anxiety Disorder’ (GAD) was 45% in MZ pairs to 15% in DZ pairs. The authors conclude that genetic factors appear to influence the development of anxiety disorders in general, with the exception of GAD.

Andrews et al. (1990) administered structured psychiatric interviews on DSM-III criteria, the Compos

ite International Diagnostic Interview (CIDI), to 186 MZ and 260 DZ twin pairs, culled from the Australian Twin Registry. Lifetime diagnoses for major depressive disorder, dysthymia, GAD, OCD, panic disorder, social phobia and agoraphobia with panic were obtained. In total, 48 twins with a diagnosis of OCD were reported, but no concordant twin pairs with OCD were found. Although there was a genetic contribution to neuropsychiatric symptoms and to symptoms of depression and anxiety, there were no apparent specific disorders were found.

Shire et al. (1993) performed a twin study of DSM-III-R anxiety disorders in 81 same-sex twin pairs. The sample of twin probands consisted of twins with non-chronic, non-malignant disorders and several subsamples of twins in Norway. One subsam

ple overlapped with the sample used in the study of Torgersen (Torgersen, 1984). In the anxiety disorder proband group containing 20 MZ and 29 DZ twins, 3 MZ twins and 2 DZ twins were found to have OCD. In the co-twins of the group of the MZ probands, all twins with OCD were found but it is not clear in the article if these are concordant MZ twins or not. In the co-twins of the comparison group with probands having no anxiety disorder at all, another DZ twin with OCD was found. The authors conclude that their results do not contrib

ute to a clarification of the etiology of OCD.

Several important limitations in the interpretation of these epidemiologic studies. Although the use of DSM-III or DSM-III-R criteria reduces the risk of false-positive results due to diagnostic criteria, interviewers for each member of a twin pair with each interviewee blind to the zygosity status of the pair introduced a large potential for inadvertent bias in the de

tection of illness (Pauls & Alsobrook, 1999). Torgersen (1983) and Andrews et al. (1990) combined different diagnostic categories to determine concordance rates. Although both groups of investigators argue that the results support the notion that there are common genetic factors for at least some anxiety disorders, by combin

ing across diagnoses, both groups could have been capi

talizing on chance (Pauls & Alsobrook, 1999). Lastly, in population-based samples, the low prevalence of DSM-diagnosed OCD generally would lead to low statistical power to ascribe the familial clustering of OCD to either shared genes or shared environment.

TWIN STUDIES OF OCD USING A DIMEN

SIONAL APPROACH, COMPARING RESE

MBLANCES IN MZ AND DZ TWINS

The classical twin method compares phenotyp

ic resemblances between MZ and DZ twins. Comp

aring the resemblance of MZ twins for a trait or disease with the resemblance of DZ twins offers an estimate of the extent to which genetic variation determines phenotypic variation of that trait (the liability heritability (Li

Boomsma et al., 2002). The classical twin method al

lows the use of categorical data like diagnoses but also continues distributed traits, such as obsessive trait or symptom scores in twins. Macdonald et al. (1991) recommended that instead of relating diagnoses to thresholds on an underlying liability distribution, we should aim for measures that are more direct indices of this liability distribution and hence examine the ge

netic and environmental basis of individual differences in vulnerability to develop clinically significant OCD.

Table 2. Twin studies of OCD meeting DSM-III or DSM-III-R criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of twin pairs</th>
<th>MZ C/D</th>
<th>DZ C/D</th>
<th>Diagnostic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marks et al. (1969)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Tarch (1978)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Hoaken &amp; Schuur (1980)</td>
<td>1</td>
<td>0/1</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>McGuffin &amp; Mawson (1980)</td>
<td>2</td>
<td>2/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Carey &amp; Gottesman (1981)</td>
<td>30</td>
<td>13/2</td>
<td>7/8</td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Torgersen (1983)</td>
<td>12</td>
<td>0/3</td>
<td>0/9</td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>McKeon et al. (1984)</td>
<td>1</td>
<td>0/1</td>
<td></td>
<td>OCD after head injury</td>
</tr>
<tr>
<td>Mialhrogbu et al. (1988)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>First-born twin has also epilepsy. Second-born twin minor OC symptoms</td>
</tr>
<tr>
<td>Kim et al. (1990)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Andrews et al. (1990)</td>
<td>48</td>
<td>0/18</td>
<td>0/30</td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Lewis et al. (1991)</td>
<td>3</td>
<td>3/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Croy et al. (1992)</td>
<td>3</td>
<td>1/0</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
<tr>
<td>Shire et al. (1993)</td>
<td>8</td>
<td>5/3</td>
<td></td>
<td>Both twins improved after leucotomy</td>
</tr>
</tbody>
</table>

MZ, monozygotic twins; DZ, dizygotic twins; C/D, concordant/discordant; OC, obsessive-compulsive; *concordance not clear.
OCD in this case viewed as the equivalent of extreme soreness on symptom or trait measures. Such a dimensional approach removes problems of scarcity of twins with the full disease and also removes the need for population-based prevalence rates for comparison.

Young et al. (1991) were the first researchers to apply a dimensional approach to OCD, using OC sympto-
table (Table 3). They conducted a small study of 17 pairs of MZ and DZ male twins and 15 pairs of fraternal twins to examine the inheritance of neuropsychiatric traits. The 32 twin pairs completed the Middlesex Hospital Questionnaire, which contains a brief obstetric traits and symptoms subscale. Comparison of the intraclass correlations between the two twin series did not reveal a significant difference on the obsessive subscale score.

Table 3. Twin studies of OCD using a dimensional approach, comparing resemblances in MZ and DZ twins

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample characteristics</th>
<th>Diagnostic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al. (1991)</td>
<td>32 MZ, 32 DZ pairs, cross-sectional data</td>
<td>Obsessive traits and symptoms according to a subscale of the Middlesex Hospital Questionnaire</td>
</tr>
<tr>
<td>Torgersen (1980)</td>
<td>99 MZ female, cross-sectional data</td>
<td>Obsessive traits according to the Lazar et al. questionnaire</td>
</tr>
<tr>
<td>Clifford et al. (1984)</td>
<td>419 MZ, DZ pairs, cross-sectional data</td>
<td>Obsessive symptoms according to the Leyton Obsessional Inventory</td>
</tr>
</tbody>
</table>

Torgersen (1980) examined 99 same-sex pairs of twins, 22 MZ female, 28 MZ male, 27 DZ female and 22 DZ male twin pairs. Eleven pairs were selected on the basis of hospitalization of one of the twins for neurotic problems. All remaining pairs were derived from the folk register of two cities to represent twin pairs from the general population. Torgersen compared intraclass variances for obsessiveness and compulsiveness factor, but could not find a significant difference between the MZ and DZ twins. The heritability of the obsessive scale was .18 for men and .23 for women. Torgersen hypothesized that in our society, a possible genetic core may perhaps be masked by the overwhelming environmental influences. It is difficult to evaluate the significance of these findings due to small sample size and the biased ascertainment of twins. Furthermore, the obsessive scale used measured persistent personality traits rather than state dependent repetitive behavior (Macdonald et al., 1991).

The paper of Clifford et al. (1984) marked the beginning of research on quantitative traits in relatively large samples of twins from the normal population, measuring OCD using standardized instruments and with a promising dimensional approach. Clifford et al. were well aware of the disadvantages of case studies and stated that ‘if obsessive neurosis is regarded as a distinct disease entity qualitatively different from normal behavior, then it is almost impossible to devise ways of examining any possible etiological role for heredity. However, a more contemporary view of the neuroses considers them as conditions to which individuals towards the extreme ends of normally distributed symptom or trait dimensions are especially prone.’

A sample of 419 twin pairs participated, with a bias towards female and MZ twins. Obsessiollarity was measured using a 42-item version of the Leyton Obsessional Inventory (Cooper, 1970). It contained 10 items of the trait scale and 32 items of the symptom scale. The heritability es-
timates for obsessive traits and symptoms were 44% and 37% respectively. No effect of common environment was found, thus unique environment explained the remaining variation. Multivariate analysis revealed two genetic factors of obsessuality, one factor related

to a general trait of neuroticism and most strongly related to MZ pairs, and the other factor related to obsessiveness and compulsiveness factor related to checking and cleanliness. Finally considerable hereditary variation appeared to be specific to each of the four factors.

TWIN STUDIES OF OCD USING A DIMENSIONAL APPROACH, ANALYZING THE DATA WITH STRUCTURAL EQUATION MODELING

The quantitative traits that have been assessed in MZ and DZ twins have traditionally been analyzed using analysis of variance and intraclass correlations to summarize (Boomsma et al., 2000). However, this approach cannot accommodate the effect of sex on variances and covariance within and between twin participants, or easily be extended to multivariate and longitudinal data. Structural Equation Model- ing (SEM), also known as covariance modeling, is a more general alternative approach, in which genotypic and environmental effects are modeled as the contribu-
tion of unmeasured (latent) variables to the potentially multivariate phenotypic differences between individu-
als (Neale & Cardon, 1992).

Jonnal et al. (2000) used this approach in a twin study of OCD, examining 527 pairs of female twins using 20 items of the Padua Inventory (Sanavio, 1988; Table 4).

The sample consisted of 334 female MZ twins and 193 pairs of DZ twins from the Virginia Twin Registry. A principal component analysis on the 20 items showed a two-factor solution, which divided twin responses into a tam-
bullipulsiveness factor and an obsessiveness factor. By using SEM, the best-fit model suggested heritabilities of 33% and 42% and a 29% and 37% respectively. Unique environmental factors accounted for 67% and 74% of the variance. The correlation between additive effects on obsessiveness and compulsiveness was .53. The main conclusion was that self-report symptoms of obsessiveness and compulsions in women in the general population are moderately heritable and perhaps to the same genetic risk factors. They also tested the equal environment assumption (EEA). Twin studies assume that MZ and DZ twin pairs are equally comparable for the exposure to environmental and gender factors of etiologic relevance to the trait under study. None environ-
mental effects that could be affecting the heritabil-
ity were observed, and it was concluded that the EEA was not violated. Jonnal et al. (2000) noted three potentially important methodological limitations. First, they only selected women, thus obscuring any sex differences. Further reducing the ability to detect a more complex and sta-
ble structure and increasing error variance. In a cross-
sectional design, error variance cannot be distinguished from true genetic or environmental variance, and with an observed additive genetic factor it may perhaps be an overestimation of the impact of genetic factors as a result. Second, the study included only women, so conclusions cannot be generalized to men. Thirdly, although the data exclude the pronouned right skew, although similar heritability estimates were produced after correction.

Chen et al. (2003) examined the phenotypic dif-
ferentiation and genetics of mother-reported anxiety-related behaviors in 4564 4-year-old twin pairs from a population-based twin study, the Twins Early Development Study. Parents completed a 16-item questionnaire on anxiety-related behaviors in young children. The items were selected to assess five dimensions, including OC behavior (four items). For OC behavior there was substantial genetic influence with a heritability estimate of 65% and a 35% estimate of nonshared environment. Small negative sibling interaction effects were found, indicating rater-contrast or sibling competition effects.

Recently Hudziak et al. (2004) examined 4246 twin pairs of the Netherlands Twin Register (NTR) and 1441 twin pairs from the Swedish Twin Registry (MOTWIN). The 4246 twin pairs of the NTR were aged 7, of whom 2841 were reexamined at age 10 and 1562 were examined at age 12. The 1441 pairs of MOTWIN were a mixed-age group with an average age of 9 years. An 8-item Obsessive-Compulsive Scale (OCS) was used from the Child Behavior Checklist (CBCL; Achenbach, 1991). The scale was validated in a clinical sample of children with OCD based on DSM-IV criteria and showed adequate predictive value (Nelson et al., 2001). Across age groups and cultures, the best fitting model indicated additive genetic influences of the CBCL OCS score between 45% and 61%, and unique envi-
ronmental influences between 42% and 55%. Only the NTR sample aged 12 years showed shared environmen-
tal influences of 16%. Minor sex differences were seen in this study, although the mixed-age MOTWIN sample did not show evidence of dominance, sibling interaction, or rater-contrast effects were seen.

In the age of the study sample, both Eley et al. (2003) and Hudziak et al. (2004) had to rely on parent reports, which may be influenced by characteristics of the rater.

CONCLUSION

Although the first twin report was written on OCD in 1929, it was not until 50 years later that Clifford et al. (1984) suggested genetic effects on obsessive symptoms in general. Pauls and Alsobrook (1999) concluded that due to the absence of twin studies to replicate the Clifford et al. findings, the effect size of genetic influences on OCD was still underdetermined.
Strikingly, 15 years lapsed since the publications of Clif ford et al: before a second informative twin study on the heritability of OCD was published in female twins (Jonnal et al., 2000). However, in their review and meta-analysis of the genetic epidemiology of anxiety disorders, Hettema et al. (2001) could not find any twin studies on OCD that met their inclusion criteria. These criteria for twin studies were the use of operational- ized diagnostic criteria and systematic ascertainment of probands. Only recently is methodologically sound research emerging, investigating the contribution of dis- ease-specific and common underlying genetic make-up in the occurrence of OC symptoms in children (Eley et al., 2003; Hudziak et al., 2004).

In conclusion, twin studies of children provide support for the hypothesis that genetic factors play a significant role in OC manifestation. Twin studies of adults are indicative, but a large twin study using a bio- metric approach with continuous data is needed to provide conclusive evidence.

FUTURE OF TWIN STUDIES AND OCD

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Obsessive-compulsive neurosis in identical twins.


Genetic and environmental influences on OC symptoms in adults: a population based twin-family study


ABSTRACT

Background The contribution of genetic factors to OC symptoms has not been examined using a large population based sample of adults. Furthermore, the extent to which there are qualitative and quantitative differences in genetic architecture between men and women with OC symptoms has not been elucidated.

Methods We obtained the Young Adult Self Report Obsessive-Compulsive Scale (YASR-OCS) from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings from the population-based Netherlands Twin Register. Structural equation modeling was used to decompose the variance in OC behavior into genetic and environmental components and analyze quantitative and qualitative sex differences.

Results Familial resemblance was the same for DZ twins and non-twin siblings, which means that there was no evidence for a specific twin environment. The same genetic risk factors for OC behavior were expressed in men and women. Depending on the choice of fit-index we found small (39% for men and 50% for women) or no sex differences (47% for both men and women) in heritability. The remaining variance in liability was due to individual-specific environment.

Conclusions OC behaviour showed a moderate heritability. At most, small quantitative sex differences were found in the genetic architecture of OC behaviour, and no qualitative sex differences.

Historically, family-genetic studies have strongly suggested genetic factors to be important in the development of obsessive-compulsive disorder (OCD). (Black et al., 1992; Pauls et al., 1995; Nestadt et al., 2000b). For the determination of the relative importance of genetic and environmental factors, twin studies are an obvious choice. Twin studies of OCD have a long history, starting with Lange (1929) and evolving from single case reports to large epidemiological studies (van Grootheest et al., 2005). A paper by Clifford et al. (1984) marked the beginning of research on quantitative obsession-compulsive (OC) traits in relatively large twin samples with standardized instruments. Clifford et al. (1984) analyzed the 42 cases from the Leyton Obsessional Inventory (Cooper, 1970), obtained in 419 adult male and female twin pairs. The heritability of the obsessive symptoms was estimated at 47%. Surprisingly, since then only one twin study on OC symptoms in adults has been published. Jooнал et al. (2000) examined data from 527 pairs of female MZ and DZ twins from the Virginia Twin Registry, using 20 items of the Padua Inventory (PI) (Sanavio, 1988). The best model for these data suggested heritabilities of 33% and 26% for obsessiveness and compulsiveness respectively. In children, a large twin study on OC behavior, assessed by the Child Behavior Checklist Obsessive-Compulsive Scale (CBCL-OCS), was conducted in an American and Dutch twin sample (Houtszik et al., 2004). OC behavior was assessed at ages 7, 10 and 12 years and showed a heritability of approximately 55%. Significant sex differences in heritability were only seen in the USA sample. Van Grootheest et al. (2007) found that stability of OC behavior in children, using the CBCL-OCS at ages 7, 10 and 12 years in a longitudinal design, was influenced by genes and both shared and non-shared environmental factors. Recently, Bolton et al. (2007) examined 6-year old twins on OC symptoms. The effect of familial aggregation was estimated as 47% for sub-threshold OCD, but the study missed power to distinguish shared environment from genetic factors.

In conclusion, twin studies are suggestive of genetic factors to be important for variation in OC behavior in children. For adults, a large twin study in males and females using a biometrical approach with continuous data is needed to provide more conclusive evidence and explore additional questions (van Grootheest et al., 2005). Especially the impact of sex on the transmission of obsessive-compulsive disorder in adults is unknown. Sex effects can either be quantitative in nature, i.e. sex differences in magnitude of heritability, or qualitative, i.e. whether the genetic risk factors for OC symptoms in men and women are the same. Knowledge about sex effects in genetic risk for OCD is important because some literature on sex differences, although not always consistent, in OCD exists. Classical studies of OCD showed that males are more likely to have a childhood onset, have a more chronic course of disease and show OC symptoms associated with a distinct pattern of comorbid psychopathology (Geller et al., 1998; Eichstedt & Arnold, 2001). A variety of association studies have produced variable evidence for association in one sex or another (Carnaere et al., 2001; Enoch et al., 2001; Alsobrook et al., 2002; Lochan et al., 2004; Hemmingsen, 2006). Segregation analyses suggest that the inheritance of OCD could be affected by sex effects (Nestadt et al., 2000a; Hanna & Nestadt, 2005).

The aim of this study is to determine the genetic and environmental contributions to obsessive-compulsive symptoms in adults by using a large sample of unselected twins and siblings. To maximize the statistical power, a classical twin design was extended by including siblings (Posthumus & Boomsma, 2000; Stroef et al., 2006). OC symptoms were assessed using the adult version of the CBCL-OCS, the Young Adult Self Report Obsessive Compulsive Scale (YASR-OCS). The criterion validity of the YASR-OCS was tested with Receiver Operating Characteristic (ROC) analyses among three different groups: an OCD group, a psychiatric control group and a population control group. We sought answers to the following questions:

1. What are the psychometric properties of the YASR-OCS?
2. Can results from our study be generalized to non-twins?
3. What role do genetic and environmental factors play in the etiology of OC symptoms?
4. Are genetic and environmental risk factors for OC symptoms similar in importance in males and females?
5. Are the genetic risk factors for OC symptoms in men the same as in women?

METHODS

Subjects

This study is part of a longitudinal survey study in twin families registered with the Netherlands Twin Register (Boomsma et al., 2002; Boomsma et al., 2006). Since 1991, every two to three years twins and their families have received a survey by mail containing questionnaires about health, personality and lifestyle. Participants in this study were adolescent and adult twins (mean age: 22.4, SD: 8.3) and their siblings (mean age: 28.0, SD: 11.0). Data were available for twins who participated in survey 1991, 1995 and 1997 and for siblings who participated in the survey of 1997. The data from these 3 surveys were used to create a large cross-sectional data set. We added, when possible, two additional sibs to each twin family. First, data of twin pairs and their siblings from the 1997 survey were used. If no twin data were available in 1997, then data of twin pairs collected in 1995 or 1991 were used. Half sibs, adoptive sibs and triplets were excluded. The final sample consists of 5893 twins: 3360 females and 2533 males from 3069 families. We were able to include 1304 additional non-twin siblings among the participants.

A non-twin sibling can form a (twin-)sibling pair with one twin brother or sister, and a (twin-)sibling pair with his other twin brother or sister. In the case of two siblings, the siblings form a sibling pair by themselves. These non-twin siblings increased the number of sibling pairs with 273. As a consequence of the inclusion of the non-twin siblings the monozygotic (MZ) to dizygotic (DZ) pair ratio decreased from 7.95 (792/1058) to 21.79 (3831). It has been shown that a MZ to DZ ratio of about 1 is optimal for research (Nance & Neale, 1989). Table 1 provides information on the twin/sibling composition and sex distribution of the participating families for each zygosity group. Zygosity of the twins was determined using items about physical similarity and the frequency of confusion of the twins by family and strangers. On 869 same sex twin pairs, information on their zygosity was available from DNA polymorphisms. The agreement between zygosity diagnoses of the questionnaire and DNA data was 98% (Willemse et al., 2004).

Receiver Operating Characteristic (ROC) analyses were conducted among three different groups: an OCD group, a psychiatric control group and a population control group. Data on patients with OCD were derived from the outpatient anxiety clinic of GGZ Buurnekool, a specialized center for OCD in Amsterdam. All participants who presented themselves for diagnosis and/or treatment of OCD between August 2004 and September 2005 were invited for a longitudinal study (Boomsma, 2005). In total, 64 participants, 22 men and 46 women with a mean age of 36.8 (SD = 10.2), were diagnosed by trained psychiatric residents using the Structured Clinical Interview (SCID), 4th edition (First et al., 1996). A group of 66 psychiatric control participants without OCD, consisting of 16 men and 50 women with a mean age of 36.2 (SD = 10.0), was obtained from an adult sample of the Netherlands Twin-family study on Anxious Depression (NETSAD) (Boomsma et al., 2000). Psychiatric diagnoses of the participants were obtained in 1997 by telephone interviews using the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992). For a detailed description of the data collection, see Boomsma et al. (2000) and Middeldorp et al. (2006). Data were used from participants with actual diagnoses within the last 12 months. The index diagnoses of the psychiatric...
control group participants varied from depression, panic disorder and social phobia to general anxiety disorder. The population control group was obtained from the NIMH study and was selected for absence of any diagnosis. The 68 participants were selected to match OCD participants in terms of age and sex.

**Measures**

The Young Adult Self Report (YASR) is a standardized self-report questionnaire for adolescents and adults (Achenbach, 1997). It is derived from the Child Behavior Checklist, a parent-derived rating instrument for children between 6 and 18 years old (Achenbach, 1997; Achenbach, 1991). The YASR roughly has the same format as the CBCL, except that items pertaining to childhood problems were replaced by items pertaining to adults functioning. The YASR comprises 110 problem items, covering emotional and behavioral problems during the previous 6 months. The participants respond on a 3-point scale ranging from 0 (not true) to 2 (very true) for each item.

A numerical value for the YASR-OCS is obtained by adding the scores on the relevant 8 items (0, 1 or 2 per item), thus limiting the scale to a range between 0 and 16.

**DATA ANALYSES**

**Psychometric analyses**

Internal consistency of the YASR-OCS was obtained by Chronbach’s α coefficient. ROC analyses were conducted to determine the extent to which the YASR-OCS can accurately identify persons with OCD. ROC analysis uses the association between sensitivity (i.e., true positives/(true positives + false negatives)), and specificity (i.e., true negatives/(true negatives + false positives)) to derive an Area Under the Curve (AUC), which indicates how well a measure distinguishes between case positive (i.e., OCD group) and case negative (i.e., psychiatric controls or population controls) irrespective of the base rate. A value of 0.5 of the AUC indicates chance level and 1.0 indicates a perfect diagnostic tool. For detailed descriptions of the underlying principles of ROC analysis see Swets (1996) and McFall et al. (1998). We furthermore calculated Positive and Negative Predictive Values, respectively abbreviated as PPV (true positives/(true positives + false positives)) and NPV (true negatives/(true negatives + false negatives)). ROC analyses were conducted with SPSS version 12 (SPSS for windows, 2003).

**Genetic analyses**

Genetic analyses include data from siblings in addition to MZ and DZ twins. This extension of the classical twin design provides increased statistical power, a statistic that is asymptotically distributed as χ² with degrees of freedom of (df) equal to the difference between the number of parameters in the two models. According to the principle of parsimony, models with fewer parameters are preferred if they do not give a significant deterioration of the fit. In addition, the Akaike Information Criterion (AIC), a goodness-of-fit index that considers the rule of parsimony, was calculated.

The comparison of MZ twin pair correlations with DZ twin pair and sibling pair correlations provides a first estimate of the sources of variation in individual differences in OC symptoms. Furthermore, to test whether a specific twin factor influences individual differences in OCD, we tested for heterogeneity of correlations between DZ twins and siblings. If DZ correlations are not equal to sib-sib correlations or twin-sib correlations, it indicates the existence of a special twin environment.

Next, a threshold model was used to partition the variance of the underlying liability for OC symptoms into additive genetic (A), shared environmental (C) and nonshared or individual-specific environment (E). Analysis using all zygosity groups (MZ twin pairs, DZ twin/sib pairs, female MZ twin pairs and DZ twin/sib pairs, female MZ opposite sex pairs and DZ opposite sex pairs) enabled us to examine two different sex effects. The magnitude of the genetic and environmental influences was constrained to be equal for men and women to test if the importance of the genetic and environmental factors is similar for men and women. By constraining the genetic and environmental influences to be equal for opposite sex pairs to 0.5, an explicit test was conducted whether the same genetic factors operate in males and females.

**RESULTS**

**Psychometric analyses**

ROC analyses showed an AUC of 0.84 (95% CI = 0.78–0.91) on the YASR-OCS when compared to clinical controls. When compared to general population controls, the AUC was 0.95 (95% CI = 0.92–0.99). At the best cut-off point of 7, the sensitivity was 82.4% and the specificity was 69.7% when compared to clinical controls.

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**Table 1. Number of families per zygosity in the study with the number of twins and siblings per family**

<table>
<thead>
<tr>
<th>Number of siblings</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex of siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZF families</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 twins</td>
<td>305</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>1 twin</td>
<td>26</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>DZM families</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 twins</td>
<td>487</td>
<td>83</td>
<td>105</td>
</tr>
<tr>
<td>1 twin</td>
<td>37</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>DZF families</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 twins</td>
<td>246</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>1 twin</td>
<td>27</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DOS families</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 twins</td>
<td>324</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>1 twin</td>
<td>38</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2 twins</td>
<td>488</td>
<td>99</td>
<td>108</td>
</tr>
<tr>
<td>1 twin</td>
<td>46</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 2. YASR items used for the YASR-OCS**

<table>
<thead>
<tr>
<th>YASR Item</th>
<th>YASR Item</th>
<th>YASR Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>I cannot get my mind off certain thoughts</td>
<td>Thought problems</td>
</tr>
<tr>
<td>31</td>
<td>I am afraid I might think or do something bad</td>
<td>Thought problems</td>
</tr>
<tr>
<td>32</td>
<td>I feel I have to be perfect</td>
<td>Anxious/depressed</td>
</tr>
<tr>
<td>52</td>
<td>I feel too guilty</td>
<td>Anxiety/depressed</td>
</tr>
<tr>
<td>86</td>
<td>I repeat certain acts over and over</td>
<td>Thought problems</td>
</tr>
<tr>
<td>95</td>
<td>I do things other people think are strange</td>
<td>Thought problems</td>
</tr>
<tr>
<td>85</td>
<td>I have thoughts that other people would think are strange</td>
<td>Thought problems</td>
</tr>
<tr>
<td>112</td>
<td>I worry a lot</td>
<td>Anxiety/depressed</td>
</tr>
</tbody>
</table>

---

**Table 3. YASR-OCS items used for the YASR-OCS**

<table>
<thead>
<tr>
<th>YASR-OCS Item</th>
<th>YASR-OCS Item</th>
<th>YASR-OCS Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>I cannot get my mind off certain thoughts</td>
<td>Thought problems</td>
</tr>
<tr>
<td>31</td>
<td>I am afraid I might think or do something bad</td>
<td>Thought problems</td>
</tr>
<tr>
<td>32</td>
<td>I feel I have to be perfect</td>
<td>Anxious/depressed</td>
</tr>
<tr>
<td>52</td>
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</tr>
<tr>
<td>86</td>
<td>I repeat certain acts over and over</td>
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</tr>
<tr>
<td>95</td>
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<td>Thought problems</td>
</tr>
<tr>
<td>112</td>
<td>I worry a lot</td>
<td>Anxiety/depressed</td>
</tr>
</tbody>
</table>
The results of genetic model fitting are summarized in Table 3. Model fitting results for heritability of YASR-OCS scores are by zygosity.

### Psychometric analyses

The YASR-OCS showed satisfactory psychometric properties with a sensitivity and specificity of 82% and 70%. These findings are comparable with the performance of the CBCL, which demonstrated a sensitivity and specificity of 92% and 95%, respectively. The major advantage of these two instruments is the fact that they provide investigators with two fully comparable screens on OC symptomatology across the lifespan. This is in line with a study of Geller et al. (2001) on developmental aspects of OCD in three age groups, children, adolescents, and adults. Specifically, while children and adolescents showed a higher prevalence of OC behavior, the differences in prevalence were not statistically significant. This suggests that the same genes account for the genetic influence in both sexes.

### Limitations

The results of this study should be interpreted in the context of four potential methodological limitations. First, the modest number of families included may contribute to increased error variance. Second, the YASR-OCS is only specific to recent symptoms, not lifetime symptoms, as it measures symptoms of the last 6 months. Thirdly, the genetic and environmental contributions presented in this report reflect YASR-OCS scores, not clinical measures of DSM-IV OCD. Although the YASR-OCS showed satisfactory criterion validity for DSM-IV OCD cases, we used the whole distribution of OC symptoms in the population with the underlying assumption that OCD reflects the end of a normal distribution.

### Table 4. Model fitting results for heritability of YASR-OCS scores

<table>
<thead>
<tr>
<th>Number of model</th>
<th>Type of model</th>
<th>χ²</th>
<th>df</th>
<th>p</th>
<th>AIC</th>
<th>Compared with model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully saturated</td>
<td></td>
<td></td>
<td></td>
<td>18477.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ACE, quantitative and qualitative sex differences allowed</td>
<td>18610.7</td>
<td>153.7</td>
<td>121</td>
<td>.02</td>
<td>4252.7</td>
</tr>
<tr>
<td>3</td>
<td>AE, quantitative and qualitative sex differences allowed</td>
<td>18610.2</td>
<td>2</td>
<td>90</td>
<td>4248.9</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>AE, quantitative sex-differences allowed, but no qualitative sex differences</td>
<td>18610.2</td>
<td>1</td>
<td>75</td>
<td>4247.0</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>AE, no qualitative and quantitative sex differences allowed</td>
<td>18630.0</td>
<td>5.0</td>
<td>0.1</td>
<td>4250.0</td>
<td>4</td>
</tr>
</tbody>
</table>

* χ² and df values are shown for the χ² test of the fit of model (30) to the full model (30). The latter may temper the heritability in adults. The remaining variance in liability for OC symptoms was attributed to nonshared environment.

DISCUSSION

This is the first adult twin-family study which investigated sex-effect on the influence of genetic and environmental factors on individual differences in OC behavior in a large population-based sample of twins and siblings. The twin major advantage of these two instruments is the fact that they provide investigators with two fully comparable screens on OC symptomatology along the lifespan. Course and stability over time of OC behavior with a follow-up period covering childhood, adolescence as well as adulthood, using age-adjusted instruments have advantages over instruments developed early-onset cases with OC symptomatology, in several familial studies no gender differences were found in patients with a positive family history (Nestadt et al., 2000b; Chabane et al., 2005; Delorme et al., 2005). On other hand, we found small sex differences in thresholds, with lower thresholds for males than females, indicating sex differences that are somewhat higher than for men, which seems to support earlier findings of a slight preponderance in prevalence of OC symptoms in women (Nestadt et al., 1998; Crino et al., 2005; Torres et al., 2006).

The conclusion that largely the same genes may account for OC behavior in men and women has implications for molecular genetic research. Our results emphasize the feasibility of treating OC behavior as a quantitative trait to which a QTL approach can be applied, besides the approaches of categorical analyses of clinical OCD cases (Miguel et al., 2005). Further, these findings suggest that data of men and women can be pooled in molecular genetic analyses. This conclusion may seem in contrast with, for example, two recent association studies, which found the glutamate transporter gene SLC1A1 to be associated with susceptibility to OCD, particularly in males (Dickel et al., 2006; Arnold et al., 2006). However, one should realize that our results reflect the sum of all possible genetic effects associated with OC behavior, which does not rule out a small sex effect of a single candidate gene.

**Psychometric analyses**

The YASR-OCS showed satisfactory psychometric properties with a sensitivity and specificity of 82% and 70%. These findings are comparable with the performance of the CBCL, which demonstrated a sensitivity and specificity of 92% and 95%, respectively. The major advantage of these two instruments is the fact that they provide investigators with two fully comparable screens on OC symptomatology along the lifespan. Course and stability over time of OC behavior with a follow-up period covering childhood, adolescence as well as adulthood, using age-adjusted instruments have advantages over instruments developed for one age period only (Wiznitzer et al., 2005). On other hand, we found small sex differences in thresholds, with lower thresholds for males than females, indicating sex differences that are somewhat higher than for men, which seems to support earlier findings of a slight preponderance in prevalence of OC symptoms in women (Nestadt et al., 1998; Crino et al., 2005; Torres et al., 2006).

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**Limitations**

The results of this study should be interpreted in the context of four potential methodological limitations. First, the modest number of families included may contribute to increased error variance. Second, the YASR-OCS is only specific to recent symptoms, not lifetime symptoms, as it measures symptoms of the last 6 months. Thirdly, the genetic and environmental contributions presented in this report reflect YASR-OCS scores, not clinical measures of DSM-IV OCD. Although the YASR-OCS showed satisfactory criterion validity for DSM-IV OCD cases, we used the whole distribution of OC symptoms in the population with the underlying assumption that OCD reflects the end of a normal distribution.
while OC symptoms represent a milder form of the latter (Jonnal et al., 2000; van den Oord et al., 2005). A quantitative approach does just this: The finding that previous studies found high rates of subclinical OC symptoms in family members of OCD probands (Pauls et al., 1995; Nestadt et al., 2000b), which in a DSI-dichotomous approach would be missed (Miguel et al., 2005), since the YASR-OCS is developed as a short screening instrument, it was not possible to distinguish various symptom dimensions within OCD (Mataix-Cols et al., 2003; Kendler et al., 2003; Boomsma et al., 2004). First, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). Maes et al. (Maes et al., 1998) found that significant but moderate assortative mating exists for psychiatric disorders but concluded that the bias in twin studies caused by the primary assortment is negligible (Maes et al., 2005). Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). Maes et al. (Maes et al., 1998) found that significant but moderate assortative mating exists for psychiatric disorders but concluded that the bias in twin studies caused by the primary assortment is negligible (Maes et al., 2005). Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). Maes et al. (Maes et al., 1998) found that significant but moderate assortative mating exists for psychiatric disorders but concluded that the bias in twin studies caused by the primary assortment is negligible (Maes et al., 2005). Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). Maes et al. (Maes et al., 1998) found that significant but moderate assortative mating exists for psychiatric disorders but concluded that the bias in twin studies caused by the primary assortment is negligible (Maes et al., 2005). Fourth, the findings of this analysis are predicated on the assumptions of the method used.

REFERENCES


Marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample

van Grootheest, D. S., van den Berg, S. M., Cath, D. C., Willemsen G. & Boomsma, D. I.

ABSTRACT

Background Resemblance between spouses can be due to phenotypic assortment, social homogamy and/or marital interaction. A significant degree of assortment can have consequences for the genetic architecture of a population. We examined the existence and cause(s) of assortment for Obsessive-Compulsive (OC), anxious and depressive symptoms in a population based twin-family sample.

Methods OC, anxious and depressive symptoms were measured in around 1400 twin-spoolde and over 850 parent pairs. Correlations of these symptoms within-twin’s spouses, spousal within-twin’s spouses of both parents and parents of twins were obtained to consider phenotypic assortment versus social homogamy as possible causes of marital resemblance. The association of length of relationship with marital resemblance was also investigated. Finally we examined if within-trait or cross-trait processes play a primarily role in marital resemblance.

Results Small but significant within-trait correlations between 1. and 2. were seen for spouse similarity in OC, anxious and depressive symptoms. Cross-correlations were significant but lower. There was no correlation between length of relationship and marital resemblance. From the pattern of correlations for twin-spouse, co-twin-spouse and spouses of both twins phenotypic assortment could not be distinguished from social homogamy. Both within- and cross-assortment processes play a role in marital resemblance.

Conclusions Small within- and across-trait correlations exist for OC, anxious and depressive symptoms. No evidence for marital interaction was found. Spouse correlations are small, which makes it difficult to distinguish between social homogamy and phenotypic assortment. It is unlikely that correlations of this size will have a large impact on genetic studies.

In many psychiatric disorders, several sub-stance disorders and in antisocial personality disorder, marital resemblance has been found, meaning that married partners are more similar on some phenotypic traits than would be expected by chance (Merikangas, 1982). Findings for depressive and anxiety disorders though are not unequivocal. For anxiety disorder, some studies found no evidence of increased resemblance in spouses of patients with an anxiety disorder (Eagles et al., 1987; Low et al., 2007), but several other studies found increased risk (Tamb, 1991; Zimmermann-Tansella & Lattanzi, 1991; McLeod, 1995; Galbaud du van Grootheest, D. S., van den Berg, S. M., Cath, D. C., Willemsen G. & Boomsma, D. I.

METHODS

Participants This study is part of an ongoing longitudinal survey study of the Netherlands Twin Register (NTR), which has assessed families with adolescent and adult twins roughly every two years since 1991. Each survey, with the exception of the 1995 wave, collected information on personality and psychopathology. Sample selection and response rates are described in detail in Boomsma et al. (2002; 2006). For this study, data from twins, their partners and parents of twins from the 2002 survey were used. We received questionnaires on OC, anxious and depressive symptoms of respectively 4406, 4382 and 4414 twins, 1442, 1439 and 1464 partners of twins, and 2189, 2167 and 2200 parents of twins. Table 1 shows the numbers of complete spouse pairs, i.e., pairs of which both members filled in a complete survey for the different symptoms. No significant differences were found between symptoms at the time of the survey were 32.8 years (SD 11.3) for twins, 36.0 years (SD 12.0) for their partners and 56.3 years (SD 5.9) for the parents of the twins.

### Table 1. Number of complete pairs per relationship for questionnaires on OC, anxious and depressive symptoms

<table>
<thead>
<tr>
<th></th>
<th>OC symptoms</th>
<th>Anxious symptoms</th>
<th>Depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin-spouse</td>
<td>1416</td>
<td>1441</td>
<td>1407</td>
</tr>
<tr>
<td>Cofarer-spouse</td>
<td>1090</td>
<td>1110</td>
<td>1083</td>
</tr>
<tr>
<td>Spouses1 - spouses2</td>
<td>264</td>
<td>272</td>
<td>263</td>
</tr>
<tr>
<td>Parents</td>
<td>875</td>
<td>881</td>
<td>857</td>
</tr>
</tbody>
</table>

In the present study we aim to examine the existence of marital resemblance for OC, anxious and depressive symptoms within a population-based sample of twins, their partners and their parents. Because we included the partners of the twins (Heath & Eaves, 1985; Reynolds et al., 2000), the present study is the first one that may, given sufficiently high correlations, disentangle the causes of spouse similarity in OC, anxious, and depressive symptoms. Furthermore, because data from two generations are included (from twins and partners plus parents of twins), data from couples with different lengths of time spent together are available. This allows for the examination of the correlation between length of marriage and similarity in psychiatric symptoms, i.e., marital interaction. We addressed the following questions:

1. Is there a significant association within and across OC, anxious and depressive symptoms between husbands and wives?
2. Can marital resemblance be explained by phenotypic assortment, social homogamy or both?
3. Is marital resemblance influenced by marital interaction?
4. Does mate selection occur primarily within or across OC, anxious and/or depressive symptoms?
If marital resemblance is due to marital interaction, we would expect the $r_{spouse}$ to be larger than $r_{twin-spouse}$ as spouses in the present generation in general married longer than spouses in the offspring generation. We calculated correlations between length of relationship and marital resemblance for twin-spouse pairs and parents in one analysis and within the two generations (i.e., separate analyses for twin-spouse pairs and parents). For this purpose, marital interaction was defined by the absolute difference in scores on the phenotypes for two partners, closer to zero indicating a larger resemblance. Length of relationship was defined by the length of the present relationship in years.

To study if marital resemblance occurs primarily within or across OC, anxious and/or depressive symptoms, we estimated within-matrix ($r_{within}$) and between-matrix correlation ($r_{between}$) between OC, anxious and depressive symptoms at once, using the conditional path method (Carey, 1996). For this method, the observed matrix of spousal correlations decomposed into

1) the matrix of correlations within husbands (Rh); 2) the matrix of correlations within wives (Rw); and 3) the matrix of correlations between the disturbances of husbands and the disorders of wives (D) (Phillips et al., 1987, Maes et al., 1998).

The latter matrix is modelled by a conditional path matrix of latent direct effect associations. As an example, we specify this matrix in model notation as follows (for two traits).

$$
M = \begin{bmatrix}
1 & h_{11} \\
1 & 1
\end{bmatrix}
\times
\begin{bmatrix}
d_{11} & d_{12} \\
d_{21} & d_{22}
\end{bmatrix}
\times
\begin{bmatrix}
1 & 0 \\
1 & 1
\end{bmatrix}
$$

We estimated the $D$ matrix and tested if within and/or across $(r_{within}, r_{between})$ differs significantly from zero. Similarity drops among other pairings, i.e., $r_{within} > r_{between}$, such a pattern among the in-laws suggests phenotypic assortment, but confidence intervals overlap around correlations. So correlations do not significantly differ from each other and social homogamy cannot be ruled out. The spouse similarity in parents is 15. This is not significantly different from the correlation in the younger generation, the absence of marital interaction this is confirmed by the fact that no significant correlation was found across generations ($r_{within}$) and within the three generations ($r_{between}$) between $d_{11}$ and $d_{12}$ (twins: $r_{within} = r_{between} = 0.05$) between duration of relationship and marital resemblance of OC symptoms.

In the table the OC data is presented, we see a similar pattern as for OC symptoms. The twin-spouse correlation is 16. No MZ and DZ differences are seen for cotwin-spouse and spousel1-spouse2 correlations. Although a pattern of $r_{within} > r_{between}$, no MZ and DZ differences are seen, confidence intervals overlap for the correlations for the different pairings. $r_{within}$ practically equals $r_{between}$ and no significant differences exist. The absence of similarity between MZ and DZ twins, marital resemblance of anxiety was seen across generations ($r_{within} = 0.05$) and within generations (twins-spouse: $r_{within} = 0.05$, parents: $r_{between} = 0.05$). For depressive symptoms, a twin-spouse correlation of 19 was found. MZ families show correlations similar to those of DZ families for cotwin-spouse and spousel1-spouse2 correlations. A pattern of $r_{within} > r_{between}$ is seen, but again there is overlap in the confidence intervals ($r_{within} = 0.05$) between $d_{11}$ and $d_{12}$, which would even suggest that the longer the relationship, the lower the similarity between partners for depression. However, no significant correlation between duration of the
Table 3: Familial correlations per relationship by zygosity for OC, anxious and depressive symptoms. Number of complete twin pairs per relationship are presented between brackets.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>OC Symptoms</th>
<th>Anxious Symptoms</th>
<th>Depressive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin-sibling</td>
<td>0.67 (0.61 - 0.73)</td>
<td>0.11 (0.03 - 0.19)</td>
<td>0.71 (0.68 - 0.74)</td>
</tr>
<tr>
<td>Twin-spouse</td>
<td>-0.11 (-0.19 - 0.03)</td>
<td>0.09 (0.05 - 0.14)</td>
<td>-0.25 (0.15 - 0.33)</td>
</tr>
<tr>
<td>Monzygotic male</td>
<td>0.48 (0.40 - 0.56)</td>
<td>0.30 (0.22 - 0.38)</td>
<td>0.50 (0.48 - 0.52)</td>
</tr>
<tr>
<td>Dizygotic male</td>
<td>0.13 (0.10 - 0.17)</td>
<td>0.24 (0.19 - 0.30)</td>
<td>0.13 (0.10 - 0.17)</td>
</tr>
</tbody>
</table>

DISCUSSION

This study examined the existence and possible cause of marital resemblance for OC, anxious, and depressive symptoms. Several importing findings emerged that are important for both future research and clinical practice. First, small but significant within- and cross-marital resemblance exists for OC, anxious, and depressive symptoms. Second, since correlations are small, it is difficult to distinguish between social homogamy and phenotypic assortment as the main cause of marital resemblance for OC, anxious, and depressive symptoms. Third, no evidence was found for marital interaction. Fourth, both within- and cross-assortment play a role in marital resemblance.

This is the first study that has examined marital resemblance for OC symptoms. The degree of correlations between partners for OC symptoms resembles those for depression and anxiety. Our findings for depression support the results of the meta-analysis of Mathews and Reus (2001), who found little, but significant marital resemblance for affective disorders. The finding of marital resemblance for anxiety symptoms in this study confirms various earlier reports in both clinical and population-based studies (Tambis, 1991; Zimmerman-Tanselli & Lattanzii, 1991; McLeod, 1995; Maes et al., 1998; Galbaud du Bois et al., 1998; Dubois-Stadelmann et al., 2001), reporting correlations between .1 and .3 using either diagnostic or dimensional ratings of anxiety. Two studies did not find marital resemblance for anxiety disorders. Lagro et al. (1997) assessed anxiety in a population-based sample of elderly couples aged over 65. They actually found a small, but significant, correlation of 0.7. Recently, Low et al. (2007) did not find spousal concordance for DSM-III anxiety disorders in a mixed patient/community sample (71.3% / 28.7%). The latter study is the only study on anxiety disorders which also included patients, while all other studies were based on community samples to overcome the problem of selection bias. This selection bias usually causes an overrepresentation of affected couples in clinical samples (Galbaud du Bois et al., 1998).

Besides clear significant assortment within traits, evidence for cross-assortment was found as well. The cross-assortment correlations were somewhat smaller than the within-assortment correlations. This could suggest that within-assortment occurs primarily within the various anxious-depressive traits, but by comparing models it appeared that cross-assortment played a significant role as well, confirming results of Maes et al. (1998). Results from direct assortment estimations,

Table 4.

| Observed cross-correlations for OC, anxious and depressive symptoms. Data of twin-spouses and parents have been pooled.

<table>
<thead>
<tr>
<th>Spouse 1</th>
<th>Spouse 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC symptoms (CI)</td>
<td>1.00 (1.00 - 1.00)</td>
</tr>
<tr>
<td>Anxious symptoms (CI)</td>
<td>1.00 (1.00 - 1.00)</td>
</tr>
<tr>
<td>Depressive symptoms (CI)</td>
<td>1.00 (1.00 - 1.00)</td>
</tr>
</tbody>
</table>
which have been controlled for comorbidity, indicate that anxious partners tend to choose anxious partners, but avoid partners with OC behavior or depressive behavior. As far as we first study to report on these assert-ment estimates, replication of these latter results are needed.

The present study attempted to test whether social homogamy or phenotypic assortment is the un-determined force of psychiatric diseases, since we had information on the spouses of identical and fraternal twins. We found roughly the same pattern of correlations for OC, anxious and depressive symp-toms. Since the correlations are small with confidence intervals overlapping, we were unable to distinguish between social homogamy and phenotypic assortment processes. As we are the first study to report on these assort-ment correlations, extremely large numbers of twins and spouses are needed to be able to distinguish between different mechanisms. On the other hand, it is also possible that both mechanisms play a role; if this is the case the observed correlations are simply too small to have reasonable power to dis-tinguish and estimate the magnitude of these different sources.

Nevertheless, there is reason to suspect that phenotypic assortment is a more probable mechanism, since shared environmental effects hardly seem to play a role in the occurrence of OC symptoms and OCD (van Grootheest et al., 2005), depression (Sullivan et al., 2000) or anxiety disorders (Hettema et al., 2001). The three existing studies on OCS did not find shared environmental factors to be important (Clifford et al., 1984, Jorde et al., 1996, van Grootheest et al., 2000). For depression, no evidence for shared environmental factors was found in a meta-analysis of Sullivan et al. (2000). For anxiety disorders we found that an unexplained variance could not be accounted for. Shared environmental factors of anxiety disorders were found to explain variance in behavioral problems and social behavior. For depression, the reliability was too small to allow for any conclusions to be drawn. In our study, it is possible that both mechanisms play a role; if the case the observed correlations are simply too small to have reasonable power to distinguish and estimate the magnitude of these different sources.

Implications

Our study has implications for both psychiatric twin research and clinical practice. To study genetic and environmental influences on psychiatric orders quantitative genetic models are usually fitted to twin data under the assumption that phenotypic assortment is absent. If phenotypic assortment would exist, a bias is seen depending of the model used: a small upward bias of the genetic variance in an AE model (Neale & Cardon, 1992), i.e., a model with add-itive genetic (A) and specific environmental (E) influ-ences on psychiatric disorders, and a downward bias of the genetic variance in an ACE model, a model also in-cluding shared environmental influences (C). In an AE model an estimate for the genetic variance is more than twice the true heritability, amounts up to 3%, for a marital cor-relation of .2. The downward bias of an ACE model is more substantial. Using a formula to correct C for pheno-type assortment (Martin, 1978), the bias for an ACE model with an estimation of 40% for the proportion of variance explained by A, 20% for C and 40% for E is about 10% for a marital correlation of 2. We mean that after correction the proportion of variance explained by A would be 50% and C 10%. In the present study, if phenotypic assortment would completely explain this resemblance, the bias in estimates reported in twin stud-ies on psychiatric diagnoses is likely to be very small. Interestingly, if gene-shared environment correlation would be present, social homogamy would have conse-quences for the genetic structure in a population, but the correlations are small and shared environment does not seem to play a role in the phenotypes of the current research, we expect this not to be a problem in the current research. The spouse correlations we found were not zero, which means that in some couples both partners similarly have anxious, depressed or OC symptoms. It is therefore important to encourage a partner to come along with the patient, not only to have better informa-tion of the situation of the patient or discussing the role of the partner in a treatment plan but also to examine if psychiatric symptoms are present in the partner (Low et al., 2007).

Limitations

The results of this study should be interpreted in the light of three possible limitations. First, for estimating marital resemblance we use information on partners who were still together. In gen-eral, the rate of divorce in subjects without interviewed partners is lower. Furthermore psychiatric pathology in divorced pairs is increased (Maes et al., 1998, Wade & Cainrey, 2000), which gives a bias in the estimation of marital resemblance. In our sample, it appears that participants who were divorced at least a year before participation and had not met a new partner, showed significantly higher rates of depression (F = 98.7, p < .001) and anxiety symptoms (F = 89, p < .001) but not of OC symptoms (F = 3.6, p = .06) compared with pairs who were still together. Second, in the current study symptoms were measured cross-sectionally. Ideally, to study marital re-semblance, partners are followed longitudinally, prefer-ably starting shortly after having met their partner. Third, although the measurements we used are well-known questionnaires showing satisfying psy-chometric properties, some limitations regarding these measurements have to be mentioned. First, we mea-sured symptoms, no DSM diagnoses. This hampers the usefulness of the current study in clinical practice and comparability with studies based on DSM diagno-sis. Nevertheless, findings from the current study are remarkably comparable with the study of Maes et al. (1998), who used DSM-III-R diagnoses. Second, distri-butions of the measurements used were skewed, which may cause underestimation of correlations. Derks et al. (2004) showed that use of a threshold model estimate polythetic correlations could be a solution, but this has the disadvantage of losing power. We therefore choose to use the raw data. Third, the reliability for cross-sectional anal-yses of symptoms at one point in time is only moderate. Lastly, high intercorrelations were found for the examined traits, ranging from .49 to .71. Although OC, anxious and depressive traits show high comor-bidity, the question remains if the intercorrelations are caused by comorbidity or by overlapping instruments. Interestingly, Maes et al. (1998) found similar intercor-relations ranging from .58 to .71 for comparable DSM diagnoses like major depression and generalized anxiety disorder. This might suggest that comorbidity could be an important cause of the high intercorrelations we found.

REFERENCES


CHAPTER 6
Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents


Wright, S. (1921). Assortative mating based on somatic resemblance. Genetics, 6, 144-151.

Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents


ABSTRACT

Background Evidence from twin studies indicates that genetic and non-shared environmental factors play a significant role in the etiology of variation in obsessive-compulsive (OC) symptoms. Although twin studies are powerful to detect genetic and environmental influences, they do not provide information on the processes of assortative mating and non-genetic parent-offspring similarities.

Methods We examined 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 to test for genetic and cultural transmission, while taking assortative mating in the parental generation into account. The 12-item Padua Inventory Revised Abbreviated was used to measure OC symptoms.

Results Both additive genetic and non-shared environmental factors contributed significantly to the variance of OC symptoms in men and women. In men, shared environmental influences played a relative large role (explaining 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.

Conclusions The effect of cultural transmission in OC symptoms is minimal, although a significant contribution of shared environmental factors is found in women. In men there is no contribution of shared environment and familial resemblance is explained by shared genes.

Obsessive-Compulsive Symptoms (OCS) tend to cluster within families (Ván Grootheest et al., 1995; Nestadt et al., 2000). The resemblance between relatives can be due to genetic transmission, environmental similarities, cultural transmission, or a combination of all these factors. The resemblance between MZ twins is suggestive of genetic influences on segregating genes (Plomin et al., 2000). The resemblance between DZ twins is suggestive of genetic influences on environmental factors (Ván Grootheest et al., 2007b) obtained a moderate heritability of 40% and effects of shared environmental factors of about 10%, if a marital correlation phenotypic assortment. If this assortment is not included in the model, a bias with in general small influences on the heritability estimates of OC symptoms is seen, depending on model and height of the estimates. For example, in models with a moderate heritability of 40% and effects of shared environmental factors of 20%, there would be an underestimation of genetic factors and an overestimation of shared environmental factors of about 10%, if a marital correlation of 0.2 is not included in the model.

In this study we use an extended twin design which includes MZ and DZ twins and their parents, to study the heritability of OC symptoms, using a 12-item version of the PI-R (Cath et al., 2008). To maximize statistical power and to test if results generalize to other groups, this study included non-twins, the study was extended by including siblings reared apart (i.e., random mating between spouses), and that heritability can be studied, while taking into account cultural transmission. Cultural transmission will increase shared (or common) environmental variance. However, note that significant cultural transmission is necessary to increase shared environmental variance.

In this paper we use an extended twin design which includes MZ and DZ twins and their parents, to study the heritability of OC symptoms, using a 12-item version of the PI-R (Cath et al., 2008). To maximize statistical power and to test if results generalize to other groups, this study included non-twins, the study was extended by including siblings reared apart (i.e., random mating between spouses), and that heritability can be studied, while taking into account cultural transmission and assortative mating.

METHODS

Participants This study is part of an ongoing longitudinal survey study of the Netherlands Twin Register (NTR), which has assessed families with adolescent and adult twins roughly every two years since 1991 (Boomsma et al., 2002b, 2006). Each survey, with the exception of the 1995 wave, collected information on personality, intelligence, neuroticism, anxiety, and psychopathology. Sample selection and response rates are described in detail in Boomsma et al. (2002b; 2006). For this study, data of twins, their sibs and their parents from the 2002 survey were used. We received complete surveys for OC symptoms of respectively 4408 twins, 1309 siblings, and 2305 parents. The self-reports of the subjects at the time of the survey were 32.8 years (SD = 11.3) for twins, 35.3 years (SD = 12.3) for the sibs and 56.4 years (SD = 5.9) for the parents of the twins.

Measures In the 2002 wave of data collection, the 12 item Padua Inventory Revised Abbreviated (PI-R ABRBR) was included (Cath et al., 2008), derived from the Padua Inventory-Revised version (PI-R), which is a well-validated self report inventory on obsessive-compulsive symp-

Chapter 5 • Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents

Article
between their additive genetic values (A) is ½ under random mating. The expectation for parent-offspring genetic correlation is also ½ under random mating. Non-random mating due to phenotypic assortment will lead to an increase in resemblance among siblings and between parents and offspring.

Figure 1 shows a path diagram of the model used in the present research (Fulker, 1982; Boomsma & Molenar, 1987). The phenotypes of the parents (parents 1 and 2) and of their twin offspring (T1 and T2) are represented by squares. The sibling data is omitted from the figure for clarity, but the expectations for twin-sib resemblance are the same as for DZ twin resemblance. Variability in OC symptoms is caused by variation in A and E, and these are represented as latent factors in the model with unit variance. The factor loadings on the latent factors are represented by b or x (for A, in male and females respectively), and e or γ (for E in male and females). Parents pass their genes to their children, which is represented by arrows going from A of the parents to A of the child, with the factor loading ½. In the children, part of the genetic variance is explained by transmission from the parents. The remaining residual additive genetic variance represents the variance that results from recombination (which is uncorrelated in siblings and correlated unity in MZ pairs).

The Greek letters on the top of the diagram in Figure 1 represent the correlations induced by polygenic assortment. Coefficient γ represents the genotypic correlation between the parents, the environmental correlation between the parents, and (1/2)2 represent the correlations of the environment of one parent with the genotype of the other parent. All three correlations are induced by phenotypic assortment that can be represented as a parameter equal to the spousal correlation. This spousal correlation can be drawn as a co-path (Cloninger, 1980) between the phenotypes of the parents instead of the paths which are represented by the Greek letters. Cultural transmission, i.e. the regeneration of the child’s environment on the parents’ phenotypes, is represented by z (to male offspring) or j (to female offspring). If z or j is not equal to 0, genotype and environment in the offspring generation become correlated. As negative cultural transmission is unlikely, γ and j had a lower bound of 0. It is assumed that the system is at equilibrium, i.e. s and e are over generations, implying that genotype and environment are correlated to the same extent in the parents as in the offspring. This GE correlation, a (for males) or q (for females), is represented by the double-headed arrow between A and E (Eaves et al., 1989). The correlation β between the E components represents the residual shared environment within the offspring generation, not caused by cultural transmission, and was estimated for twins and sibs.

The OC symptom scores were first analyzed by fitting a saturated model to the data from DZ and MZ twin families. This model specifies all correlations between family members, and estimates means and variances. Several assumptions were tested, such as equality of means and variances between MZ and DZ twins and between twins, siblings and parents. Next, a genetic model was fitted to the data. In model fitting procedures, the saturated model is used as a starting-point for the comparison of different, nested models. The fit and parsimony of the various nested models are judged using likelihood ratio tests in which the negative log-likelihood (-2LL) of the nested model is compared with -2LL of the saturated model. Subtracting the two -2LLs from each other yields a statistic that is asymptotically distributed as χ² with degrees of freedom (df) equal to the difference between the number of parameters in the two models. All models were tested in the statistical modelling package Mx (Neale et al., 2003). Each model in the model fitting sequence was evaluated at a significance level of 0.1.

RESULTS

Working from a fully saturated model, there were no sex differences in means (χ²(19) = 1, p = .17) and variances (χ²(5) = (1), p = .48). MZ twins had the same variances as DZ twins across sexes (χ²(14) = 5, p = .04).

The mean scores (see table 2) could be constrained to be equal for twins, sibs and parents (χ²(15) = (2), p = .06).

The variances across sibs and parents were equal (total variance of 26.5 (χ²(9) = (1), p = .99), but the variance in twins was slightly larger (total variance of 31.1 (χ²(24) = 1, p < .01). This difference in variances was taken into account in subsequent analyses.

The twin-sib, DZ twin-DZ twin and sib-sib correlations could be constrained to be equal for males (χ²(19) = 2, p = .39), females (χ²(11) = 2, p = .58) and opposite sex pairs (χ²(39) = 2, p = .14). The correlations based on the constrained model are shown in Table 3. For women the MZ twin correlation was more than twice the combined DZ/sib correlation. Therefore, we chose to fit an AE model for women. For men, the MZ correlation is less than twice the combined DZ/sib correlation, indicating that shared environmental effects may play a role in individual differences in OC symptoms, besides additive genetic effects. We decided to fit an ACE model for men, i.e., we estimated β, the correlation between E, only for men. Correlations for parents and offspring are of the same order of magnitude as the DZ-FF and DOS correlations and may point to both genetic and cultural inheritance. Finally we observed a significant correlation between scores of spouses (0.17) which was modelled as the result of phenotypic assortment (Van Grootheest et al., 2008).

The results of genetic analyses are summarized in Table 4. An ACE model for men and AE model for

Table 1. The 12 items of the PI-R ABR

<table>
<thead>
<tr>
<th>Items</th>
<th>Original Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am afraid of losing my self-control and doing embarrassing things</td>
<td>Impulses</td>
</tr>
<tr>
<td>2. I feel obliged to follow a particular order in dressing, undressing and washing myself</td>
<td>Checking</td>
</tr>
<tr>
<td>3. I feel I have to repeat certain numbers for no reason</td>
<td>Precision</td>
</tr>
<tr>
<td>4. I return home to check doors, windows, drawers etc., to make sure they are properly shut</td>
<td>Impulses</td>
</tr>
<tr>
<td>5. I start thinking of certain things, I become obsessed with them</td>
<td>Rumination</td>
</tr>
<tr>
<td>6. I feel I have to wash or clean myself immediately because I think I may be dirty or ‘contaminated’</td>
<td>Washing</td>
</tr>
<tr>
<td>7. I get upset and worried at the sight of knives, daggers and other pointed objects</td>
<td>Impulses</td>
</tr>
<tr>
<td>8. Unpleasant thoughts come into my mind against my will and I cannot get rid of them</td>
<td>Rumination</td>
</tr>
<tr>
<td>9. I sometimes have to wash or clean myself simply because I think I may be dirty or ‘contaminated’</td>
<td>Washing</td>
</tr>
<tr>
<td>10. I get upset and worried at the sight of knives, daggers and other pointed objects</td>
<td>Impulses</td>
</tr>
<tr>
<td>11. I have to wash or clean myself immediately because I think I may be dirty or ‘contaminated’</td>
<td>Washing</td>
</tr>
<tr>
<td>12. If I touch something which I think is ‘contaminated’, I immediately have to wash or clean myself</td>
<td>Impulses</td>
</tr>
</tbody>
</table>

Table 2. Estimates of Mean and Standard Deviation (SD) of the sum score of the PI-R ABR

<table>
<thead>
<tr>
<th>N</th>
<th>Min</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fathers</td>
<td>1045</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Mothers</td>
<td>1260</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Brothers</td>
<td>482</td>
<td>25</td>
<td>8.1</td>
</tr>
<tr>
<td>Sisters</td>
<td>828</td>
<td>33</td>
<td>8.2</td>
</tr>
<tr>
<td>Male twins</td>
<td>1406</td>
<td>33</td>
<td>7.9</td>
</tr>
<tr>
<td>Female twins</td>
<td>3002</td>
<td>47</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Figure 1. The psychometric model for multiple raters
women describe the data adequately when compared with the fully saturated model (model 1). There was no significant contribution of cultural transmission for women, but we found cultural transmission for men (model 3). There was a significant spousal correlation (model 4). Shared environmental factors (C) for men also appeared to be significant (model 5). Furthermore, genetic influences were significant for men (model 6) and women (model 7) and could not be dropped with- out a significant loss in fit.

The best-fitting model (model 3) estimated the heritability of OC symptoms for men at 1%, the effect of cultural transmission for men at 4%, and the remaining nonshared environmental influence large at 27% and non-shared environmental effects at 71%. For women, the heritability was estimated at 37% and non- shared environmental explained 63% of the total variance in individual differences in OC symptoms.

If the found shared environmental influences for men are not a coincidental finding, one wonders what causes these shared environmental influences. These influences can arise from non-parental sources, special twin environment and cultural transmission (i.e., paren- tal influences). We could not find evidence for a special twin environment as we could equal DZM, twin-sibM and sib-sibM correlations, but did find significance for cultural transmission. However, the variation among twin environments is minimal and the remaining nonshared environmental influence large. This would imply that the shared environmental influences were mainly non-parental sources like co-twins, sibs and peer groups. A well-known example of within-generational influences is found for smoking, where the association between smoking behavior in parents and their children can be most likely accounted for by their genetic relatedness. The idea of social learning in smoking may apply to siblings or peers but does not appear to apply to children learning by modeling from their par- ents (Maes et al., 2006). As expected we found a significant influence of assortative mating, but because of the low spousal correlations, the bias in estimates caused by these correla- tions is minimal (van Grootheest et al., 2008). Together with the finding of a minimal effect of cultural transmis- sion, and thus gene-environment correlation, and the finding of Jonnal et al. (2000), who concluded that the equal environment assumption for OC symptoms was not violated, the assumptions for twin design are met. It furthermore appears that adding the parental data to the twin design does not provide much additional infor- mation for this phenotype. Note that the present design is not suited to uncover gene-environment correlations other than resulting from simultaneous genetic and cultural transmission (i.e., passive gene-environmental correlations). Evocative gene-environment correlation, where individuals are reacted to on the basis of their genetically influences phenotype, or an active gene-en- vironment correlation, where individuals seek or cre- ate environments correlated with their genetic back- ground.

The results of this study should be interpreted in the context of several potential limitations. First, al- though the PADUA ABRBR showed a moderately high sen- sitivity and specificity in diagnosing DSM IV OCD (Cath et al., 2008), the genetic and environmental contributions presented in this report reflect OCS scores, not clinical measures of DSM-IV OCD. Because of the relatively low prevalence of OCD, twin studies rely on dimensional measures with the underlying assumption that OCD re- flects the end of a normal distribution, while OC symp- toms represented a milder form of the latter presented in this report (Jonnal et al., 2003; Kendler, 2005).

Second, the PADUA ABRBR showed a skewed distribution, One could use a threshold model to deal with this problem, but the disadvantage of a threshold model is the loss of power (Derks et al., 2004). There- fore, we decided to use the continuous scales with the disadvantage of possibly underestimating the twin correlations, resulting in understimating the genetic proportions and overestimating the nonshared proportions a bit.

Table 3. Twin, twin-sib, parent and parent-child correlations for the PI-R ABRBR

<table>
<thead>
<tr>
<th></th>
<th>MZF</th>
<th>DZF</th>
<th>DZM</th>
<th>MZM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father-daughter</td>
<td>0.44</td>
<td>0.28</td>
<td>0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>0.44</td>
<td>0.28</td>
<td>0.17</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Table 4. Model fitting results using the PI-R ABRBR

<table>
<thead>
<tr>
<th>Model</th>
<th>Type of model</th>
<th>-2LL df p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully saturated model</td>
<td>4937.8 1</td>
</tr>
<tr>
<td>2</td>
<td>ACE model for males and All for females</td>
<td>4937.0 196 98 1</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + no cultural transmission for women</td>
<td>4934.0 0.0 1 0.99 2</td>
</tr>
<tr>
<td>4</td>
<td>Model 3 + no cultural transmission for men</td>
<td>4935.6 15.6 &lt;0.01 3</td>
</tr>
<tr>
<td>5</td>
<td>Model 3 + no cultural transmission for men</td>
<td>4946.4 30.4 1 0.01 3</td>
</tr>
<tr>
<td>6</td>
<td>Model 3 + no A for males</td>
<td>4950.3 65.6 1 0.01 3</td>
</tr>
<tr>
<td>7</td>
<td>Model 3 + no A for females</td>
<td>4956.1 111 1 0.01 3</td>
</tr>
</tbody>
</table>

*ACE: additive genetic effects, E: nonshared or individual-specific effects, C: common or shared environmental effects

REFERENCES


Page 57
PART III. GENETIC AND ENVIRONMENTAL INFLUENCES ON OCs OVER TIME

CHAPTER 7
Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior


Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior


ABSTRACT
Background Little is known about the stability of obsessive-compulsive (OC) behavior during childhood. The objective of this study is to determine the developmental stability of pediatric OC behavior and the genetic and environmental influences on stability in a large population-based twin sample.

Methods Maternal and paternal ratings on the 8-item Obsessive Compulsive Scale of the Child Behavior Checklist (CBCL-OCS) on Dutch mono- and dizygotic twin pairs from 8083 families were collected at ages 7, 10, and 12 years. Using the original scale design, stability of OC behavior and genetic and environmental influences on stability were determined. Using cut-off criteria, persistent, and new onset cases were identified in this sample.

Results 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 by genetic factors, by environmental factors shared by children growing up in the same family and by non-shared environmental factors. Stability for OCS was lower when categorical data were analyzed, than when quantitative definitions were used.

Conclusions OC behavior is moderately stable in childhood. Stability of OC behavior is influenced by genetic, shared and non-shared environmental factors.

Given how common and impairing obsessive-compulsive disorder (OCD) is in children (Piacentini et al., 2003), a better understanding of the etiology and course of OCD is important. One of the factors that limits a clear understanding of the etiology and development of OCD is a lack of epidemiological studies. Recently, a useful screening measure was developed to identify children at risk for OCD in the population, the Childhood Obsession Checklist (CBCL-OCS (Nielsen et al., 2001). Hudziak et al. (2006) used the CBCL-OCS to determine the prevalence of OCD in US and Dutch population twin samples. They found higher prevalence rates than previously reported. Genetic contributions (Hudziak et al., 2004) accounted for at least 50% of individual differences in CBCL-OCS scores in children growing up in the same family and by non-shared environmental factors. Stability for OCS was lower when categorical data were analyzed, than when quantitative definitions were used.

MeTHODs AnD MATeRiAls

The study is part of a longitudinal twin study on emotional and problem behavior in the Netherlands. The subjects are all registered with the Netherlands Twins Registry (NTR), established by the Department of Biological Psychology at the Vrije Universiteit in Amsterdam (Boomsma et al., 2002a). For this study, we included 7-year-old twin pairs from both cohorts 1986-1996, 10-year-old twin pairs from cohorts 1986-1993 and 12-year-old twin pairs from cohorts 1986-1990. Both parents were asked to complete a Child Behavior Checklist (CBCL) (Achenbach 1991). Parental ratings did not return the forms within 2 months received a reminder. If finances permitted, persistent non-responders were contacted by phone. Families who did not participate at one age of the twins could enter the study at subsequent ages. Among those who received a questionnaire, response rates were 66% at age 7, 64% at age 10, and 62% at age 12. From the original sample, 208 families were excluded because either one or both twins had a disease or handicap that interfered severely with daily functioning at age 12 or younger. The total sample consists of 8083 twins families. Table 1 shows the numbers of maternal and paternal reports on the CBCL-OCS per zygosity and age. Ratings from both parents were available for 5433 twin pairs at age 7, 3172 pairs at age 10 and 1787 pairs at age 12. Maternal ratings were available in 3857, 1217 and 558 same-sex pairs at ages 10 and 12 respectively. For a small number of twin pairs, only father ratings were available, respectively 92, 74 and 40 twin pairs at ages 7, 10 and 12. For mother rat- ings, 1582 twin pairs participated at age 7, 10 and 12, 1970 twin pairs at age 7 and 10, 144 twin pairs at age 7 and 12 and 224 twin pairs at ages 10 and 12. For father rat- ings, 1338 twin pairs participated at age 7, 10 and 12, 1347 at age 7 and 10, 160 twin pairs at age 7 and 12 and 182 twin pairs at age 10 and 12. To examine the effects of sample attrition, data from twins who participated three times were compared to data from twins who participated at age 7, but whose parents did not return the CBCL at age 10 and 12. Equal numbers of drop-out were observed for boys and girls. For girls, there were no differences in means between these groups. For boys, the non-response group showed somewhat larger means in CBCL-OCS at age 7. These differences in means were significant, but small (< one standard deviation). Any effect of the sample attrition on the results at ages 10 and 12 are accounted for by inclu- sion of all available data in the analyses, irrespective of the number of times that a family participated.

Zygosity was based on DNA or blood group polymorphisms for 1258 same-sex pairs. For the remain- ing same-sex twin pairs, zygosity was determined by questionnaire, or by phenotype. Concordance rates per zygosity and age are shown in Table 2. Concordance rates were based on the results at ages 10 and 12 are accounted for by inclu- sion of all available data in the analyses, irrespective of the number of times that a family participated.
psychometric stability of the CBCL have been well established (Achenbach 1991; Verhulst et al., 1996). DC Anh was measured using the CBCL Obsessive- Compulsive Scale (CBCL-OCS) (Nelson et al., 2001). A numerical value for the OCS scale is created by summing the scores on the 8 relevant items, creating a range between 0 and 16. Using a cut-off score of 5 on the CBCL-OCS, 91% of all DSM-IV-TR OC cases were identified in a clinical sample with reasonable specificity (67.2%) (Hudziak et al., 2006). The cut-off of 5 is used in this study to screen for OCD cases. The CBCL-OCS has been validated in several samples (Geller et al., 2006; Storch et al., 2006).

STATISTICAL ANALYSES

Descriptives and correlations

Means, standard deviations and the effects of sex, zygosity and age on mean scores were estimated and evaluated with the statistical software program Mx (Neale et al., 2003). Differences in means were tested by likelihood ratio tests. These tests were performed while taking into account the dependency that exists between scores of the twins. The p-level was set at .01. To get a first impression of the underlying sources of variance and stability of the CBCL-OCS, Mx was used to calculate within-pair (genetic) and between-pair (environmental) correlations (phenotypic stability of CBCL-OCS), within person inter-parent correlations (parental agreement), twin correlations (cross-sectional twin-1 twin-2 correlations) and cross-twin cross-age correlations (e.g. twin 1 at age 7 with twin 2 at age 10). Further, to take rater differences into account, cross-rater twin correlations within and across age were estimated. Cross-correlations between mother ratings of oldest twins with father ratings of youngest twins, or the other way around, form the basis for the decomposition of the variance into a part on which both raters agree and a part on which they disagree. The cross-rater twin correlations over time (the cross-twin cross-age across rater correlations), are used to investigate the underlying developmental patterns of the distinct common and rater specific variance components.

Genetic Modeling

In the classical twin design the relative contributions of genetic and environmental factors to individual differences in OCS scores can be inferred from the different levels of genetic relatedness between MZ and DZ twins. Individual differences may be due to additive genetic (A), shared environmental (C) or non-shared environmental (E) factors (Boomsma et al., 2002b). Additive genetic factors are correlated 1.0 in MZ twins, since MZ twins are genetically identical. For DZ twins, the additive genetic factors are correlated 0.5, because DZ twins share on average half of their segregating genes. The environment shared by a twin pair is assumed not to contribute to the correlations across time, and thus shared environmental factors correlate 1.0 in both MZ and DZ twins. E or non-shared environment is by definition uncorrelated. All uncorrelated error is also absorbed in the E term.

To model the ratings from two parents for each twin, we used a psychometric model (see figure 1) (Bartels et al., 2003, Bartels et al., 2004a; Hewitt et al., 1992) and expanded this model to longitudinal data.

The psychometric model allows the parental ratings to be influenced by aspects of the child’s behavior perceived commonly by both parents (common or rater independent phenotype) and by aspects of the child’s behavior that are perceived uniquely by each parent (the unique or rater-specific phenotype). In this model, both the variation of the rater-independent and rater-specific aspects can be influenced by genetic, shared environmental and non-shared environmental factors. The common phenotype represents the part of behavior similarly assessed by both parents and can be considered as independent of rater bias and unreliability of the ratings. Unique perceptions of the child’s behavior can arise if the child behaves differentially towards the parents or if the parents observe the children in different situations. By testing the significance of genetic effects on the unique phenotype, it can be established whether the raters must have been assessing a “real” but unique aspect of the child’s behavior. Error and/or unreliability of the unique phenotype may be confounded by rater bias, such as using normative standards or response styles. Because rater bias is independent of zygosity, it mimics shared environmental effects. A further advantage of the longitudinal psychometric model is that genuine unique non-shared environmental effects can be distinguished from random measurement error. Random errors are age specific and are unlikely to contribute to the correlations across time in non-shared environmental effects.

To expand the psychometric model to a longitudinal design we used a Cholesky or triangular decomposition. This decomposition is descriptive and not driven by a specific developmental hypothesis. It decomposes a covariance matrix into genetic and non-genetic covariance matrices and may be used to obtain genetic and environmental correlations across time in longitudinal datasets.

RESULTS

Descriptive statistics

Table 1 summarizes the means and standard deviations for the CBCL-OCS by age and sex in mother and father reports. Mothers reported significantly more OC symptoms than fathers for both boys and girls, except for female DZ twins at age 12 (μ²(1) = 50, p = .48).

No significant differences were seen between boys and girls. No differences found between zygosity groups were found with the exception of age 7. At that age, DZ female twins had a higher OCS score than MZ female twins (μ²(1) = 7.78, p = .01). OC symptoms are higher in MZ male twins according to mother ratings and DZ male twins had higher means than MZ male twins according to father ratings (μ²(1) = 9.65, p = .01).

Persistence of cases of OCD

Table 2 shows persistence of cases with a CBCL-OCS score of 5 or higher. It is clear that the stability of cases meeting cut-point criteria for pediatric OCD is low. Most cases had a score of 5 or higher at one specific age only. When using a categorical approach such as this, we can identity cases of persistence, remission, and new-onset. For example, for boys rated by mother, only four cases had a score of 5 or higher at all three ages. These data shed light on computing stability according to diagnostic cutpoints, versus using quantitative computations as below. The lower mean CBCL-OCS scores of fathers (see descriptive statistics) is reflected in the fact that cases rated by mother outnumber cases rated by father. Interestingly, using a cutoff of 4 for fathers gave almost exactly the same pattern (not shown) as for mothers, using a cutoff of 5.
Table 2. Cases with score of 5 or higher on the CBCL-OCS at different ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Girls rated by mother</th>
<th>Boys rated by mother</th>
<th>Girls rated by father</th>
<th>Boys rated by father</th>
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Bold-faced numbers show the number of cases of OCD at that specific age. Normal-sized numbers show the cases which persist at a specific age. For example, boys rated by mother at age 7, 13 cases occurred at age 7 of which persisted at age 10. The cases from age 7 which showed up at age 10 had an onset lower than 6 years old.

Correlations

Table 3 contains the within-twin phenotypic correlations over time. These correlations provide an indication of the stability of the expression of CBCL-OCS, irrespective of possible changes in group means. Both boys and girls displayed a comparable degree of stability of about .50 from ages 7 to 10 and from ages 10 to 12 for both mother and father ratings. Within-person inter-parent correlations were comparable over the distinct zygosity groups and at the distinct ages (not shown). The correlations ranged between .48 and .73 with an average of .58.

Table 4 presents cross-sectional twin correlations (diagonal) for MZ and DZ pairs. MZ correlations are higher than DZ correlations, suggesting genetic influences. MZ correlations were lower than one, which suggests influences of non-shared environment. Further, shared environmental influences were implied by the fact that the MZ correlations are less than twice the DZ correlations. Twin correlations over time (cross-twin-cross-age correlations) are given on the off-diagonal of table 4. These correlations are informative with respect to the proportion of longitudinal covariance explained by genes and environment for CBCL-OCS over time. Across-age MZ correlations were higher than DZ correlations, with a larger difference for mother ratings, suggesting that additive genetic effects are more important in phenotype stability of mother ratings compared to father ratings.

Table 5 gives the percentages of the genetic, shared and non-shared environmental contribution to the variances (diagonal) and covariances across time (off-diagonal) of the CBCL-OCS for the common phenotype, respectively at older ages, the DZ cross-twin correlations seemed to be larger than expected on the basis of genetic influences alone, and therefore shared environmental influences seemed to contribute to the common parental phenotype. For each age, the cross-twin-cross-correlations were given on the off-diagonal (see Table 4). The differences indicate the part which is unique to a particular rater (i.e. the unique or rater-specific phenotype). A same pattern of higher MZ than DZ correlations is seen for the cross-twin-cross-age twin correlations (off-diagonal), indicating genetic influences on the stability of the common parental phenotype. The differences between the within twin correlations over time (table 4, off-diagonal) were quite small, which means a relatively small influence of the unique or rater-specific phenotype on stability compared to the larger influence of the common phenotype.

Table 6 gives the percentages of the genetic, shared and non-shared environmental contribution to the variances (diagonal) and covariances across time (off-diagonal) of the CBCL-OCS for the common phenotype, respectively at older ages, the DZ cross-twin correlations seemed to be larger than expected on the basis of genetic influences alone, and therefore shared environmental influences seemed to contribute to the common parental phenotype. For each age, the cross-twin-cross-correlations were given on the off-diagonal (see Table 4). The differences indicate the part which is unique to a particular rater (i.e. the unique or rater-specific phenotype). A same pattern of higher MZ than DZ correlations is seen for the cross-twin-cross-age twin correlations (off-diagonal), indicating genetic influences on the stability of the common parental phenotype. The differences between the within twin correlations over time (table 4, off-diagonal) were quite small, which means a relatively small influence of the unique or rater-specific phenotype on stability compared to the larger influence of the common phenotype.

Table 7 gives the percentages of the genetic, shared and non-shared environmental contribution to the variances (diagonal) and covariances across time (off-diagonal) of the CBCL-OCS for the common phenotype, respectively at older ages, the DZ cross-twin correlations seemed to be larger than expected on the basis of genetic influences alone, and therefore shared environmental influences seemed to contribute to the common parental phenotype. For each age, the cross-twin-cross-correlations were given on the off-diagonal (see Table 4). The differences indicate the part which is unique to a particular rater (i.e. the unique or rater-specific phenotype). A same pattern of higher MZ than DZ correlations is seen for the cross-twin-cross-age twin correlations (off-diagonal), indicating genetic influences on the stability of the common parental phenotype. The differences between the within twin correlations over time (table 4, off-diagonal) were quite small, which means a relatively small influence of the unique or rater-specific phenotype on stability compared to the larger influence of the common phenotype.
Table 6. Percentages of the genetic (A), shared (C) and non-shared (E) environmental contributions to the total variances (diagonal; bold) and covariances (off-diagonal) of the CBCL-OCS for the common phenotype and the unique/rater-specific phenotype based on the Cholesky decomposition model for boys (below diagonal) and girls (above diagonal). Note that common and unique phenotype add up to 100%.

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<th></th>
<th>Total common phenotype</th>
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<td></td>
<td>Mother ratings</td>
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Agonal of the CBCL-OCS, the common phenotype and rater-specific phenotype have been added together.

For boys, analyses of the covariates in adults, which means, as only one-third to one-half of adults with OCD develop the disorder in childhood (Pauls et al., 1995), a considerable proportion of youth with OCD becomes subhydral (Stewart et al., 2004).

We found neither sex differences in prevalence of CBCL-OCS (Hudziak et al., 2006), in persistence. This is confirm Stewart et al. (2004), who found sex to be a non significant predictor of persistence in OCD. If sex differences in prevalence of pediatric OCD are report-
ed by others, boys outnumber this, but this is mostly done in clinical samples (Geller et al., 1998; Eichstedt & Arnold, 2001). This may imply that girls with OCD are less likely to be clinically diagnosed, although their symp-
toms are present and may persist into adolescence.

Table 7. Percentages of the genetic (A), shared (C) and non-shared (E) environmental contributions to the total variance (diagonal; bold) and total covariance (off-diagonal) of the CBCL-OCS for boys (below diagonal) and girls (above diagonal). Common phenotype and unique/rater-specific phenotype have been added together.

|         | Mother ratings          | Father ratings |
|---------|------------------------|---------|---------|
| age     | 7 | 10 | 12 | 7 | 10 | 12 |
| 7       | 53.49 | 40 | 27 | 59.49 | 34 | 35 |
| 10      | 57 | 58.46 | 36 | 44 | 48.42 | 16 |
| 12      | 54 | 43 | 35.12 | 43 | 19 | 17.30 |
| C       | 7 | 10 | 12 | 7 | 10 | 12 |
| 7       | 10.11 | 18 | 39 | 13.15 | 21 | 50 |
| 10      | 13 | 6.9 | 30 | 16 | 8.12 | 36 |
| 12      | 18 | 17 | 34 | 26 | 12 | 18 |
| 14      | 21 | 17 | 34 | 26 | 12 | 18 |
| E       | 7 | 10 | 12 | 7 | 10 | 12 |
| 7       | 37.41 | 42 | 34 | 28.35 | 41 | 15 |
| 10      | 30 | 33.45 | 34 | 40 | 44.46 | 40 |
| 12      | 38 | 33.45 | 34 | 40 | 44.46 | 40 |

Common phenotype and unique/rater specific phenotype have been added together.
In particular, fathers seem to add little extra information on stability of OC behavior. One might cog that mothers have a longer view of OC behavior of their children.

Limitations
The results of this study should be interpreted in the context of several potential limitations: First, maternal and paternal skewness were found. However, Derks et al. (2004) found that skewness in the data lead to biases in parameter estimates, i.e. underestimated the sharing of the environmental and shared environments and overestimated the non-shared environmental estimates. One approach to deal with this problem is using a liability threshold model (Lynch & Walsh, 1998). For the longitudinal design of this study, however, a liability threshold model is practically not feasible.

Second, the genetic and environmental contributions to this report are for CBCL-OCS, not for clinical measures of DSM-IV OC. Although we have performed prior studies (Nelson et al., 2001; Huizinga et al., 2005), replicated by others (Geller et al., 2006, Storch et al., 2006), to demonstrate the validity, specificity, sensitivity and predictive power of the CBCL-OC in DSM-IV OC, it remains possible that the CBCL-OC may over identify cases in general populations. However, as we have shown, the quantitative approach may be useful to identify children at risk, but not yet expressing DSM-IV OC.

Third, despite the fact that we used both maternal and paternal ratings, reliance on parent reports is still a matter of concern. To control for this, we will use information on the stability and change of OC behaviors across adolescents and young adults, where self reports become the mainstay of assessment. As a result, we aim currently to collect YSR data on these twins as they reach adolescence and young adulthood.

Fourth, one assumption underlying most twin studies is the stability of OC behaviors. The regression of OC behaviors will be valuable in order to test the stability and change of OC behavior, our data point out the necessity of longitudinal studies with multiple raters for different phenotypes.

Implications
Our study has implications for clinical intervention. First, our data, consistent with those of others, points to the fact that OC diagnosis is a somewhat unstable condition for which remission from ‘clinical deviation’ is a relatively common phenomenon. These data allow the clinician to make a diagnostic optimism when a parents asks about the future.

Second, and consistent with the literature on the power of behavioural approaches such as Exposure and Response Prevention (ERP) (Fisher & Wells, 2005) to positively affect OC behavior, our data point out the contribution of shared and unshared environment to phenotypic stability. Put simply, this finding argues strongly for changing the environment in which children are raised. As parents of children with OC behaviors, we should try to collect data from different informants. For analyses of stability, mother ratings seem more informative than father ratings in our study. However, more longitudinal studies with multiple raters for different phenotypes are necessary to see if this is only the case for OC behavior. Within a clinical setting this could mean that the demonstration both parents is important to get a good view about how the child is doing at the moment, while the information of the mother is important to get a long view term.

Lastly, this research has implications for molecular genetic research. Within the common phenotype of OC behaviour the same genes influence OC behaviour throughout a wide age range. However, one should note that one may pool data from children of different ages together in link-up analyses, obtaining an increase of power, and that no age-specific effects are to be expected in candidate gene studies.

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Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at age 12, 14 and 16


Abstract
To determine the contributions of genetic and environmental influences to variation in self-report of Obsessive Compulsive (OC) symptoms in a population-based twin sample of adolescent boys and girls.

Methods
Self report ratings on the 8-item Obsessive-Compulsive Scale of the Youth Self Report (YSR-OCs) were collected in Dutch mono- and dizygotic twin pairs, who participated at age 12 years (N = 746 twin pairs), at 14 years (N = 963 pairs), or at 16 years (N = 1070 pairs). Structural equation modelling was used to decompose the variation in liability to OC symptoms into genetic and environmental components.

Results
At age 12 no difference in prevalence was found for OC symptoms in boys and girls. At ages 14 and 16, however, the prevalence was significantly higher in girls. At all ages, dyadic correlations significantly to variation on OC liability, 27% at the age of 12, 57% at the age of 14 and 54% at the age of 16. There were no sex differences in heritability. Only at age 12, environmental factors shared by children from the same family contributed significantly (16%) to individual differences in OC symptom scores.

Conclusions
During adolescence, OC symptoms are influenced by genetic and non-shared environmental factors. Sex differences in prevalence, but not in heritability, emerge in adolescence. At age 12, shared environmental factors are of importance, but their influence decreases at later ages. This is in line with earlier research at age 12 which used parental ratings of OCs. Thus, between family factors play a significant role in explaining individual differences in OC symptoms at this age.

When considering the etiology of Obsessive-Compulsive Disorder (OCD) or Obsessive-Compulsive Symptomatology (OCS) in children and adolescents as a cross-sectional experiment during which a wide range of developmental and environmental changes occur over a short period of time, therefore, this episode is of special interest when studying the dynamics between genes, development and environment. In OCD a bimodal distribution of age at onset has been found, with one peak occurring in preadolescent childhood and another peak in adulthood (Delorme et al., 2005; Chabane et al., 2005). Early age at onset of OCD is also associated with tic disorder (Swerdlow et al., 1989; Rosario-Campos et al., 2001) and the morbidity risk for OCD in family members of OCD subjects with early-onset of OCD is higher than in family members of late-onset OCD probands (Pauls et al., 1995; Nestadt et al., 2000). Furthermore, adult studies report an equal representation of men and women for OCD, or a slight female preponderance, where in clinical studies early age at onset of OCD is associated with male preponderance (Geller et al., 2001). These observations would suggest that adolescence could be a period in which genetic and environmental etiological factors in OCD change over a relatively short period of time, offering a window of opportunity to study the genetics of OCD and OC symptoms. The aim of this study is to estimate the genetic and environmental contributions to OC symptoms in the adolescent period. Although some genetic and environmental factors, twin or adoption studies are needed. No adoption studies of OCD have been published. Twin studies of OCD have evolved from case-studies with patients with OCD to large-scale studies of unselected subjects. In these studies, the entire distribution of OC Symptoms (van Grootheest et al., 2003) is analyzed, assuming that OCs is continuous with OCD. Mathews et al. (2007) substantiated this assumption by finding evidence for a heritable unidimensional symptom factor underlying obsessive-compulsiveness. In a recent genetic study of latent OC disorder probability, the heritability of OC symptoms was 55% at age 7 and 30% at age 10 (van Grootheest et al., 2007a). A moderate sex difference in heritabilities and significant correlations of around .50 were found for boys and girls for OC symptoms. Studies of OCS behavior has been performed using parental reports, adopted children and showed a heritability of 33% in men and 50% in women. As far as we know, no study has examined the genetic and environmental contributions to OC symptoms in adolescence. In the current cross-sectional study, Dutch twins completed a self-report on OC behavior around their 12th, 14th or 16th birthday. We aim to determine the genetic architecture of OCS self report items in adolescence and to address the following questions:

1. What is the contribution of genetic and environmental influences on self-reported OC behavior in adolescence?
2. Are there sex differences in the contributions of genetic and environmental risk factors for OC symptoms in adolescence?

Methods
Participants
The study was part of an ongoing study of emotional and problem behavior in young twins who are registered with the Netherlands Twin Register (NTR) (Boomans et al., 2006; Bartels et al., 2007). We analyzed data from twin pairs who reported on their behavior with the Youth Self Report Obsessive Compulsive Scale when they were 12, 14 or 16 years old (Bartels et al., 2007). A survey that contained the YSR-OCs was send by mail to the twins, after parents gave consent. Twins who did not return the forms within 2 months received a reminder. The overall family response rate was 56.1%.

Zygosity was determined by DNA or blood group polymorphisms in the same sex twin pairs. For the remaining same-sex twin pairs, zygosity was assessed by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers. Zygosity was correctly classified by questionnaire in 93% of the cases (Rietveld et al., 2006).

Measures
The twins completed the 8 item Obsessive Compulsive Scale of the Youth Self Report (YSR-OCs) (see table 1). The YRS-OCs was first developed and tested in young children using CBCL parental report (CBCL-OCs) (Nelson et al., 2001; Hudziak et al., 2006), and then tested on self-report data in the Young Adult Self Report, the YASR-OCs (van Grootheest et al., 2007a). The YASR-OCs has been used to study obsessive-compulsive symptoms in non-clinical samples of young adults. The effect of familial factors was estimated at 47% for the American sample (Bolton et al., 2007) substantiated by a recent twin study of the family aggregation and found a heritability of 39% in men and 50% in women. As far as we know, no study has examined the genetic and environmental contributions to OC symptoms in adolescence. In the current cross-sectional study, Dutch twins completed a self-report on OC behavior around their 12th, 14th or 16th birthday. We aim to determine the genetic architecture of OCS self report items in adolescence and to address the following questions:

1. What is the contribution of genetic and environmental influences on self-reported OC behavior in adolescence?
2. Are there sex differences in the contributions of genetic and environmental risk factors for OC symptoms in adolescence?
Hudziak et al., 2006. We have summarized the psychometric results of the CBCL-OCSS of these studies in table 2.

### Analyses

MZ twins share all their genes, while DZ twins share on average half of their segregating genes. This different degree of genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twins is used to estimate the genetic and environmental contributions to the variance of a trait. The total variance can be decomposed into additive genetic variance (A), shared environmental variance (C) and non-shared environmental variance (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes measurement error and is therefore always included in the models.

Because the data exhibited a pronounced right skew at all ages, we used a threshold model with three thresholds. By using a threshold model, genetic analyses are carried out on an underlying continuous distribution of liability to the disorder. The number of thresholds, defining categories (e.g., unafflicted, mildly and severely affected) (Derks et al., 2004), are chosen in such a way that the number of individuals was roughly similar in each of the categories without the presence of empty cells (e.g., category not including any person). We started with a saturated model, in which all thresholds and all twin correlations were estimated freely. Because a threshold model was used, polygenic correlations were obtained, which represent the resemblance between twins on the liability for OC symptoms. We tested whether thresholds were the same for first and born second-born twins, for MZ and DZ twins to examine effects on prevalence of OC symptoms, and for boys and girls to examine sex differences in prevalence of OC symptoms. The saturated model provides a baseline model against which genetic models were compared. In the genetic models the significance of sex differences in the estimates for the influences of A, C and E were tested. The significance of the contributions of additive genetic influences and shared environmental influences was tested by assessing the deterioration in model fit after each component was constrained at zero in the full model.

### RESULTS

In the saturated model, no effect of birth order or zygosity was detected at any age (all p-values > .05) on the thresholds. There was no sex effect on the thresholds at age 12 (χ²(2) = 2.1, p = .34). However, at ages 14 and 16, the thresholds were significantly lower for girls (χ²(3) = 43.94, p < .001) and (χ²(2) = 42.37, p < .001) respectively compared to boys on the YSR-OCSS at the age of 14 and 16. Polychoric twin correlations are presented in table 3 and 4. Genetic and environmental factors seems to be of importance, because MZ correlations are lower than twice the DZ correlations.

### Table 4. Model fitting results for YSR-OCSS scores

<table>
<thead>
<tr>
<th>Study Sample</th>
<th>Type of model</th>
<th>AIC Compared with model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>c²</td>
<td>e²</td>
</tr>
<tr>
<td>Age 12</td>
<td>Full model</td>
<td>3395.9</td>
</tr>
<tr>
<td>2. AE sex</td>
<td>3554.8</td>
<td>15.3</td>
</tr>
<tr>
<td>3. ACE no sex</td>
<td>3580.8</td>
<td>3.2</td>
</tr>
<tr>
<td>4. AE no sex</td>
<td>3606.5</td>
<td>3.5</td>
</tr>
<tr>
<td>5. CE no sex</td>
<td>3960.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Age 14</td>
<td>Full model</td>
<td>4913.4</td>
</tr>
<tr>
<td>2. AE sex</td>
<td>4915.7</td>
<td>12.3</td>
</tr>
<tr>
<td>3. ACE no sex</td>
<td>4936.9</td>
<td>3.2</td>
</tr>
<tr>
<td>4. AE no sex</td>
<td>4936.9</td>
<td>3.0</td>
</tr>
<tr>
<td>5. CE no sex</td>
<td>4936.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Age 16</td>
<td>Full model</td>
<td>5246.2</td>
</tr>
<tr>
<td>2. AE sex</td>
<td>5260.7</td>
<td>4.5</td>
</tr>
<tr>
<td>3. ACE no sex</td>
<td>5262.7</td>
<td>2.0</td>
</tr>
<tr>
<td>4. AE no sex</td>
<td>5262.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>

### Table 3. Number of complete twin pairs and twin correlations at ages 12, 14 and 16

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Age 12</th>
<th>Complete twin pairs</th>
<th>Complete twin correlations</th>
<th>Incomplete twin pairs</th>
<th>Incomplete twin correlations</th>
<th>Age 14</th>
<th>Complete twin pairs</th>
<th>Complete twin correlations</th>
<th>Incomplete twin pairs</th>
<th>Incomplete twin correlations</th>
<th>Age 16</th>
<th>Complete twin pairs</th>
<th>Complete twin correlations</th>
<th>Incomplete twin pairs</th>
<th>Incomplete twin correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZM</td>
<td>140</td>
<td>3</td>
<td>50</td>
<td>134</td>
<td>5</td>
<td>57</td>
<td>175</td>
<td>13</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZM</td>
<td>138</td>
<td>3</td>
<td>38</td>
<td>128</td>
<td>7</td>
<td>17</td>
<td>150</td>
<td>16</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZF</td>
<td>162</td>
<td>3</td>
<td>45</td>
<td>222</td>
<td>9</td>
<td>60</td>
<td>209</td>
<td>17</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZF</td>
<td>124</td>
<td>6</td>
<td>36</td>
<td>144</td>
<td>10</td>
<td>30</td>
<td>189</td>
<td>13</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOS</td>
<td>162</td>
<td>12</td>
<td>57</td>
<td>172</td>
<td>9</td>
<td>22</td>
<td>240</td>
<td>68</td>
<td>22</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

### Table 2. Summary of studies examining psychometric properties of the CBCL-OCSS that include the same items as the YSR-OCSS

<table>
<thead>
<tr>
<th>Study</th>
<th>N of children/adolescents</th>
<th>Mean age (SD)</th>
<th>Sensitivity (compared to clinical controls)</th>
<th>Specificity (compared to clinical controls)</th>
<th>Cronbach's alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neilson et al., 2001</td>
<td>73 OCD patients and 73 clinical controls</td>
<td>12.3 (2.8) for boys 12.0 (2.4) for girls</td>
<td>73.5% - 84.9% (depending on percentile scores)</td>
<td>72.1% - 87.7% (depending on percentile scores)</td>
<td>84</td>
</tr>
<tr>
<td>Hudziak et al., 2006</td>
<td>61 OCD patients and 64 clinical controls (in essence same population as used by Neilson et al.)</td>
<td>See Neilson et al. 92% (using a cut-off of 5)</td>
<td>67% (using a cut-off of 5)</td>
<td>See Neilson et al.</td>
<td></td>
</tr>
<tr>
<td>Geller et al., 2006</td>
<td>64 OCD patients and 64 clinical controls</td>
<td>11.2 (3.5)</td>
<td>78.1% - 92.2% (depending on percentile scores)</td>
<td>75% - 89.1% (depending on percentile scores)</td>
<td>87</td>
</tr>
</tbody>
</table>
DISCUSSION

To our knowledge, this is the first twin study of OCS in adolescents, revealing that individual differences in OCS around puberty are already shared, with substantial environmental influences only playing a role at the beginning of adolescence. No sex differences in heritability estimates and individual differences in OCS are influenced by the same additive genetic factors in boys and girls. Female adolescents scored higher on OCS than males at the age of 14 and 16, but not at the age of 12.

The finding of equal prevalence of OCS symptoms in boys and girls at age 12 is in line with the study of Hudziak et al. (2004), who found no sex differences in scores at ages 7, 10 and 12. The prevalence of OCS in boys and girls within community samples seems to be more similar than in samples with clinic OC, where boys outnumber girls. Interestingly, at the age of 14 and 16 girls showed a higher OCS prevalence than boys. This is in line with a recent study using the YASR-OCS in adults, which found significantly higher prevalence for women and also with clinical and epidemiological findings in the context of several potential limitations. First, the EEA was not violated. Gene-environment interaction could affect twin similarity in either direction depending on whether both twins are exposed to the specific environmental factor in question. Second, our knowledge, gene-environment interaction and/or correlation have yet to be demonstrated for the phenotype studied.

Thirdly, the 8-item YSR-OCS is not a final version to examine OCS symptom dimensions. More and more evidence is coming out that OCS or OCD appears to encompass at least four consistent and temporally stable symptom dimensions (Mataix-Cols et al., 2005). By considering these OCS symptom dimensions as quantitatively different from clinical OCD, the prevalence in the general population may be higher than currently estimated (Delorme et al., 2008a), which is in agreement with the high heritability estimates for the OCS in girls (Orr et al., 2008b). In conclusion, we propose that OCS and OCD are different entities, and more research to OCS in the adolescent period is needed.

In sum, the present study suggests that heritability estimates of OCS symptoms in adolescence are similar (55 %) to the heritability estimates in children, with a drop around the age of 12. At 12 years a clear contribution of shared environment was found to the variation of OCS symptoms. Sex differences in scores on OCS symptoms were found, with girls scoring higher than girls on OCS at age 14 and 16. This longitudinal study will focus on the age 12. The current study underscores the importance of conducting more research to OCS in the adolescent period.
Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register


ABSTRACT

Background The contribution of genetic and environmental factors to the stability of OC symptoms has not been examined before in a population based sample of adults.

Methods We obtained the Young Adult Self Report Obsessive-Compulsive Subscale (YASR-OCS) in a group of mono- and dizygotic twins from the population-based Netherlands Twin Register in 1991, 1995 and 1997 and the Padua Inventory Revised Abbreviated in 2002. Stability of obsessive-compulsive (OC) symptoms was examined and analysed as a function of genetic and environmental components.

Results Heritability of OC behavior was around 40% at each time-point, independent of the instrument used. OC symptoms were moderately stable with correlations between time-points. However, genetic correlations across time were much higher, varying between 61 and 90 for subsequent time-points, indicating that the stability of OC symptoms is mainly due to the same genetic factors.

Conclusions Stability of OC behavior was predominantly due to stable genetic factors.

To date, research on persistence of Obsessive-Compulsive Disorder (OCD) and/or Obsessive-Compulsive (OC) symptoms has concentrated on subjects who are patients. Several older studies on the course of OCD have suggested it to be a chronic and lifelong illness with waxing and waning symptom severity (Goodwin, et al., 1969). More recent studies on the course of OCD showed varied results; some studies concluded that OCD is a chronic illness with low rates of remission (Rasmussen & Tsuang, 1986; Eisen, et al., 1999; Alonso, et al., 2001), whereas other studies showed less pessimistic findings with conclusions that about 50% of patients remit (Orloff, et al., 1994; Skog & Skog, 1999; Sterkete, et al., 1999; Reddy, et al., 2005; Angst, et al., 2004). Reddy et al. (2006) concluded that poor outcome in previous studies may have been due to the inclusion of severely and chronically ill patients. Only one study examined OCD and psychiatric disorders in a longitudinal cohort. The Zurich community cohort study (Angst, et al., 2004) followed a group of adolescents for almost 20 years and concluded that, although the course of OC symptoms was described as chronic by 60% of the subjects, symptoms ameliorated in most subjects. Within paediatric obsessive-compulsive disorders, Stewart et al. (2004) conducted a meta-analysis of the long-term outcome and found pooled mean persistence rates of 41% for full OCD and 60% for full or subthreshold OCD. OCD is a chronic longitudinal condition on OC and OC symptoms in adults, but no investigations have been conducted to date into its underlying etiology. To our knowledge, only one study has examined stability of OC symptoms including the genetic architecture of stability, but this study comprised a young twin sample aged 7 to 12 (van Gootheest et al., 2007a). Van Gootheest et al. (2007a) found that OC behavior is moderately stable in childhood with correlations of 5 across age. Stability of OC behavior was influenced for roughly 40% by genetic factors and the rest of the variance was explained by shared (e.g., family factors) and non-shared environmental factors (e.g., individual experiences).

The purpose of the present study is to explore the stability of OC symptoms and determine the genetic and environmental contributions to stability of OC symptoms using longitudinal OC symptom data from a large sample of adult twins. OC symptoms were measured in 1991, 1995, 1997 and 2002. We aimed to address the following questions:

1. What is the stability of OC behavior in adults over time?
2. To what extent do genetic or environmental influences account for stability of OC behavior?

METHODS AND MATERIALS

Subjects and Procedure

This study is part of a longitudinal survey study in twin families registered with the Netherlands Twin Register (Boomsma, et al., 2002); Boomsma et al., 2006). Since 1991, every two to three years twins and their families have received a survey by mail containing questionnaires about health, personality and lifestyle. For the present study, we included OC data of adult and adolescent twins from wave 1991, 1995, 1997 and 2002. Table 1 gives an overview of the complete and incomplete twin pairs included in the study, presented by time-point and zygosity. The total sample consists of twins from 418 different families. Four hundred and forty one twin pairs participated at time-point 1; 102 twin pairs participated twice, and 192 twin pairs participated once. If a twin did not respond at a particular time point they were approached for the next mailing. In 1991 and 1995, adolescent and young adult twins were recruited through City Council Registrations. From 1997 onwards an additional effort was made to recruit older twins for this study. This effort is reflected by the mean ages per time-point, which were 17.8 (SD 2.3) in 1991, 19.8 (SD 3.2) in 1995, 22.5 (SD 2.9) in 1997 and 30.3 (SD 13.5) in 2002.

Table 1. Number of complete and incomplete twin pairs with OC data at time-points 1991, 1995, 1997, and 2002

<table>
<thead>
<tr>
<th>Year</th>
<th>Complete twin pairs</th>
<th>Incomplete twin pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>0</td>
<td>272</td>
</tr>
<tr>
<td>1995</td>
<td>0</td>
<td>272</td>
</tr>
<tr>
<td>1997</td>
<td>10</td>
<td>216</td>
</tr>
<tr>
<td>2002</td>
<td>76</td>
<td>236</td>
</tr>
</tbody>
</table>

Notes: MZM = monozygotic male, MZF = monozygotic female, DZM = dizygotic male, DZF = dizygotic female, DOS = opposite sex.

RESULTS

Background

of the scale was 0.69. The Padua Inventory Abbreviated (PI-ABR) (Cath, et al., 2008b) has been derived from the Padua Inventory-Revised (PI-R), the latter being a widely used self report inventory on obsessive-compulsive symp-

Table 2: Stability of OC behavior across time-points (1991, 1995, 1997 and 2002) expressed as within-sibling reliability (WRR) and heritability (H2)

<table>
<thead>
<tr>
<th>Year</th>
<th>WRR</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>0.59</td>
<td>0.52</td>
</tr>
<tr>
<td>1995</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td>1997</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td>2002</td>
<td>0.63</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Measures

At wave 1991, 1995 and 1997, OC symptoms were measured with the Young Adult Self Report Obsessive-Compulsive Subscale (YASR-OCS) (van Gootheest et al., 2007b). At wave 2002, OC symptoms were measured with the Padua Inventory Abbreviated (PADUA ABR) (Cath, et al., 2008b).

The Young Adult Self Report (YASR) encompasses a standard self-report questionnaire for adolescents and adults (Achenbach, 1991). It is derived from the Child Behavior Checklist, a parent-derived rating instrument for children between 4-18-years old (Achenbach, 1991). The YASR roughly has the same format as the CBCL, except that items pertaining to childhood problems are replaced by items pertaining to adult problems. The YASR comprises 100 problem items, covering emotional and behavioral problems during the previous 6 months. The participants respond on a 3 point scale with the code of 0 for not true, 1 for somewhat or sometimes true and 2 for very true of of-

ten true. A good reliability and validity of the YASR has been reported by Achenbach (Achenbach, 1997) and was supported for the Dutch version (Verhulst et al., 1991; Verbost et al., 1996). The YASR-OCS contains 8 OC items from the YASR, and is similar to the CBCL-OCS (Achenbach et al., 2006), except that items are worded in the first per- son. A numerical value for the YASR-OCS is obtained by adding the scores on the relevant 8 items (0, 1 or 2 per item), thus limiting the scale to a range between 0 and 16. Using a cut-off of 7 on the YASR-OCS, 84.2% of all DSM-diagnosed OCD cases were identified in a clinical sample of children with reasonable specificity (60.7%). Cronbach’s α of the scale was 0.69.

The Padua Inventory Abbreviated (PI-ABR) (Cath, et al., 2008b) has been derived from the Padua Inven-
tory-Revised (PI-R), the latter being a widely used self report inventory on obsessive-compulsive symp-
toms (Sanavio E., 1988; van Oppen et al., 1995). The PI-ABR is a 41 item self-report instrument that measures OC symptoms on a 0-4 scale, and contains 5 subscales, i.e. washing, checking, rumination, obsessions, and impulses (Oppen et al., 1995). It has been validated in the Netherlands, shows good psychometric qualities, and moderately correlates (Densys, et al., 2004) with the Y-BOCS symptom checklist, a clinical-dementia-rated symptom checklist, on OC symptoms (Goodman, et al., 1989). For the aim of this epidemiological twin study, the PI-R was reduced to 12 items. Item choice was based on items of each subscale with highest factor loadings in a previous valida-
tion study (Oppen van et al., 1995), and with one ad- ditional item for each of the four remaining obsessive symptom subscales rumination and impulses. Cronbach’s α of the scale was 0.73, which is an indication of good internal consistency. Sensitivity and specificity of the PI-ABR to detect DSM IV OCD was 74. and 72 respectively, when compared to clinical controls (Cath, et al., 2008).

Analyses

Analyses were conducted using structural equa-
tion modelling, with the statistical software package Mx (Neale et al., 2006). In longitudinal studies such as the
current one, not all subjects have taken part in the study at all occasions. To be able to use all data, full-infor-
mation maximum likelihood estimation with raw data was used. For each family, twice the negative log-likeli-
hood (2LL) of the data is calculated, and parameters are estimated so that the overall likelihood of the raw
data is maximized. The fit of the genetic models and
environmental factors that influence the variance of each observed
variable (Cornes et al., 2007). In a genetic study, the genetic innovations represent the
expression of a new set of genes.

In a genetic study, the genetic innovations represent the
expression of a new set of genes.

Then, the model includes innovations (ζ in figure 1) between genetic (A) or
environmental (C or E) latent factors that influence the
variances of individual innovations (ε in figure 1) and “real” non-shared environmen-
tal factors (e). Further, the model includes the correlations over time for men and women. OC behav-
ior for the last time-point (2002) is a saturated unconstrained model and it decomposes
a covariance matrix into genetic and non-genetic cova-
rance matrices and thus is a first approach to obtain genetic and environmental correlations across time in
longitudinal datasets.

RESULTS
Sample characteristic and descriptive statistics
Table 2 summarizes the means and variances for the
VASC-OCS and the PI-R ABBR. No significant differences in means and variances over zygosity were seen for men and women at all 4 time-points, except at time-point 1995 (\(t(8.74) = 2\), \(p < 0.01\)). At that time-
point MZ men scored higher on the VASC-OCS than MZ men.
Significant sex differences were seen at time-point 1991, 1995, 1997 and 1999 when comparing the
VASC-OCS than men (all \(p < 0.01\)). At time-point 2002, women seem to score higher on the PI-R ABBR, but this was non-significant (\(t(0.49) = 1\), \(p = 0.48\)). The
pattern is also seen for the variances; significant vari-
ance differences between men and women for the first
time points (all \(p < 0.01\)) and a non-significant dif-
ference for the last time-point (\(t(0.03) = 1\), \(p = 48\)). Table 3 shows the within-person phenotypic correlations over time for men and women. OC behav-
ior was moderately stable with correlations between 0.39
and 0.61 for subsequent time-points for men and women, with somewhat lower correlations between 16 and 42 for non-subsequent time-points with lower correlations


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<td></td>
</tr>
<tr>
<td>MZM</td>
<td>1.0</td>
<td>0.62</td>
<td>0.61</td>
<td>0.51</td>
</tr>
<tr>
<td>DZM</td>
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<td>1.0</td>
<td>0.61</td>
<td>0.51</td>
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<tr>
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<td>0.61</td>
<td>0.61</td>
<td>1.0</td>
<td>0.51</td>
</tr>
<tr>
<td>DZF</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>1.0</td>
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</table>

correlations decrease with increasing distances between
time-points (Boomsma & Molenaar, 1987). Figure 1 re-
presents the simplex model, because of space limits only for 3 time-points. It includes causal pathways or trans-
mision effects (β in figure 1) between genetic (A) or
environmental (C or E) latent factors that influence the
difference in variances of the same variables. Correlations between same factors for additive gene-
innovation (β) and between factors for MZ twins (ε) are one for both MZ and DZ twins. Non-shared environmental factors are uncorrelated
between co-twins.

To test the fit of the simplex model, a Cholesky model was used as reference model (Neale & Cardon, 1992). The Cholesky decomposition is descriptive and not driv-
erven by a specific developmental hypothesis. The model can be regarded as a saturated unconstrained model and it decomposes
a covariance matrix into genetic and non-genetic cova-
rance matrices and thus is a first approach to obtain genetic and environmental correlations across time in
longitudinal datasets.


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<tr>
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<td>17.6 (2.3)</td>
<td>17.9 (1.7)</td>
<td>17.5 (1.9)</td>
<td>17.2 (1.9)</td>
</tr>
<tr>
<td>DDM</td>
<td>17.6 (2.2)</td>
<td>17.8 (2.2)</td>
<td>17.5 (1.9)</td>
<td>17.2 (1.9)</td>
</tr>
<tr>
<td>MZF</td>
<td>17.8 (2.4)</td>
<td>17.9 (2.2)</td>
<td>17.7 (2.2)</td>
<td>17.4 (2.2)</td>
</tr>
<tr>
<td>DZF</td>
<td>17.8 (2.4)</td>
<td>17.9 (2.2)</td>
<td>17.7 (2.2)</td>
<td>17.4 (2.2)</td>
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Figure 1. Full ACE simplex model for the observed variable OC symptoms

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<td>MZF</td>
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<td>DZF</td>
<td>17.8 (2.4)</td>
<td>17.9 (2.2)</td>
<td>17.7 (2.2)</td>
<td>17.4 (2.2)</td>
</tr>
</tbody>
</table>

GENETIC MODELLING
Twins may resemble each other because they share their pre-and postnatal environment, often referred
to as shared or common environment (C). In addition,
DZ twins may resemble each other because they share 50% of their additive genetic factors. Thus, additive genetic factors are correlated 1 across MZ twin pairs and 0.5 across DZ twin pairs.

The saturated model, a model in which the covariance
matrix and the mean structures are computed without
restriction, was used as a reference test for the
homoogeneity of means and variances, constraining
them to be equal across zygosity and sex. The
type-I error rate of all statistical tests was set at 0.01
to accommodate multiple testing.

To analyze the longitudinal data for twins, a simplex model or transmission model was employed, which is a developmental model that may explain the
pattern of correlations across time-points. The simplex model is most suitable for longitudinal series in which there is occasion-to-occasion transmission and when
For longer time intervals. The correlations between the YASR-OCS at time-point 1997 and PI-R ABBR at time-
point 2002 were essentially the same (0.39 for men and 0.40 for women) as between the YASR-OCS at time-point 1991 and 1995 (0.41 for men and 48 for women), both intervals covering about the same time interval.

The summary of twin correlations at each time-
point and of the cross-twin-cross-time correlations is shown in Table 4. The twin correlations within time-
points show that MZ correlations are generally higher than DZ correlations in both men and women. This sug-
gests that both genes and non-shared environmental in-
fluence explain individual differences in OC symptoms.

Only at time-point 2002 and only in men, the DZ cor-
relation is close to the MZ correlation, suggesting the in-
fluence of shared environment at that time-point. Cross-
twin-cross-time correlations represent the correla-
tions between the OC symptom score at one time-point (e.g., 1991) in one twin, with the OC symptom scores of another time-point for another twin. Correlations be-
tween first-born and second-born twins are constrained to be equal. Inequalities between second-born and first-born twins. As can be seen, for almost all cross-cor-
relations the MZ correlations are higher than DZ corre-
lations, indicating the influence of genes on covariance of OC symptoms across time.

Genetic analyses

The squares represent the observed variance. The additive genetic influences (A), nonadditive genetic influences (D), common environmental influences (C), and non-shared environmental influences (E) are indicated by the numbers enclosed in the squares. The non-shared environmental influences are partitioned into residual influences and error (underscore).

Table 4. Twin correlations for YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002) and cross-twin-cross-time correlations

<table>
<thead>
<tr>
<th>Type of model</th>
<th>Additive genetic influences</th>
<th>Non-shared environmental influences</th>
<th>error</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0.39/0.27</td>
<td>0.61/0.59</td>
<td>0.20</td>
</tr>
<tr>
<td>A2</td>
<td>0.40/0.28</td>
<td>0.60/0.58</td>
<td>0.20</td>
</tr>
<tr>
<td>A3</td>
<td>0.41/0.29</td>
<td>0.60/0.58</td>
<td>0.20</td>
</tr>
<tr>
<td>A4</td>
<td>0.42/0.30</td>
<td>0.60/0.57</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Note: On the diagonals, the genetic influences are partitioned into transmission effects (bold) and innovation effects (italic).

The correlations in Table 7 indicate the degree of overlap between genetic and environmental influenc-
es at one age and influences at subsequent time-points. The additive genetic correlations are estimated between 63.6 and 70.2 for the first three time-points and between 59.3 and 66.5 between the first three time-points and the last time-point. For women, the correlations varied between 60 and 70 between the first three time-points, and 49 and 64 for the last time-
point. These high genetic correlations suggest that there is a high overlap between time-points of the same ge-
etic influence in adulthood using the same scale, but somewhat lower between different two measures. This last finding was already reflected in the high genetic in-
avation at the last time-point in figure 2.

Table 5. Model fitting results; Cholesky and Simplex models for OC symptoms at four time-points for men (left) and women (right)

<table>
<thead>
<tr>
<th>Type of model</th>
<th>Additive genetic influences</th>
<th>Non-shared environmental influences</th>
<th>error</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>0.39/0.27</td>
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<td>0.20</td>
</tr>
<tr>
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<td>0.40/0.28</td>
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<tr>
<td>A3</td>
<td>0.41/0.29</td>
<td>0.60/0.58</td>
<td>0.20</td>
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<tr>
<td>A4</td>
<td>0.42/0.30</td>
<td>0.60/0.57</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Note: On the diagonals, the genetic influences are partitioned into residual influences and error (underscore).

The ratios represent the observed variance. The additive genetic influences (A), nonadditive genetic influences (D), common environmental influences (C), and non-shared environmental influences (E) are indicated by the numbers enclosed in the squares. The non-shared environmental influences are partitioned into residual influences and error (underscore).
The factor structure for the QTL will be parameterized in terms of a simplex process, consisting of a innovation parameter at the first time-point and transmission parameter between the different time-points (Evans, 2003).

The results of this study should be interpreted in the context of four potential limitations. First, although both the YASR-OCS and PI-R ABBR show both a moderately high sensitivity and specificity in diagnosing DSM-IV OCD, the genetic and environmental contributions presented in this report reflect OCS scores, not clinical measures of DSM-IV OCD. Because of the relatively low prevalence of OCD, twin studies rely on dimensional measures with the underlying assumption that OCD reflects the end of a normal distribution, while OC symptoms represent a more discrete-like distribution. Second, the YASR-OCS and PI-R ABBR were used in a combination survey at any known study about the relationship between the measurements cross-sectionally. Both measurements were developed to screen for OC symptoms and both show good psychometric properties, but the correlation between the measurements has yet to be established. However, in view of the fact that the estimates of the proportions of variance at different time-points are very stable and that genetic correlations are moderate, we expect that both questionnaires are measuring the same underlying factor in question, with the PI-R ABBR capturing some extra information.

Third, both the YASR-OCS and PI-R ABBR showed sex differences at the last time-point, when the PI-R ABBR is used. It implies that the YASR and the PI-R ABBR questionnaires, besides measuring a partly similar concept of OC symptoms, are measuring different information scales with OC symptoms. As both questionnaires are different in several ways, this is not surprising. It again emphasizes the need to use different questionnaires at the same age, to screen for OC symptoms and both show good psychometric properties, but the correlation between the measurements has yet to be established. However, in view of the fact that the estimates of the proportions of variance at different time-points are very stable and that genetic correlations are moderate, we expect that both questionnaires are measuring the same underlying factor in question, with the PI-R ABBR capturing some extra information.

Fourth, the use of twin models requires several assumptions, including the absence of assortative mating, the equal environment assumption, and the absence of measurement error. Van Grootheest et al. (2008) found small, but significant assortative mating for OC symptoms but concluded that the bias is not marked by similarity. Taking into account the small amount of assortment is negligible. Jonnal et al. (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated. Gene-environment interaction could affect twin similarity in either direction depending on whether both twins are exposed to the same environmental factor in question, to our knowledge, gene-environment interaction and/or correlation have yet to be demonstrated for the phenotype studied here.

In summary, this study provides evidence from a large sample of twins that OC symptoms are moderately stable over time and this stability is strongly influenced by additive genetic factors. We did find higher heritability for men than for women, which is consistent with the findings in general that the same genes influence OC symptoms over time.

Table 7. Correlations calculated for additive genetic and non-shared environmental sources of variance between the different time-points. Correlations for men and women are reported below and above diagonal, respectively.

<table>
<thead>
<tr>
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<th>Additive genetic architecture</th>
<th>Non-shared environmental architecture</th>
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<tr>
<td>1991</td>
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</tr>
<tr>
<td>1995</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td>1997</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>2002</td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>1991</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td>1995</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td>1997</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>2002</td>
<td>0.80</td>
<td>0.75</td>
</tr>
</tbody>
</table>

DISCUSSION
This is the first study that examined genetic and environmental contributions to stability over time of OC symptoms in adults. We found that OC symptoms are moderately stable across time with correlations of around .4 between measurement occasions. In contrast to the modest longitudinal phenotypic correlations, the longitudinal genetic correlations were substantially higher. We observed genetic correlations between roughly .4 and .9, with most genetic correlations varying around .8. So, the main reason for stability of OC symptoms was that the genetic influences on OC symptoms are stable across time. This means that to a large extent the same genes are expressed across time.

The moderate phenotypic stability seems in line with the clinical papers, which presented a more optimistic view of the course of OCD (Orloff et al., 2005). These studies suggested a relatively favorable course and outcome of OCD that is otherwise considered to be a chronic illness with waxing and waning course. Our results support the notion that having OC symptoms at one age does not automatically imply having OC symptoms for the rest of one’s life.

Interestingly, in our paper examining stability for OCS in children (van Grootheest et al., 2008), we came to the same conclusion, but one big difference appeared between the two studies. Where genetic factors explained 70% of the stability in adults, in children a percentage of around 40% was found. In children, part of the stability was also due to common environmental factors shared by children growing up in the same house. These influences are not seen in adults. Although phenotypic stability is roughly the same in children and adults, the causes of stability differ. The influence of genes on stability is more important in adults than in children and environmental factors are of more importance in children than in adults. We also found that there is little transmission of unique environmental factors. This means that, on a population level, individual experiences have limited impact on the stability of OC symptoms in adults.

We found sex differences in OC symptom scores at three time-points, but not at the last time-point. For the last time-point we used the PI-R ABBR, instead of the VASR-OCS. So the diminishing sex differences in OC-symptoms scores could well be caused by the use of a different measurement, although the possibility that the sex differences are age-dependent cannot be excluded. As longitudinal prevalence studies are scarce, we cannot compare these results with other studies. However, the results are in line with several studies which found no sex differences or at the highest a slight preponderance for women having OCD (Nestadt et al., 1998; Crino et al., 2005; Torres et al., 2006). With the simplex model we were able to estimate the variance associated with measurement error. Around 25% of the total variation of OC symptoms was accounted for by measurement error. This means that 75% of the variation is “true” variance due to genetic and environmental effects. This means that, after correcting for measurement errors, genetic factors account for more than 50% of the variation in OC symptoms.

Additive genetic factors are mainly responsible for the stability of OC symptoms. Even more important is the finding from the simplex model that in general the same genes account for OC symptoms at different ages. Genetic innovations are apparent but small, except at one time-point, when the PI-R ABBR is used. It implies that the YASR and the PI-R ABBR questionnaires, besides measuring a partly similar concept of OC symptoms, are measuring different information scales with OC symptoms. As both questionnaires are different in several ways, this is not surprising. It again emphasizes the need to use different questionnaires at the same age, to screen for OC symptoms and both show good psychometric properties, but the correlation between the measurements has yet to be established. However, in view of the fact that the estimates of the proportions of variance at different time-points are very stable and that genetic correlations are moderate, we expect that both questionnaires are measuring the same underlying factor in question, with the PI-R ABBR capturing some extra information.

Although we found differences in variances for men and women, the proportions of variances and general architecture of the longitudinal analyses are remarkably similar. Taking into account the small amount of assortment, where we concluded that the same genes accounted for OC symptoms in men and women (van Grootheest et al., 2007b) plus the existence of stable genetic factors, it would imply that data of men and women at different ages can be pooled together in molecular genetic research projects, obtaining an increase of power. In the near future, we intend to conduct QTL linkage analyses using the data of the current study, gaining power by using multivariate techniques that analyze pleiotropic action of the QTL on several variables (Boomsma, 1996).


PART IV. ENVIRONMENTAL FACTORS AND SYMPTOM DIMENSIONS ON OCS

CHAPTER 10

Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins

Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monzygotic twins


ABSTRACT

Background Research about environmental factors causing Obsessive-Compulsive symptoms is scarce. By using a discordant monozygotic twin design it is possible to investigate environmental factors that protect against or exacerbate OC symptoms.

Methods We selected 25 MZ twin pairs discordant, 17 MZ twin pairs concordant high and 34 MZ pairs concordant low on OC symptoms from a large longitudinal Dutch sample of adult twin pairs and their family members, applying stringent criteria for OC symptomatology. Data were collected on psychopathology, family history, quality of life, birth complications and life events. Unique environmental factors were studied using within-discordant MZ pair comparisons, whereas between-discordant MZ pair comparisons were used to study environmental factors that are shared by the twins of an MZ pair.

Results The high-scoring MZ twins of the discordant group reported more life events (especially sexual abuse) than their low-scoring twin-siblings. The between-pair comparisons showed lower weight in the discordant MZ pairs than in the concordant MZ pairs. Further, the concordant high MZ pairs as well as their spouses had a lower educational level than the two other groups. On scale scores of anxious-depression, neuroticism, and somatic complaints, concordant high MZ pairs showed highest scores, and the discordant MZ pairs scored intermediate, except for neuroticism, on which the high-scoring twins of discordant MZ pairs were equal to the twins of the concordant high pairs. Discordance on psychological scale scores between the concordant MZ pairs was evident from 1991 onward, and within the discordant MZ pairs from 1997 onward, confirming previous reports of an association of early onset OC symptoms with higher genetic load.

Conclusions This study reports on both unique and shared environmental factors associated with OC symptomatology. Whether these factors operate in addition to or in interaction with genetic disposition is to be elucidated in future studies.

Obessive-Compulsive Disorder (OCD) is charact-terized by recurrent and anxiety-provok- ing intrusive thoughts, mostly in combination with time-consuming repetitive actions designed to reduce tension or anxiety caused by the disturbing thoughts (American Psychiatric Association, 1994). OCD can run, if untreated, a chronic and disabling course (Nestadt et al., 1998). Family studies have quite convincingly shown that early-onset OCD is familial (Pauls et al., 1995; Nestadt et al., 2000). Studies in 7-12 year old twins have indicated that between 47% and 58% of the variance in Obsessive Compulsive (OC) behavior is explained in future studies. The course of OCD is moderately stable: longitudinal studies showed that caudate nucleus D2-receptor binding increased by 20% from the age of 12 to 18 years, while the other basal ganglia structures did not show age-related changes (van Grootheest et al., 2004). Finally, ß-haemolytic streptococcal infections have been displayed (religious obsessions) (Tek & Ulug, 2001). Religious protestants in comparison with less or non-religious members, applying stringent criteria for OC symptomatology. Data were collected on psychopathology, family history, quality of life, birth complications and life events. Unique environmental factors were studied using within-discordant MZ pair comparisons, whereas between-discordant MZ pair comparisons were used to study environmental factors that are shared by the twins of an MZ pair.

The comparison of monozygotic (MZ) twins who score high on a trait with their low-scoring con-"
1995). It has been validated in the Netherlands, shows good psychometric qualities, and moderately correlates with the Y-BOCS symptom checklist, a clinician-derived checklist on OC symptoms (Dyers et al., 2004). For the purpose of this epidemiological twin study, the PI-R was reduced to 12 items. Item choice was based on 2 items of each subscale with highest factor loadings in a previous validation study (van Oppen et al., 1995), and with one additional item for each of the more equivocal obsession subscales: rumination and impulses. The PI-R ABBR is shown in Table 1. To investigate its psychometric qualities, psychiatric analyses have been conducted in three groups derived from an earlier study by Van Oppen et al. (1995). These groups encompassed a population-based control group (n = 428), a psychiatric control group (n = 272) and a clinical OCD group (n = 120), for an extensive study of the three groups (see van Oppen et al., 1995). Cronbach’s α of the scale was 0.73, which is an indication of good internal consistency. Analyses of Variance (ANOVA) of PI-R ABBR scores within the 3 groups revealed a significant main group between-effect (p < 0.001). Post-hoc t-tests showed that the mean PI-R ABBR score (20.7 ± 8.1) was significantly higher than scores of the psychiatric control group (12.4 ± 7.4) as well as the population control group (6.6 ± 5.6; p < 0.001 in both comparisons). 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 conducted. ROC analyses use the association between sensitivity and specificity to derive an Area Under the Curve (AUC), which indicates how well a measure discriminates between case and non-case (i.e., OCD group) and case negatives (i.e., psychiatric controls or population controls) irrespective of the base rate. A value of 0.5 of the AUC indicates chance level and 1.0 indicates a perfect diagnostic tool (Swets, 1996; McFall and Treat, 1999). The AUC for the PI-R ABBR when compared with clinical controls was 0.78 (95% CI = .73 – .83). When compared with the population controls, the AUC was 0.93 (95% CI = 0.90 – 0.95). At the best cut-off point of 16 (i.e., maximum difference between sensitivity and specificity), the sensitivity, specificity, the drinking, smoking, the sensitivity was 74 with a specificity of 72, when compared with clinical controls.

Matching with concordant high pairs

For the adult twins, 2672 pairs, their family members and – in some instances - their spouses (a total of 9950 individuals) returned the survey. Monozygotic twin pairs were selected on the basis of high or low scores on the PI-R ABBR. Using the stringent criteria derived from the analyses described above, discordant, concordant high and concordant low MZ twin pairs were selected. Twin pairs were full concordant to be discordant when one twin scored > 17 (in the clinical range), and his/her MZ twin sibling scored < 7 (popula- tion control). The prevalence of OC among children was a result of a longitudinal study, where the first wave was a sample of children from primary education. From this, we concluded that the research on the family of origin was an appropriate point in time to assess our findings. The familial aggregation of OC symptoms was assessed with: the Spielberger State-Trait Anxiety Inventory (Spielberger, 1985), the Young Adult Self report, anxious-depressed subscale (Scheneveld, 1979), and the Young Adult Self report, anxious-depressed subscale (Potenza, 1996). The AUC for the PI-R ABBR was calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR). Differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR).

AUC: The occurrence of negative life events throughout the lifespan was measured in the 2002 survey, using an adapted version of the Dutch life event scale (Schook-werkers Inventarisatie Lijst = Sichl) (van der Velden et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of a self or significant other; divorce/break-up of a relationship; traffic accident; violent was assessed by the CAGE (4 questions) (Bush et al., 1987).

The occurrence of negative life events throughout the lifespan was measured in the 2002 survey, using an adapted version of the Dutch life event scale (Schook-werkers Inventarisatie Lijst = Sichl) (van der Velden et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of a self or significant other; divorce/break-up of a relationship; traffic accident; violent was assessed by the CAGE (4 questions) (Bush et al., 1987).

Finally, we used child-derived information on their parents’ level of education. Direct parent information from the child was used to collect information on their smoking and drinking behavior and on their scores of OC behavior, anxiety and depression.

Table 1. The Padua Inventory-Revised abbreviated (PI-R ABBR)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Original Factor</th>
</tr>
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<tbody>
<tr>
<td>MZ twins</td>
<td>high pairs</td>
<td>Impulses</td>
</tr>
<tr>
<td>MZ discordant pairs</td>
<td>N=129</td>
<td>Checking</td>
</tr>
<tr>
<td>MZ concordant pairs</td>
<td>N=1129</td>
<td>Preoccupation</td>
</tr>
<tr>
<td>DZ twins</td>
<td>pairs N=1075</td>
<td>Impulses</td>
</tr>
<tr>
<td>MZ discordant pairs</td>
<td>N=25</td>
<td>Checking</td>
</tr>
<tr>
<td>MZ concordant pairs</td>
<td>N=510</td>
<td>Preoccupation</td>
</tr>
<tr>
<td>Matching with concordant high pairs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2672 adult twin pairs + family members
Total N=9950

Matching with discordant low pairs

MZ concordant low pairs N=17
MZ discordant low pairs N=25
MZ matched low pairs N=34

Concordant low pairs were matched on age and sex.

Exclusion of incomplete pairs, selection based on stringent OC criteria

Matching with discordant low pairs

Of the adult twins, 2672 pairs, their family members and – in some instances - their spouses (a total of 9950 individuals) returned the survey. Monozygotic twin pairs were selected on the basis of high or low scores on the PI-R ABBR. Using the stringent criteria derived from the analyses described above, discordant, concordant high and concordant low MZ twin pairs were selected. Twin pairs were full concordant to be discordant when one twin scored > 17 (in the clinical range), and his/her MZ twin sibling scored < 7 (population control). The prevalence of OC among children was a result of a longitudinal study, where the first wave was a sample of children from primary education. From this, we concluded that the research on the family of origin was an appropriate point in time to assess our findings. The familial aggregation of OC symptoms was assessed with: the Spielberger State-Trait Anxiety Inventory (Spielberger, 1985), the Young Adult Self report, anxious-depressed subscale (Scheneveld, 1979), and the Young Adult Self report, anxious-depressed subscale (Potenza, 1996). The AUC for the PI-R ABBR was calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR). Differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR).

AUC: The occurrence of negative life events throughout the lifespan was measured in the 2002 survey, using an adapted version of the Dutch life event scale (Schook-werkers Inventarisatie Lijst = Sichl) (van der Velden et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of a self or significant other; divorce/break-up of a relationship; traffic accident; violent was assessed by the CAGE (4 questions) (Bush et al., 1987).

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Finally, we used child-derived information on their parents’ level of education. Direct parent information from the child was used to collect information on their smoking and drinking behavior and on their scores of OC behavior, anxiety and depression.

Statistical analyses

Within-pair analyses. Within-pair discordant pair differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR). Differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR). Differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR). Differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests between the high and low-scoring twins on the PI-R ABBR).
Variables that measure psychological health, as well as measures of environmental influences on OC symptoms were compared between the concordant high, the concordant low and the discordant MZ twin pairs, using one-way ANOVAs for continuous data, Kruskal-Wallis tests for ordinal data and McNemar tests for nominal data. Post-hoc comparisons were conducted using post-hoc Scheffé’s (continuous ANOVAs for continuous data, Kruskal-Wallis tests for ordinal data) Post-hoc Scheffé testing, although more liberal than Bonferroni correction, provide some correction of type I error. Two-tailed probabilities were used in all analyses, since we had no clear expectation of the direction of the findings. To adjust for correlated error in the between-group comparisons of common environment variables, separate regression analyses (multiple regression for continuous measures and logistic regression for categorical measures) were conducted in STATA 9.2 for these variables (StatCorp, College Station, Texas, USA). The robust cluster option was used to account for nonindependence of the twin pairs on the variables that reflected common environmental influences (i.e. caregiving, shared birth weight, and religious upbringing of the twin, parental death and divorce, death of a sibling, and level of education, alcohol use and smoking behavior of the parents). Alpha was set at 0.05.

RESULTS

WITHIN-PAIR ANALYSES OF DISCORDANT PAIRS

Twenty-five MZ twin pairs discordant on OC behavior were included, of whom 18 pairs were female. Their mean age was 29.6 years (SD 6.8 years). Mean PI-R ABBR OC scores in the high scoring twins of the discordant pairs were 21.4 (SD 5.9), in the low scoring twins 4.5 (SD 2.0).

Table 2. Within-Discordant twin pair characteristics

| Birth weight (g) | 2189 (806) | 2028 (667) | n.s. |
| Birth order (first born) | n=10 | n=14 | n.s. |
| General health (1-5) | 4.1 (0.7) | 3.8 (0.6) | 0.03 |
| Mental health contacts ever | n=7 | n=9 | n.s. |
| Somescore impediments physical activity | 43.5 (22.5) | 53.9 (12.4) | <0.001 |
| Number of persons drinking ever | n=23 | n=23 | n.s. |
| N drinks per wk (past 12 months) | 11.1 (4.4) | 13.4 (0.7) | n.s. |
| CAGE score alcohol dependence | 4.0 (2.2) | 4.3 (0.7) | n.s. |
| Total score life events | 5.9 (7.4) | 3.0 (0.6) | n.s. |
| Number of children | 1.1 (2.0) | 0.7 (0.6) | n.s. |
| Education level (1-3) | 7.9 (0.0) | 8.3 (2.6) | n.s. |
| Education level partner (1-3) | 8.3 (3.3) | 8.1 (3.1) | n.s. |
| Living situation (1-4) | 2.8 (0.8) | 2.7 (0.8) | n.s. |
| PA-ABBR OC scale | 4.5 (2.0) | 21.4 (5.9) | <0.001 |
| YASR anxious depression scale | 4.3 (2.8) | 11.6 (4.3) | <0.001 |
| STAI-trait extraversion | 51.0 (16.7) | 46.9 (12.2) | n.s. |
| ABV neuroticism | 48.6 (23.1) | 85.3 (27.4) | <0.001 |
| ABV somatic complaints | 16.6 (5.1) | 24.4 (10.3) | <0.001 |
| STAI-trait | 31.6 (4.7) | 46.4 (10.4) | <0.001 |
| Satisfaction with life scales | 27.4 (4.1) | 23.8 (7.0) | 0.02 |
| Happiness scores | 22.7 (3.9) | 17.9 (5.8) | <0.001 |
| Self-efficacy scale | 33.4 (4.0) | 27.5 (4.7) | 0.006 |

The concordant high group showed the highest scores on alcohol dependence (p = 0.02 and 0.04 in comparison with the concordant low and discordant group), although they scored intermediate between the low and discordant groups on current number of drinks per week. On religious upbringing, there were no significant differences between the study groups concerning the concordant low MZ twin pairs, as well as their spouses, reported to have a higher level of education than the concordant high and discordant twin pairs (p = 0.02 in both comparisons). On life-events, the concordant high MZ twin pairs reported more often that they had been divorced from work than the concordant low scoring pairs (p = 0.04), with the discordant pairs scoring between the concordant high and low pairs. Further, the discordant pairs reported more often to have been sexually assaulted in comparison with both the concordant low and high scoring pairs; n = 7 individuals in the discordant group versus n = 0 and n = 1 individual in the concordant high and low groups (p = 0.02 and 0.03 respectively).

Unique environment influences (table 3)

The only within-pair difference found on unique life events, was the tendency of the high-scoring twins of the discordant pairs to have experienced more sexual assault than the low-scoring twins (p = 0.08). All persons who had experienced sexual assault were women. Two low-scoring twins of the discordant pairs reported on sexual assault, versus 5 high-scoring twins. The low-scoring twins and 4 of the 5 high-scoring twins of the discordant pairs reported to have experienced the assault more than 5 years ago, versus 1 twin who had experienced sexual abuse between 1 and 5 years ago.

Longitudinal data

YASR-OC subscale scores, taken in 1991, 1995 and 1997, revealed significant differences between high and low-scoring twins of the discordant pairs in 1997 (p = 0.007). Further, scale scores between 1991-2002 revealed significant within-pair differences on the YASR anxious-depressed subscale from 1997 onward (p<0.001). On the neuroticism subscale from 1993 onward (p between 0.01 and <0.001 at wave 2-5), on the ABV subscale of somatic complaints (p<0.001), and on STAI-trait (p<0.001). On the ABV extraversion scale, no within-pair differences were found.

BETWEEN-PAIR ANALYSES OF CONCORDANT AND DISCORDANT PAIRS

Seventeen MZ twin pairs were included who were discordant high on OC behavior, of whom 14 pairs were female. Their mean age was 30.0 years (SD 11.2 years), mean PI-R ABBR OC scores were 23.7 (SD 6.7). Thirty-four MZ twin pairs were included who were discordant low on OC behavior, of whom 28 pairs were female. Their mean age was 30.0 years (SD 11.3 years), mean PI-R ABBR OC scores were 3.8 (SD 2.2).
Finally, the discordant pairs reported more traffic accidents than the other groups (p = 0.05 and 0.02 when compared with the concordant low and high pairs respectively). On psychological scale scores, the concordant high group scored, as expected, overall higher on the PII-ABBR (p’s < 0.001), the VASR anxious-depressed scale (p’s < 0.001), ABV neuroticism (p < 0.001 in high comparison; p’s = n.s. between high and discordant twin pairs), somatic complaints (p’s < 0.001 and 0.003), and STAI-trait anxiety (p’s < 0.001). Further, the concordant high group had lower scores on ABV extraversion (p’s < 0.001), satisfaction with life (p’s between 0.01 and 0.001), happiness (p’s between 0.01 and <0.001) and self-efficacy (p’s < 0.001) than the concordant low and discordant pairs.

Shared environment influences (table 5)
Between-group analyses revealed that the discordant group had the lowest rate of cesarean sections (p’s = 0.005 and 0.006 in comparison with the concordant low and high groups), while there was no difference between the concordant groups. The discordant group had the lowest birth weight (p = 0.008 compared with the concordant low pairs and p < 0.001 compared with the concordant high pairs). There were no between-group differences on level of education of the parents (p’s = non significant in all comparisons). There were no between-pair differences in the occurrence of parental death. The discordant low MZ pairs reported most on death of a sibling (p = 0.03 between concordant low and high pairs). There were no between-group differences with respect to relationship termination of the parents. On both drinking and smoking behavior of the parents, surprisingly the concordant low pairs reported more drinking than the discordant parents, although alcohol consumption as well as number of cigarettes was low on average.

Longitudinal data
VASR OC scale scores revealed significant differences between low and high-scoring twin pairs in the 1995 (p = 0.02) and 1997 wave (p < 0.001). VASR anxious-depressed scale scores revealed significant differences between the concordant low and high groups from 1991 on (p’s < 0.05 in all comparisons). ABV extraversion scores revealed significant between-group differences from 1993 onward (p’s < 0.001 and 0.008), whereas ABV neuroticism scores revealed significant between-group differences at all waves (P’s < 0.05 and <0.001). ABV somatic complaints showed significant between-group differences from 1997 on (p < 0.001).

Table 4. Between concordant and discordant twin pair comparisons for health and lifestyle characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Concordant low pairs</th>
<th>Concordant high pairs</th>
<th>Discordant pairs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarian section (yes)</td>
<td>N=5 pairs</td>
<td>N=6 pairs</td>
<td>N=4 pairs</td>
<td>ns</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2650 (876)</td>
<td>2685 (795)</td>
<td>2100 (736)</td>
<td>0.004</td>
</tr>
<tr>
<td>Religious upbringing</td>
<td>N=45 (67%)</td>
<td>N=16 (47%)</td>
<td>N=34 (69%)</td>
<td>ns</td>
</tr>
<tr>
<td>Education level father (1-13)</td>
<td>7.5 (4.0)</td>
<td>5.5 (3.7)</td>
<td>5.7 (3.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Education level mother (1-13)</td>
<td>6.3 (3.7)</td>
<td>5.2 (3.4)</td>
<td>4.7 (3.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Death mother (0-2) yes</td>
<td>n=2 (3%)</td>
<td>n=3 (10%)</td>
<td>n=4 (8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Death father (0-2)</td>
<td>n=12 (29%)</td>
<td>n=7 (24%)</td>
<td>n=6 (12%)</td>
<td>ns</td>
</tr>
<tr>
<td>Death sibling (0-2)</td>
<td>n=6 (10%)</td>
<td>n=0</td>
<td>n=1 (2%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Relationship termination parents (0-2)**</td>
<td>n=4 (14%)</td>
<td>n=2 (25%)</td>
<td>n=1 (7%)</td>
<td>ns</td>
</tr>
<tr>
<td>N parents drinking (ever; yes)**</td>
<td>91%</td>
<td>100%</td>
<td>74%</td>
<td>0.06</td>
</tr>
<tr>
<td>N drinks/wk parents (7-12)**</td>
<td>3.5 (2.4 drinks/wk)</td>
<td>2.7 (2.3 drinks/wk)</td>
<td>2.3 (2.2 drinks/wk)</td>
<td>0.03</td>
</tr>
<tr>
<td>N parents smoking ever (yes)**</td>
<td>71%</td>
<td>89%</td>
<td>48%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 5. Between twin-pair comparisons: comparison of common environment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Concordant low pairs</th>
<th>Concordant high pairs</th>
<th>Discordant pairs</th>
<th>p-value</th>
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<tr>
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<td>N=4 pairs</td>
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</tr>
<tr>
<td>Education level mother (1-13)</td>
<td>6.3 (3.7)</td>
<td>5.2 (3.4)</td>
<td>4.7 (3.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Death mother (0-2) yes</td>
<td>n=2 (3%)</td>
<td>n=3 (10%)</td>
<td>n=4 (8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Death father (0-2)</td>
<td>n=12 (29%)</td>
<td>n=7 (24%)</td>
<td>n=6 (12%)</td>
<td>ns</td>
</tr>
<tr>
<td>Death sibling (0-2)</td>
<td>n=6 (10%)</td>
<td>n=0</td>
<td>n=1 (2%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Relationship termination parents (0-2)**</td>
<td>n=4 (14%)</td>
<td>n=2 (25%)</td>
<td>n=1 (7%)</td>
<td>ns</td>
</tr>
<tr>
<td>N parents drinking (ever; yes)**</td>
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<td>100%</td>
<td>74%</td>
<td>0.06</td>
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<td>2.7 (2.3 drinks/wk)</td>
<td>2.3 (2.2 drinks/wk)</td>
<td>0.03</td>
</tr>
<tr>
<td>N parents smoking ever (yes)**</td>
<td>71%</td>
<td>89%</td>
<td>48%</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Table 6. Between-parents comparisons of psychological scales

<table>
<thead>
<tr>
<th>Psychological Scale</th>
<th>Parents concordant low</th>
<th>Parents concordant high</th>
<th>Parents discordant</th>
<th>High-low p-value</th>
<th>Low discordant p-value</th>
<th>High discordant p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-low p-value</td>
<td>0.002</td>
<td>0.002</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low discordant p-value</td>
<td>0.002</td>
<td>0.001</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High discordant p-value</td>
<td>0.002</td>
<td>0.002</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PI-R ABBR mean score of 9.9 (SD 5.7). Between-group analyses of psychological scale scores showed that the parents concordant high scored between the parents concordant low and high parents on anxious complaints. On somatic complaints and extraversion they showed higher scores than the other groups. On the PI-R ABRB, STAI trait and neuroticism they scored equal to the parents of the concordant high groups.

**Discussion**

The most important aim of this MZ twin study has been to explore unique and shared environmental factors involved in OC symptoms.

**Unique and shared environmental factors**

The within-twin pair comparisons to study environmental factors associated with OC symptoms. Although the discordant pairs were genetically identical, they were raised at the same time in the same family, and were selected from an epidemiological sample, the foetuses of the discordant pairs reported on sexual assault as well, underscoring the complexity of presumed causality in the interplay between environmental and genetic factors in OCD. Interestingly, no sexual assault events were reported by the discordant twins. Thus, although the high-scoring respondents of the discordant pairs show similar OC symptomatology when compared with the concordant high MZ pairs, the pathways along which similar OC symptoms develop seem to differ between the high-scoring discordant twins on the one hand, and the high-scoring concordant pairs on the other. Although one can only speculate about causal relationships in this explorative study, the OC symptoms in the high-scoring twins of the discordant pairs seem to be associated with environmental stressors (i.e. sexual assault) than are the OC symptoms in the concordant high-scoring pairs.

The between-twin pair comparisons to study environmental factors that are shared by the twins of a pair revealed low birth weight and low rates of caesarean section in the discordant pairs. There were no differences in prenatal care, which suggests that low level of education and alcohol use by the mothers was associated with OC symptoms in the concordant high or discordant groups of this study. Further, there was no association between OC symptoms and a religious upbringing in the study groups, which is in line with the literature on the lack of association between religiosity and OC symptoms (Olatunji et al., 2005). Thus, assuming that OC symptoms in the high scoring concordant MZ pairs is better explained as a verifiable alcohol problem, this study is in line with clinical studies indicating that age at onset might be an important phenotypic characteristic that mediates than in the discordant pairs, this study is in line with the literature on the lack of association between religious upbringing and OC symptoms. Apparently, different problem behavior is associated with different environmental risk factors.

Children with low birth weight appeared to be more vulnerable to negative environmental factors than normal birth weight children possibly in association with a genetic factor. However, low birth weight was not associated with OC symptoms, anxiety and depressive symptoms in the concordant low or discordant groups over the past twelve months, with the number of drinks per week well below the quantity required to fulfill criteria for alcohol abuse or dependence according to DSM IV criteria. However, subjective reports of alcohol withdrawal and alcohol dependence (AS and AD) were increased in the high-scoring twins pairs compared with the low-scoring and discordant pairs. This might be an indicator that genetic factors in OCD are associated with a well-known phenomenon in persons with OC symptoms, (Olatunji et al., 2006), related to alcohol use and its toxic effects rather than a verifiable alcohol problem in the discordant high scoring MZ pairs.

A protective effect of level of education on OC symptoms was suggested by the finding of a higher level of education in the concordant low-scoring twin pairs than in the concordant high and the discordant pairs. Not only the concordant high scoring twins but also their spouses had a lower level of education, which suggests that low level of education and OC symptomatology might share genetic vulnerability. Deficits in encoding complex information, subsequent memory impairments have been reported in OCD (Buhlmann et al., 2005; Deckerbach et al., 2000). These deficits are unique to persons with OC symptoms in the concordant low educational level. On the other hand, low level of education in the concordant high scoring group might be a consequence of the OC symptomatology in itself, which is supported by the literature (Sorensen et al., 2004).

The longitudinal data

As expected, the longitudinal data on OC symptoms, anxiety and depressive symptoms in the concordant high scoring discordant and low scoring discordant groups over the past twelve months showed a decrease in OC symptoms, anxiety and depressive symptoms in the concordant low and high scoring discordant groups (from 1991 on) than in the discordant group (mostly from 1997 on). This confirms data from family-based studies where an earlier age at onset was associated with higher familial load (do Rosario-Campos et al., 2005). Thus, assuming that OC symptoms in the concordant high scoring twins pair are more genetically mediated than in the discordant pairs, this study is in line with clinical studies indicating that age at onset might be an important phenotypic characteristic that mediates.
obsession

reflected differences in genetic characteristics underlying OCD (Delorme et al., 2008).

The parent data

As parent scores on OC symptoms and related psychopathology were expected to reflect genetic vulnerability, we expected scores to be highest in the concordant high parents, to be intermediate in the discordant parents and to be low in the discordant low parents. On most measures of psychopathology, this assumption was confirmed. Thus, the intermediate scores in the parents of discordant twins on OC, anxious-depression and neuroticism scales may be the consequence of the intermediate amount of genetic vulnerability to OC symptoms in this group. Therefore, these parent data suggest that the symptoms in the high-scoring twins of the MZ discordant group may be likely to be the consequence of a moderate genetic sensitivity to OC pathology in addition to or in combination with environmental mediators.

Limitations

First, sample size is small; although we sampled a large group of MZ twins, only a small sample was retained due to the use of rigorous criteria. Consequently, especially in the within-discordant pair comparisons, some of the negative outcomes might in fact be the result of lack of power to detect within-pair differences. Alternatively we could have relaxed the stringent selection criteria, with the disadvantage of including twins pair not scoring in the clinical range of ROC, thus representing an unclear group of problem behavior. Second, considering the large number of tests relative to the small sample size, we only mildly correct for type II errors by correction of type I errors was undesirable. Therefore, we decided to compromise by only applying a mild correction of type I errors (Perneger, 1998). Accordingly, especially in the within-discordant pair comparisons, we only mildly correct for type I errors by correction of type I errors was undesirable. Therefore, we decided to compromise by only applying a mild correction of type I errors (Perneger, 1998).

Finally, the database used in this study was not primarily designed to specifically inquire about environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins


CHAPTER 11
Heritability of Obsessive-Compulsive Symptom Dimensions

Heritability of Obsessive-Compulsive Symptom Dimensions

ABSTRACT

Background Recent research has shown that Obsessive-Compulsive Symptoms differ remarkably among patients, and are divided into several symptom dimensions. Obsessive-Compulsive Symptoms (OCS) were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

Methods 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, “impulsions”, “symmetry/ordering”, and “aggressive/sexual/religious obsessions and checking compulsions” were included in the Young Adult Self Report Obsessive-Compulsive Subscale from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings and found a moderate heritability of 39% for men and 50% for women. A next step would be to use OC symptom dimensions in an epidemiological twin sample, allowing one to investigate the genetic and environmental factors underlying different OC symptom dimensions. The (most) heritable symptom dimensions may be used as a refined phenotype for further linkage or association studies. In this study, we present multivariate analyses of the OCS data by Jonnal et al. (2000). Instead of heritabilities of the classic obsession/compulsion factor model as originally proposed, we present results of multivariate genetic analyses of empirically-defined symptom categories giving the opportunity to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions. We aim to address three major questions:

1. Can distinct dimensions within OCS be found in a general population sample of women?
2. What role do genetic and environmental factors play in the etiology of these OC symptom dimensions?
3. Are different symptom dimensions influenced by the same or by different genetic factors?

MATERIALS AND METHODS

Sample

Sample characteristics are extensively described in the publication of Jonnal et al. (2000). Briefly, participants in this study were from a population sample of Caucasian female twins from the Virginia Twin Registry (Kendler and Prescott, 2006). Self-report questionnaires on OC items were mailed to 1426 twins of whom 1382 returned completed questionnaires, the subjects of the current analyses. Zygosity was determined by analysis of a questionnaire with 88 polymorphisms. Zygosity classifications were more than 95% accurate. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4).

Scale

Twenty items of the Padua Inventory (PI) (Sanavio, 1988) were included in a self-report questionnaires. Items were chosen from all four OC dimensions of the original 60-item PI scale based on their factor loadings but also to maintain a diversity of item content. Items with loadings greater than .3 were retained, by DNA polymorphisms. Zygosity classifications were more than 95% accurate. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4).

In recent years, research on Obsessive-Compulsive Disorder (OCD) symptoms is remarkably heterogeneous, so that two patients with this diagnosis can display completely non-overlapping symptom patterns (Mataix-Cols et al., 2005). The current concept adopted was derived by the DSM-IV, which defines OCD as a unitary nosological entity (American Psychiatric Association, 1994). This variability in phenotype may impact not only the findings of clinical, natural history and treatment response studies, but also replicate genetic and the search for vulnerability genes (Miguel et al., 2005). Obsessive-Compulsive Symptoms (OCS) as the use of OC symptoms to study genetic factors and related complexes can be divided into several symptom dimensions. Obsessive-Compulsive Symptoms (OCS) is the use of OC symptom dimensions in sib pairs affected with OCD. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4). Zygosity classifications were more than 95% accurate. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4).

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 may impact not only the findings of clinical, natural history and treatment response studies, but also replicate genetic and the search for vulnerability genes. Obsessive-Compulsive Symptoms (OCS) are influenced by environmental risk factors that contribute to OC behavior. Several OC symptom dimensions, “impulsions”, “symmetry/ordering”, and “aggressive/sexual/religious obsessions and checking compulsions” were included in the Young Adult Self Report Obsessive-Compulsive Subscale from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings and found a moderate heritability of 39% for men and 50% for women. A next step would be to use OC symptom dimensions in an epidemiological twin sample, allowing one to investigate the genetic and environmental factors underlying different OC symptom dimensions. The (most) heritable symptom dimensions may be used as a refined phenotype for further linkage or association studies. In this study, we present multivariate analyses of the OCS data by Jonnal et al. (2000). Instead of heritabilities of the classic obsession/compulsion factor model as originally proposed, we present results of multivariate genetic analyses of empirically-defined symptom categories giving the opportunity to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions. We aim to address three major questions:

1. Can distinct dimensions within OCS be found in a general population sample of women?
2. What role do genetic and environmental factors play in the etiology of these OC symptom dimensions?
3. Are different symptom dimensions influenced by the same or by different genetic factors?

Materials and Methods

Sample

Sample characteristics are extensively described in the publication of Jonnal et al. (2000). Briefly, participants in this study were from a population sample of Caucasian female twins from the Virginia Twin Registry (Kendler and Prescott, 2006). Self-report questionnaires on OC items were mailed to 1426 twins of whom 1382 returned completed questionnaires, the subjects of the current analyses. Zygosity was determined by analysis of a questionnaire with 88 polymorphisms. Zygosity classifications were more than 95% accurate. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4).
Table 1. Results of factor analysis of 17 Padua Inventory items used in present study

<table>
<thead>
<tr>
<th>Factor</th>
<th>PI-20 items</th>
<th>PI-R items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rumination</td>
<td>.649</td>
<td>.687</td>
</tr>
<tr>
<td>Contamination</td>
<td>.602</td>
<td>.652</td>
</tr>
<tr>
<td>Impulses</td>
<td>.220</td>
<td>.054</td>
</tr>
<tr>
<td>Checking</td>
<td>.027</td>
<td>.046</td>
</tr>
</tbody>
</table>

The results of the factor analysis using the 20 PI items were unclear and showed a difficult to interpret five-factor solution. We then decided to include only those Padua Inventory items which were used in the 41-item PI-R (Van Oppen et al., 1995). Of the 20 items we collected, 17 met this criterion. Interestingly, the factor structure of the two inventories was not identical. We then arrived at an interpretable four-factor solution, which explained 46.6% of the variance (Table I). Inspection of the items included in these factors suggested that the components represented (1) Rumination, (2) Contamination, (3) Impulses or Aggressiveness/Harm, Obsessions, and (4) Checking. The internal consistency of each factor was 67, 62, 48, and 64 respectively. The factor Impulses clearly showed a lower internal consistency. Further inspection of this factor revealed that more than 90% of the participants scored 0 on this dimension, which caused very low variation within this factor. We decided not to include this factor in our genetic analyses. Table II shows the phenotypic correlations between the dimensions Rumination, Contamination, and Checking.

RESULTS

Factor analysis

The results of the factor analysis of the 20 PI items were unclear and showed a difficult to interpret five-factor solution. We then decided to include only those Padua Inventory items which were used in the 41-item PI-R (Van Oppen et al., 1995). Of the 20 items we collected, 17 met this criterion. Interestingly, the factor structure of the two inventories was not identical. We then arrived at an interpretable four-factor solution, which explained 46.6% of the variance (Table I). Inspection of the items included in these factors suggested that the components represented (1) Rumination, (2) Contamination, (3) Impulses or Aggressiveness/Harm, Obsessions, and (4) Checking. The internal consistency of each factor was 67, 62, 48, and 64 respectively. The factor Impulses clearly showed a lower internal consistency. Further inspection of this factor revealed that more than 90% of the participants scored 0 on this dimension, which caused very low variation within this factor. We decided not to include this factor in our genetic analyses. Table II shows the phenotypic correlations between the dimensions Rumination, Contamination, and Checking.

Genetic analyses

Tetrachoric twin correlations, both within dimensions and across dimensions, are seen for both gonzgy groups in Table III. For all dimensions, MZ correlations were higher than DZ correlations, indicating the influence of genetic factors on OC dimensions (diagonal). However, for the factor Checking, shared environmental factors also seem important, because the MZ correlation is less than twice the DZ correlation. The cross-dimension twin correlations (off-diagonal), i.e. the correlation between a OC dimension of the first-born twin with a different OC dimension of the second-born twin and vice-versa, give insight into the role of genes and environment in explaining the sources of within and between dimension correlations. Here we also see that MZ cross-dimension correlations are larger than DZ cross-dimensional correlations.
common pathway model structure is different from that of the independent pathway model (it introduces a latent variable) and can be formally tested as a nested sub-model. Comparing the fit of the common pathway model to the independent pathway model produced a non-significant chi-square test ($\chi^2(4) = 6.0, p = .30$). This indicates that the more restrictive common pathway model provides a more parsimonious explanation than does the independent pathway model. The common pathway model is therefore the model of choice. Figure 1 displays the common pathway model with the estimates of the structural parameters. The total variance of the latent phenotype (OC behavior) and observed variables (Ruminating, Contamination, and Checking) is constrained to be 1. The proportions, the square of the factor loadings, of the variance explained by the latent variable across the different dimensions are given in Table V.

For the latent OC behavior construct, 36% of its variance was attributed to genetic factors (A) and the rest of the variance was explained by nonshared environmental factors (E). Shared environmental factors (C) could be dropped without any loss of fit, which means that the influence of shared environmental factors is zero on the latent OC construct, and this factor is not shown in Figure 1. For clarity, a CE model also fitted the data ($\chi^2(1) = 1.4, p = .23$), though worse than the AE model. Dropping both A and C resulted in a significantly worse fit ($\chi^2(2) = 13.5, p = .001)$. The latent OC behavior phenotype explained more than half of the variation of the Contamination dimension is explained by specific factors, with 33% explained by genetic factors and 67% by nonshared environmental factors. This indicates that the more restrictive common pathway model fits the data, which means that there is a common OC behavior phenotype explaining variance of all three dimensions. This latent phenotype is influenced by genes and nonshared environmental influences. Third, besides genes for the broad OC behavior phenotype, specific genetic influences are also seen for the Contamination dimension, explaining a fair amount of its variation. The factor structure of the PI items we found was similar to that found in another study using PI-R items within OCD patients (Van Oppen et al., 1995, Deynys et al., 2004) and general population samples (Van Oppen et al., 1995, Burns et al., 1996). We could not identify the dimension related to precision because no corresponding items were included in this study.

The results of this multivariate analyses show the extent to which symptom dimensions that cluster share a common genetic basis. The common factor model fitted the data best. The common factor, i.e., OC behavior phenotype, was influenced by both genetic and nonshared environmental influences. Twin studies of OCD in adults so far also found no evidence for shared environment (Van Groovehout et al., 2005). Our results further indicate that, in addition to a common factor, sharing genes related to three dimensions, only the contamination dimension may possess also specific genetic factors, while for the other two dimensions we have to conclude that specific familial influences are not of importance. Interestingly, the Contamination dimension is also the dimension of which only a quarter of the variation is explained by the common OC behavior phenotype. This means that the Contamination dimension is a relative independent dimension.

These results support the findings of some of the family studies investigating the familiality of OC symptom dimensions, based on Y-BOCS items (Leckman et al., 2003; Hasler et al., 2007) found significant sib-sib correlations for Checking compulsions and the Contamination/Cleaning dimension. These results seem also in line with Mathews et al. (2004) who examined the structure of OC symptoms in a non-clinical population and concluded that this broad OC behavior phenotype, they call it “obsessiosity”, is phenotypically similar to OCD and is likely to comprise a continuum with OCD. This may implicate that, besides a traditional categorical model of OCD, an underlying quantitative OC behavior phenotype could be used to provide an alternative strategy for the detection of genetic susceptibility loci that contribute to OCD or OCD (Miguel et al., 2005).
Another approach would be the use of the contamination dimension, showing clear specific genetic influences explaining a substantial amount of its variance.

These results should be interpreted in the context of four limitations. First, we only selected a subset of items from the PI which probably increased total error variance. Error variance cannot be distinguished from nonshared or individual-specific environment, and therefore it is likely that the impact of genetic influence on the etiology of OCs is underestimated. Second, the present study only included women, so results cannot be assumed to hold equally for males, although Van Groot- heest et al. (2007) recently found in a large twin-family study, that the same genetic risk factors were expressed in men and women for OC behavior. Third, because of the use of a threshold model (Derks et al., 2004), and the fact that number of MZ twins exceeded the number of DZ twins (Posthuma and Boomsma, 2000), the power to distinguish genetic influences from shared environmental influences was moderate. Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include no large degree of assortative mating and the validity of the equal environment assumption (EEA). The EEA states that environmental influences are shared to the same extent by MZ and DZ twins. Maes et al. (1998) found that significant but moderate primary assortment exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assort- ment is negligible. Jonnal et al. (2000) tested the EEA for OC symptoms in the current sample and concluded that the EEA was not violated.

The limitations of the present study give direction for future twin studies investigating OC dimensions. First step is to replicate our results in a large twin sample with an adequate MZ/DZ twin ratio to overcome power limitations (Posthuma and Boomsma, 2000). Second, assessing OC symptoms in both male and female twins allows one to test for sex differences within symptom dimensions. Finally, it is preferable to assess OC symptoms with the complete PI-R and/or Y-BOCS (Cooper et al., 1989). The relatively new self-report version of the Dimensional Y-BOCS (DY-BOCS) (Rosario-Campos et al., 2006), especially developed to assess OC dimensions in affected sibling pairs diagnosed with obsessive-compulsive disorder (OCD-Affected Sibling Pairs from the OCD Collaborative Genetics Study (OCD-CGS)), might be an interesting instrument for assessing obsessive-compulsive symptom dimensions.

REFERENCES


Rumination is represented solely in the (D)Y-BOCS and PI-R and “hoarding obsessions/compulsions” solely in the PI-R. and “somatic/religious/sexual obsessions” in the (D)Y-BOCS.
CHAPTER 12
Discussion & Summary
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, such as 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 monzygotic and dizygotic twins, and (4) twin studies of OCD using a dihensional 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 differences 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 biomedical approach with complete data is needed to provide conclusive evidence, including a closer look at sex-differences, issues of phenotypic assortment and cultural transmission in longitudinal analyses. 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 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 were 82.4% and 69.7%, respectively, when compared to clinician diagnosis. Cronbach’s coefficient of .69. YASR-OCS data were available in 5893 mono- and dizygotic twins, and 1304 triplets and 1257 additional siblings. The design allows for 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 homogeneity or marital interaction. Phenotypic assortment means that partner selection is based directly on a phenotype and there is a preference for a phenotype like one’s own, resulting in marital resemblance. Social homogeneity refers to the tendency for individuals to have partners with similar social background, e.g. coming from the same religious background. Under social homogeneity 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 assortative, if it is due to phenotypic assortment, has consequences for the genetic architecture of a population. We found small but significant within-trait correlations between .1 and .2 for spouse similarity in observ- sive, anxious and depressive behavior as measured by the YASR-OCS 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 re- semblance between spouses does not increase as a function of duration of marriage. Marital correlations were small (r=.08-.12). The study was difficult to distinguish between social homogeneity and phenotypic assortment, but as 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 this approach with continuous data is still needed to provide more conclusive evidence for the role of genetic and environmental factors to variation in OC symptoms using an extended twin design, including 4408 twins, 1304 triplets and 1257 additional siblings. The design allows for test to 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 role (27%) with a small non-shared environmental role for genetic factors (1%). Significant influence of cultural transmission was only found for men, but was mimicked by non-shared factors, while OC culture of the variance of OC symptoms. For women, the heritabil- ity was estimated at 37% and non-shared environmental explained 71% of the variance of OC symptoms. The YASR-OCS contained the same 8 items as the YASR-OC, YASR anxious-depressed subscale and environmental factors to variation 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 OCs provides a solid basis for two large twin studies using two different OC questions. 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-ABRR. The results for 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) which was based on a small sample and has low correlations with for example the YBOCS. The greatest differences between YASR-OC and Padua-OC were seen for the DZM-correla- tions, which are quite high for Padua-OC in comparison with the DZM-correlations in the YASR-OCS study. The MZ correlations of the Padua-ABBR are in the same range as in the YASR-OCS study. More research must establish whether the shared influences in men for the Padua-ABBR is a coincidental finding or that it was “real” shared environment. Earlier, C had not been detected in twin studies of OC symptoms, except in children at the age of 12 years (chapter 7). Fur- thermore, when YASR-OCs and Padua-ABBR data were spliced together, no difference could be found between shared environmental factors were found (chapter 9).

Another focus of Part I was testing of several twin studies using different twin studies, using different Twin Affective mating or gene-environment correlation induced by simultaneous cultural and genetic transmission. As- sortative mating exists for OC symptoms, but it is still, 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., 2003) no evidence was found for a special twin environment for women.

One assumption which was not tested in this thesis is whether OCD reflects the extreme of a normal distribution of personality dimensions, it is not a malform of the latter. There is indirect evidence that this is the case, but it is not explicitly tested yet, for example by testing for a genetic and environmental interaction (Rutter et al., 2003) did not 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 general population, but more than controls and their families. However, without directly proving this assumption, one should be cautious when interpreting findings in the general population to a specific disease.

Part II of this thesis (Heritability, assortative mating, cultural transmission and gene-environment correlation) has clinical consequences. It is not long ago that parents of patients with psychiatric disorders, such as schizo- phrenia, were blamed for the disease of their offspring. Twin studies can be particularly effective in disentan- gling myths from facts, thus providing a tool for health care workers to inform patients and their families on the etiology of the disease, which is often 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
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 an unique perception of each parent on the behavior of the children (i.e., common perception). This may affect the stability of OC behavior over time.

Chapter 8 described a cross-sectional study of genetic and environmental contributions to self-report obsessive-compulsive symptoms in children. Adolescents and adults. The longitudinal study in children assessed a moderate stability with genetic effects of about 50% and environmental effects of about 50%. The stability of OC symptoms was analyzed with a cross-tabulation of the instrument used. OC behavior was moderately stable with correlations ranging from .39 to .61 within 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 9 presented the first estimates of genetic and environmental contributions underlying stability in adult obsessive-compulsive behavior. The YSR-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 cut-off points was observed for the OCI symptoms in children. 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: 12, 14, and 16. The cross-sectional analysis at the age of 12, age 14 and 16, the recurrence 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 assessed a moderate stability with phenotypic correlations of around .50 for boys and .45 for girls. Stability of OC behavior was influenced mainly by genetic factors, but environmental factors shared by children growing up together (i.e., by the same parents) also contributed. Genetic 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 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 theMZ pairs for the study, the use of the Padua Inventory Revised ABBR was evaluated. To investigate whether the PI-R ABBR can assess OC symptoms in childhood, 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.
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 1997 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 II 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: Ruminating, 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 genetic 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 focus on environment in the next decade, following large groups over time, while precisely registering environment, for example by computerized diaries. This 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 a 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 MRI 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 obsessivity 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-BROCS 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 instability caused by genes or environment?
REFERENCES


Tweelingonderzoek

Tweelingonderzoek is een veelgebruikte benadering in gedraggenetische en psychiatrisch onderzoek en maakt gebruik van het feit dat er twee type tweelingen zijn: eenzige en twee-eiige tweelingen. Eenzige of mono-gezwommen tweelingen zijn genetisch identiek, terwijl twee-eiige of dizygoë (DZ) tweelingen gemiddeld de helft van hun genen delen. Dit laatste geldt ook voor hun gedragsspecificaties en hun geestelijke of psychische能s. De tweede fase bestudeert studies die gebruik maken van DSM-IV criteria voor OCS. De DSM is het meest gebruikte klassieke systeem voor psychiatrische aan.

Hoofdstuk 3 geeft een literatuuroverzicht van meer dan 140 gedurende de jaren 1980 en 1990 gepubliceerde studies. De oorzaak van deze correlaties is een samenvatting van de bijbehorende hoofdstukken. De correlaties gebeuren bij de algemene tijd van 60% van de partnames in de derde fase alleen naar de eigenschap die wordt bestudeerd. Zo niet, dan is er een correlatie van 0 (al enkele samenhang) tot en met 1 (volledige samenhang).

Deel II. Erfelijkheid, Selectieve Partnerkeuze en Culturele Transmissie

Deel II. Erfelijkheid, Selectieve Partnerkeuze en Culturele Transmissie

In hoofdstuk 4 worden de erfelijkheidschattingen van OC symptomen onderzocht in een groot familieonderzoek. Voor niet-tweeling broertjes of zusjes. De mate waarin de helft van hun genen delen. Dit laatste geldt ook voor hun gedragsspecificaties en hun geestelijke of psychische能s. De tweede fase bestudeert studies die gebruik maken van DSM-IV criteria voor OCS. De DSM is het meest gebruikte klassieke systeem voor psychiatrische aan.

Hoofdstuk 3 geeft een literatuuroverzicht van meer dan 140 gedurende de jaren 1980 en 1990 gepubliceerde studies. De oorzaak van deze correlaties is een samenvatting van de bijbehorende hoofdstukken. De correlaties gebeuren bij de algemene tijd van 60% van de partnames in de derde fase alleen naar de eigenschap die wordt bestudeerd. Zo niet, dan is er een correlatie van 0 (al enkele samenhang) tot en met 1 (volledige samenhang).

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In hoofdstuk 4 worden de erfelijkheidschattingen van OC symptomen onderzocht in een groot familieonderzoek. Voor niet-tweeling broertjes of zusjes. De mate waarin de helft van hun genen delen. Dit laatste geldt ook voor hun gedragsspecificaties en hun geestelijke of psychische能s. De tweede fase bestudeert studies die gebruik maken van DSM-IV criteria voor OCS. De DSM is het meest gebruikte klassieke systeem voor psychiatrische aan.

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relatief hoge correlatie bij mannelijk twee-eiige tweelingen. Gezien het feit dat de groep mannelijke twee-eiige tweelingen relatief klein was, kan de vraag gesteld worden of deze bevinding niet op toeval berust. Toekomstig onderzoek zal dit moeten uitwijzen.

**DEEL III. INVLOED VAN GENEN EN OMGEVING OP OC SYMPTOMEN OVER DE TIJD**

Doel van de studie in hoofdstuk 7 was om de stabiliteit, ofwel persistentie, van OC symptomen te bekijken bij kinderen en nader te onderzoeken in hoeverre deze stabiliteit beïnvloed werd door genen of omgeving. Er werd gebruik gemaakt van zowel vader- als moederbeoordelingen van hun kinderen op het gebied van OC symptomen. Hiervoor werd de OC schaal uit het Child Behavior Checklist (CBCL-OCS) gebruikt, bestaande uit 8 vragen. Doordat deze schaal voor de vader- als moederbeoordelingen werd gebruikt, kon gebruik worden gemaakt van overeenkomst tussen deze beoordelingen waarmee een hoge mate van betrouwbaarheid werd verkregen. In totaal werden data op drie verschillende leeftijden (tweelingen op de leeftijd van 7, 10 en 12 jaar) van in totaal 8083 families geanalyseerd. Er werd een onderlinge correlatie over de tijd gevonden tussen OC symptomen van .50. Dit duidt op een redelijke stabiliteit van OC symptomen. Deze stabiliteit werd veroorzaakt door invloeden van zowel genen (ruwweg 35%) als omgeving (65%), waarbij beide het zeggen. Het bijdragen aan deze stabiliteit van OC symptomen, ofwel persistentie, kan worden gedaan door hoge invloeden van genen, maar ook door omgevingsfactoren zoals buitenhuisbezit. Betekent het dat de invloeden van genen en omgeving op OC symptomen tijdens de puberteit op de leeftijden van 12, 14 en 16 jaar. Er werd gebruik gemaakt van de YSR-OCS schaal uit het Youth Self Report (YSR-OCS). Deze lijst omvat overeenkomstig de CBCL-OCS, met dit verschil dat de YSR-OCS door de tweelingen zelf werd ingevuld en niet door de ouders. Op leeftijd van 12 jaar werd er geen verschil gevonden tussen de twee-eiige tweelingen (tweelingen met verschillende leeftijden) en de kinderen. De correlatie tussen de leeftijden variert tussen 39 en .61. Deze stabiliteit werd door 70% veroorzaakt door genetische factoren. Daarnaast werden er grotere correlaties tussen de leeftijden gevonden. Dit duidt erop dat dezelfde genen verantwoordelijk zijn voor OC symptomen over de tijd. Deze bevindingen zijn erg belangrijk voor verder onderzoek, want dit betekent dat volwassenen van verschillende leeftijden tegenkort in de stabiliteit hebben geprobeerd om deze te vinden in studies waarin daadwerkelijk naar genen wordt gezocht voor OC symptomen.

**DEEL IV. OMGEVINGSFACTOREN EN SYMPTOMOEMENSITIES VAN OC SYMPTOMEN**

In hoofdstuk 10 is onderzocht welke omgevingsfactoren hebben bijdragen aan de OC symptomen behoren tegen OC symptomen of juist OC symptomen veroorzaken. Hiervoor werd een bijzondere onderzoeksmethode gebruikt: het discordante monozygote tweelingexperiment. Discordant betekent dat het einde lid van een eeneiige tweeling wel OC symptomen heeft en de andere niet. Deze discordantie kan worden verklaard vanuit unieke omgevingsfactoren die de ene tweeling wel heeft beïnvloed en de andere niet. Op basis van de PI-R ABBR werden 25 discordante eeneiige tweelingenpaar geselecteerd. Tevens werd een groep eeneiige tweelingen geselecteerd, waarvan beide hoog scoorden (concordant hoog), een groep waarvan beide eeneiige tweelingen laag scoorden (discordant laag), en een groep waarvan beide eeneiige tweelingen laag scoorden ( Discordant laag, 34 paren). Door de discordant hoge scorende tweelingen te vergelijken met de concordant lage groep is het mogelijk om omgevingsfactoren die OC symptomen beïnvloeden te onderzoeken. Deze omgevingsfactoren werden in tegenstelling tot de discordante tweetweelingen Methode gedeeltelijk door beide binnen. De discordante groep was het opvallend dat seksueel misbruik veel voor kwam bij de hoog scorende tweelingen. Verder werd er ook een hogere piegelement van de discordant groep lager dan dat van de concordant hoog scorende tweelingen. Ook vonden we dat concordant hoog scorende tweeling- gen relatief lager opgegeld waren en minder vaak een religieuze achtergrond hadden of naar de kerk gingen dan de laag scorende concordante tweelingen. Kijken we naar eerdere metingen binnen het tweelingregister dan valt op dat de concordant hoge groep al vroeg OC symptomen vertoont en de discordante groep relatief laat discordant geworden zijn. Dit bevestigt de genetische invloed van bij het vroege ontstaan van OC symptomen.

In hoofdstuk 11 is de erfelijkheidschattende onderzoek van OC dimensies. Eerder onderzoek geeft aanwijzingen dat OC symptomen te verdelen zijn in verschillende clusters of factoren van symptomen, zoals symptomen rondom het cluster kontroleren en cluster wassen. In deze studie werden 1383 vrouwelijke tweelingen van het Virginia Twin Registry onderzocht. OC symptomen waren genetisch met behulp van 20 vragen van de Padua Inventory. Na factor analyse werden drie factoren gevonden: ruminatie (herhalen van gedachten), smetvrees/wassen en controleeren. In een “multivariate” (alle factoren werden tegelijkertijd meegenomen) analyses werden verschillende modellen onderzocht om te zien welk model het beste bij de data past. Uit deze analyses kwam een universeel OC symptomen factor voor die op zijn beurt de diverse specifieke OC clusters of factoren beïnvloedt. Deze universele OC symptomen factor wordt door zowel genen (36%) als unieke omgevingsfactoren (74%) beïnvloed. In tegenstelling tot de factoren ruminatie en controleeren, werd een universeel OC symptomen factor aangegeven door specifieke (onafhankelijk van de universele factor) genetische en omgevingsfactoren.

Het is nog maar relatief kort geleden dat genetische oorzaken voor OC-symptomen was niet genetisch, maar genetisch en omgevingsfactoren van cruciaal belang zijn voor het ontstaan van OC-symptomen.
List of Publications

Published articles


Bookchapters


Het is een bijzonder moment in mijn leven om mijn promotietraject met dit proefschrift af te kunnen ronden. Uiteraard is ook dit proefschrift een project van velen en mijn dank gaat dan ook uit naar allen die aan dit proefschrift hebben meegewerkt. In het bijzonder wil ik de volgende mensen danken:

Mijn promotoren: Dorret, voor het vertrouwen bij haar onderzoek te mogen doen, de buitengewoon snelle correcties en natuurlijk de altijd vooropstaande inheemse bijdragen. Aartjan, voor zijn altijd aanwezige optimisme en pragmatische adviezen.

Mijn co-promotor: Danielle, voor het feit dat ze mij gevraagd heeft voor dit onderzoek, voor haar talent om geld te werven voor (ook dit!) onderzoek en voor haar toneloze energie.

De leescommissie dank ik voor het lezen en beoordelen van mijn proefschrift. Jim Hudziak en David Pauls, thank you so much for reading my thesis and for coming to the Netherlands!

Al mijn co-auteurs dank ik voor hun bijdrage en visie. Zowel de AGIKO-intervisie als de AIO-intervisie club voor het delen van (promotie)lief en leed.

Het secretariaat, in het bijzonder Natasha Stroo, voor de dagelijkse ondersteuning.

De bibliothecaressen van de Valeriuskliniek, in het bijzonder Marijke van ter Toolen, voor hun hulp bij het vinden van artikelen.

Roman Jans voor de prachtige lay-out.

Al mijn collega’s van de afdeling Biologische Psychologie en drie collega’s in het bijzonder: Dirk en Marleen voor hun regelmatige hulp op gebied van statistiek en Christel, mijn voorganger, AGIKO-collega en nu zelfs opponent, veel dank!

Als laatste mijn kamergenoten waarmee het altijd goed en gezellig toeven was. Eske, voor wie statistiek geen geheimen kent. Tinca, altijd vrolijk en energiek en nu zelfs paranimf!
Daniël Sebastiaan van Grootheest was born on May 29th, 1973 in Amsterdam. After living in Amsterdam for a year he moved with his parents to Zaire, nowadays called Democratic Republic Congo, where they stayed for three years. He grew up with two younger sisters (no twins!) in Veenendaal for the remaining part of his childhood. He graduated from high school in 1991, and subsequently started his study at the Medical school at the VU University in Amsterdam. In 1997 he attended a scientific internship with psychiatrist Aartjan Beekman at the Longitudinal Aging Study Amsterdam examining the effects of bereavement in men, which resulted in his first scientific publication. In 1999, he graduated as MD and worked one year as a resident of psychiatry in the former psychiatric hospital Duin & Bosch in Castricum. This was followed by a job as coordinator of education at the Department of Psychiatry of the VU University Amsterdam. In October 2001 he started his training as a psychiatrist at GGZ Buitenamstel in Amsterdam. His twin research on obsessive-compulsive symptoms started three years later (2004) at the Department of Biological Psychology in collaboration with the Department of Psychiatry. This year he hopes to finish his training as a psychiatrist. In addition to his training and research, he is since 2007 partner of Anno73, a company that publishes medical websites. He lives with Liesje van Leeuwen, and has 2 children, Crispijn (2005), and Jonathan (2007).