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.
OBSESSION
The genetic and environmental architecture of obsessive-compulsive symptoms

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CHAPTER 1
Aims and outline

van Groothorst, D. S.
Aims and outline

Lewis could not imagine in 1935, that twin research would achieve such popularity nowadays. It still took more than 70 years for 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 I 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 siblings. 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 YASR-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 phenotypic assortment, social homogamy and/or marital interaction. A significant degree of assortment, if it is due to phenotypic assortment, has consequences for the genetic architecture of a population. 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.

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)

REFERENCES


CHAPTER 2

Obessive-compulsive symptoms and disease: an overview

This chapter is based on:


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 persist 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., 1995) and 1-2% in children and adolescents.

EPIDEMIOLOGY

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 had access to treatment sooner. Individuals with OCD frequently present to non-psychiatrists for treatment (Table 3) and psychiatric symptoms go undetected. There is a need for greater awareness of OCD in a range of non-psychiatric health care settings, and clinicians need to be confident about recognizing it.

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

<table>
<thead>
<tr>
<th>Obsessions N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contamination</td>
<td>208</td>
</tr>
<tr>
<td>Aggressive</td>
<td>246</td>
</tr>
<tr>
<td>Sexual</td>
<td>68</td>
</tr>
<tr>
<td>Religious</td>
<td>95</td>
</tr>
<tr>
<td>Symmetry</td>
<td>159</td>
</tr>
<tr>
<td>Hoarding</td>
<td>77</td>
</tr>
<tr>
<td>Smoking</td>
<td>103</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compulsions N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleaning</td>
<td>232</td>
</tr>
<tr>
<td>Checking</td>
<td>253</td>
</tr>
<tr>
<td>Ordering</td>
<td>121</td>
</tr>
<tr>
<td>Repeating</td>
<td>176</td>
</tr>
<tr>
<td>Counting</td>
<td>125</td>
</tr>
<tr>
<td>Hoarding</td>
<td>73</td>
</tr>
</tbody>
</table>

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 (Fogt et al., 1994). Screening for, and treating these co-morbidities is an important part of the management of the disorder (see Table 2).

Table 2. Conditions commonly occurring with OCD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</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 Mataix-Cols et al. (1999)

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 had access to treatment sooner. Individuals with OCD frequently present to non-psychiatrists for treatment (Table 3) and psychiatric symptoms go undetected. There is a need for greater awareness of OCD in a range of non-psychiatric health care settings, and clinicians need to be confident about recognizing it.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Professional</th>
<th>Reason for consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, anxiety</td>
<td>General practitioner</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Chapped hands, eczema</td>
<td>Dermatologist</td>
<td>Chapped hands, eczema, compulsive hair pulling</td>
</tr>
<tr>
<td>Compulsive hair pulling</td>
<td>Cosmetic surgeon</td>
<td>Concerns about appearance</td>
</tr>
<tr>
<td>Fear of contamination, vaginal discomfort from douching</td>
<td>Oncologist</td>
<td>Fear of cancer</td>
</tr>
<tr>
<td>OCD associated with Tourette’s Disorder</td>
<td>Genito-urinary specialist</td>
<td>OCD during pregnancy or puerperium</td>
</tr>
<tr>
<td>OCD during pregnancy or puerperium</td>
<td>Neurologist</td>
<td>Fear of contamination, vaginal discomfort from douching</td>
</tr>
<tr>
<td>Obstetrician</td>
<td>Obstetrician</td>
<td></td>
</tr>
<tr>
<td>Gynaecologist</td>
<td>Gynaecologist</td>
<td></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 came from the advent of modern neuroimaging techniques, which provided a direct window into the OCD brain in vivo. Currently, the most widely accepted neuropsychanatomical 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 and thalamus, 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 or indirect pathway provides a mechanism of negative feedback which is important for the inhibition of behaviors and in switching between behaviors. Abnormalities in the direct-frontal-striatal circuit might mediate the symptoms of OCD: an excess tone in the direct relative to the indirect frontal-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 serotoninergic 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-frontal-striatal pathways. In the human brain, D receptor expression 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 D1 influence on the direct pathway of the ventromedial-frontal-striatal circuit and a stronger D2 influence on the indirect pathway of the dorsolateral-frontal-striatal circuit, resulting in a hyperactivated ventral and an inhibited dorsal frontal-striatal circuit (see Figure 3). This corresponds with the results of functional neuroimaging studies in OCD, showing increased activation of limbic and ventral frontal-striatal regions at rest and in response to disease-relevant event information (Remijnse et al., 2005) and decreased responsiveness of dorsal frontal-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 to 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. In addition, there is evidence for both obsessive-compulsive symptoms themselves (Pauls et al., 1995; Nestadt et al., 2000). These studies however do not allow disentangling whether these familial associations are due to genetic or environmental factors. For this purpose adoption or twin studies are needed. Adoption studies show that OCD is more frequent in adoptees than in to whom no known cases have been published concerning OCD. 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 region of chromosome contains the genetic susceptibility factor for a disorder. Genomic linkage analysis has been performed in a number of psychiatric disorders including OCD. Although hereditary factors are important, a large proportion of the variation in OCDs is mediated by environmental factors. Research into environmental factors of OCD is obscure and the quality of the studies was moderate. There are indications of a variety of risk factors for OCD, including prenatal and perinatal complications, pregnancy and postpartum period, and severe life events, particularly sexual trauma (Miguel et al., 2005). Much research is done to the relationship between infection and streptococcus OCD in children, the so-called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) (Snider & Swedo, 2004). The controversy over this diagnosis and clinical consequences continues. Chapter ten further explores possible environmental factors of OCD.

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 techniques most strongly associated with good outcome in CBT studies is exposure and response prevention.
to these treatments. Recent studies suggest that patients and SSRIs, up to 40% of cases fail to respond adequately to these strategies in resistant cases, including in obsessive-compulsive disorder. There is evidence that these treatments have been used in controlled trials and remain controversial.

More recently a reversible form of neurosurgery consisting of deep-brain stimulation of the anterior cap-

Sofia conditions offer neurosurgery (cingulotomy or anterior cingulotomy) 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

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 research on 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 monzygotic and dizygotic twins, and (4) twin studies of OCD using an 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 50%. 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 biometric approach with continuous data is still needed to provide conclusive evidence. Strategies for future twin studies of OCD are discussed.

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by intrusive, unwanted thoughts, fears and images (obsessions) on 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/precision and checking, washing, counting, symmetry/precision and holding on to possessions. 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 by the current concept of Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision; DSM-IV; 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., 2000). The lifetime prevalence of OCD is estimated between 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 monzygotic (MZ) twins are genetically identical, whilst dizygotic (DZ) twins share on average 50% of their segregating genes, which is similar to any non-twin 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 to the present (Pauls & Alasbrook, 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 (Hoaken & Schnurr, 1980). The history of OCD can partly explain this observation. In 1878, Westphal considered genetics to represent the most prominent etiological factor in OCD (Westphal, 1878). 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 wrote on the ideas of Frenkel (1896), based on the theory of OCD changed and by the second half of the twentieth century OCD was (1) separated into obsessive neurosis 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 insufficient 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 twin 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 tentatively calculated prevalence of the OCD of 0.05% in the general population (Woodruff & Pitts, 1964). They wrote that one in 132 twin pairs 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 were to arise independently in each co-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 more commonly occur in identical twins than in nonidentical twins, was already formulated in 1924 (Siemens). But around 1960 the debate continued as to whether 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 occur 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.
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- timalized 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 determin- ation diminish some limitations of the case studies de- scribed 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 following head injury, one from a concor- dant 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 extensive precautions to avoid con- tamination in the bathroom. His early development had been normal and closely similar to that of his co-twin, who had no history of OC symptoms at that time. He was diagnosed with OC disorder after he was 10 years old and his parents brought him to a hospital for treatment.

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>Tars (1978)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>OCD after head injury</td>
</tr>
<tr>
<td>Hoaken &amp; Schurr (1980)</td>
<td>1</td>
<td>0/1</td>
<td></td>
<td>First-born twin has also episode. Second-born twin minor OC symptoms</td>
</tr>
<tr>
<td>Carey &amp; Gottsmann (1981)</td>
<td>30</td>
<td>13/2</td>
<td>7/8</td>
<td>All three twins concordant for schizophrenia/schizoaffective disorder</td>
</tr>
<tr>
<td>Torgersen (1983)</td>
<td>12</td>
<td>0/3</td>
<td>0/9</td>
<td>Both co-twins with OCD and Paraphilia. Twin part of triplet</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>Mulgrob et al. (1988)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>OCD after head injury</td>
</tr>
<tr>
<td>Kim et al. (1990)</td>
<td>1</td>
<td>1/0</td>
<td></td>
<td>All three twins concordant for schizophrenia/schizoaffective disorder</td>
</tr>
<tr>
<td>Andrews et al. (1990)</td>
<td>48</td>
<td>0/18</td>
<td>0/30</td>
<td>All three twins concordant for schizophrenia/schizoaffective disorder</td>
</tr>
<tr>
<td>Lewis et al. (1991)</td>
<td>3</td>
<td>3/0</td>
<td></td>
<td>Both co-twins with OCD and Paraphilia. Twin part of triplet</td>
</tr>
<tr>
<td>Stier et al. (1993)</td>
<td>8</td>
<td>5/3</td>
<td>0/3</td>
<td>Both twins improved after leucotomy</td>
</tr>
</tbody>
</table>

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

The authors conclude that OCD can be drawn from this literature. Finally, in many cases the method of zygosity determination is unclear or there is lack of information to definitively establish monozygosity. With these limi- tations in mind, no conclusions on the heritability of OCD can be drawn from this literature.

TWIN STUDIES OF OCD USING A DIMEN- SIONAL APPROACH, COMPARING RESEMB- LANCES IN MZ AND DZ TWINS

The classical twin method compares phenotyp- ic resemblances between MZ and DZ twins. Compar- ing 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 (Boomsma et al., 2002). The classical twin method al- lows the use of categorical data like diagnoses but also continuously distributed traits, such as obsessive or symptom scores in twins. The authors conclude that their results do not contrib- ute to a clarification of the etiology of OCD.

Several important aspects may limit the inter- pretation of these epidemiologic studies. Although the use of DSM-III or DSM-III-R criteria reduces the risk of false-positive diagnoses, they were 80% to 85% reliable interviews for each member of a twin pair with each interviewer blind to the zygosity status of the pair in- troduces 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 re- sults 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 disorders in general will generally lack the statistical power to ascribe the familial clustering of OCD to either shared genes or shared environment.
OCD is in this case viewed as the equivalent of extreme sores on symptom or trait measures. Such a dimensional approach removes the problem of scarcity of twins with the full disease and also removes the need for population-based prevalence rates for comparison. Young et al. (1971) were the first researchers to apply a dimensional approach to OCD, using OC symptoms (Table 3). They conducted a small study of 17 pairs of non-twin male twins and 15 pairs of fraternal twins to examine the inheritance of neurasthenic traits. The 32 twin pairs completed the Middlesex Hospital Questionnaire, which contains a brief obstreperous traits and symptoms scale. 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>No. of twin pairs</th>
<th>Sample characteristics</th>
<th>Diagnostic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al. (1971)</td>
<td>32</td>
<td>Only men, cross sectional data</td>
<td>Obstreperous traits and symptoms according to a subscale of the Middlesex Hospital Questionnaire</td>
</tr>
<tr>
<td>Torgersen (1980)</td>
<td>99</td>
<td>Men and women, cross sectional data</td>
<td>Obstesial traits according to the Lazar et al. questionnaire</td>
</tr>
<tr>
<td>Clifford et al. (1984)</td>
<td>419</td>
<td>Men and women, cross sectional data</td>
<td>OC-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 twins. Eleven pairs were selected on the basis of hospitalization of one of the twins for neurotic problems. The remaining pairs were derived from the follic register of two cities to represent twins from the general population. Torgersen compared intrapair variations of the personality obsessionality factor, but did 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 the statistical power 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 neurasthenics considers them as conditions to which individual differences towards the extreme ends of normally distributed symptom or trait dimensions are especially prone. A sample of 419 twin pair participants, with a bias towards female MZ twins. Obsessiality 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 estimates for obsessive traits and symptoms were 44% and 47% respectively. No effect of common environment was found, thus unique environment explained the remaining variation. Multivariate analysis revealed two genetic factors of obsessiality, one factor related to a general trait of neurotism and the other most strongly related to obsessive-compulsive behavior. This approach cannot accommodate the effect of sex on variances and covariance within and between twin pairs, nor can results easily be extended to multifactorial genetic studies.

**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 & Cardon, 1992). However, this approach cannot accommodate the effect of sex on variances and covariance within and between twin pairs, nor can results easily be extended to multivariate and longitudinal data. Structural Equation Modeling (SEM), also known as covariance modeling, is a more general alternative approach, in which genotypic and environmental effects are modeled as the contribution of unmeasured (latent) variables to the potentially multivariate phenotypic differences between individuals (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).

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of twin pairs</th>
<th>Sample characteristics</th>
<th>Diagnostic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonnal et al. (2000)</td>
<td>527</td>
<td>Only women, Cross-sectional data</td>
<td>OC symptoms according to 20 items of the Padua-Inventary</td>
</tr>
<tr>
<td>Eley et al. (2003)</td>
<td>4564</td>
<td>Children aged 4 years, Cross-sectional data</td>
<td>OC behavior according to a 4 item OC scale</td>
</tr>
<tr>
<td>Hudzik et al. (2004)</td>
<td>4246</td>
<td>Children aged 7, 10 and 12 years, longitudinal data</td>
<td>OC-symptoms according to a 8-item OC scale contained in the Child Behavior Checklist.</td>
</tr>
</tbody>
</table>

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 the scale into a symptom and an obsessive-compulsiveness factor and an obsessness factor. By using SEM, the best-fit model suggested heritabilities of 33% and 31% and covariances and compulsiveness respectively. Unique environmental effects accounted for 67% and 74% of the variance. The correlation between additive genetic 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 parallel 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 familial factors of etiological relevance to the trait under study. No environmental effects that could be affecting the heritability were found and it was concluded that the EEA was not violated. Jonnal et al. (2000) noted three potentially important methodological limitations. First, they only selected children with symptoms of an obsessive-compulsiveness trait. Second, they were able to reduce the impact of the study sample, both Eley et al. (2003) and Hudzik et al. (2004) 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 a population-based twin study. This study showed a first clear indication for the heritability of OC symptoms, moreover displaying a foreseeing notion of the multidimensionality of OCD. Although earlier twin studies have sometimes suggested the role of genes in OCD, several limitations diminish the utility of this literature (Billett et al., 1998, Black, 1974). Therefore both Macdonald et al. (1991) and 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.

Jonnal et al. (2000) examined the predictive ability of a child behavior inventory (CBCL) for OC-symptoms according to the Leyton Obsessional Inventory. OC-symptoms according to a 8-item OC scale contained in the Child Behavior Checklist.
FUTURE OF TWIN STUDIES AND OCD

Recent research on OCD has made clear that OCD appears to encompass a heterogeneous phenotype with at least four symptom dimensions (Mataix-Cols et al., 2005). This heterogeneity may obscure the findings of clinical, natural history and treatment response studies and complicates the search for vulnerability genes (Miguel et al., 2005). A better description of clinical phenotypes should facilitate genetic studies. In fact, dissecting the complex clinical components may be an important tool in the identification of susceptibility genes in OCD. Miguel et al. (2005) suggested three possible approaches for simplifying the phenotype to identify categorically defined homogeneous and mutually exclusive subtypes of OCD like tic-related OCD or phobic, an Obsessive Disorders. In D.F. Klein & J. Rabkin (Eds.), Anxiety: New research and changing concepts (pp. 115-164). New York: Raven Press.


Obsessional illness, especially its heredity. [A contribution to questions about
Rüdin, E. (1953). Ein Beitrag zur Frage der Zwangskrankheit, insbesondere
und Nervenkrankheiten, 191,
study of DSM-III-R anxiety disorders.
identical twin pairs.
Obsessive compulsive neurosis in identical twins.
dimensional model of obsessive-compulsive disorder.
symptoms in adults: a population-based twin-family study.
in adults: a population-based twin-family study.
Genetic and environmental influences on OC symptoms in adults: a population based twin-family study


Chapter 4  Genetical 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 (YSR-OCS) from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings from the population-based Netherlands Twin Register. Structural Equation Modeling (SEM) was used to decompose the total variance of non-twins and 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 special 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 obsessional-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 in 1929 (Lange) and evolving from single case reports to large epidemiological studies (van Goozen et al., 2005). A paper by Clifford et al. (1984) marked the beginning of research on quantitative obsessional-compulsive (OC) traits in relatively large twin samples derived from the normal population, measuring OCD with standardized instruments. Clifford et al. (1984) analyzed the 42 original families of 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. Jonnal 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 compulsion 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 (Huizink 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 heritabilities were only seen in the USA sample. Van Goozen 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 genes 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 Goozen 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. Clinical 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 with a well-defined pattern of comorbid psychopathology (Geller et al., 1998; Eichert & Arnold, 2001). A variety of association studies have produced variable evidence for association in one sex or another (Camarena et al., 2001; Enoch et al., 2001; Alischrook et al., 2002; Loehlin et al., 2004; Hemmings & Stein, 2006). Segregation analyses suggest that the inheritance of OCD could be affected by sex effects (Nestadt et al., 2000a; Hanna et al., 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 the risk of the siblings to get the genetica lly transmitted disorder was increased by including siblings (Posthumus & Boomsma, 2000; Stoel et al., 2006). OC symptoms were assessed using the adult version of the CBCL-OCS, the Young Adult Self Report Obsessive Compulsive Scale (YSR-OCS). The criterion validity of the YSR-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 YSR-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 of similar 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 twins 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. From the data of 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 resulting sample consists of 5893 twins: 3360 females and 2533 males from 3069 families. We were able to include 1304 additional non-twin siblings and adoptive half sibs.

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 additional siblings the monozygotic (MZ)-pair ratio decreased from .75 (792/1058) to 21 (792/3831). It has been shown that a MZ to DZ ratio of about 1 to 4 is optimal in classical twin design (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% (Willems et al., 2004).

Receiver Operating Characteristic (ROC) analyses were conducted among three different groups: an OCD group, a psychiatric and a population control group. Data on patients with OCD were derived from the outpatient anxiety clinic of GGZ Buitenpost, a specialized anxiety disorder clinic 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 (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 of DSM-IV (SCID-I), 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 44.5 (SD = 15.7), was obtained from an adult sample of the Netherlands Twin-family study on Anxious Depression (NESTAD) (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 NIBH 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, 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 with the code of 0 for not true, 1 for somewhat or sometimes true and 2 for very true of often true. A good reliability and validity of the YASR has been obtained by Engeland (Achenbach et al., 1992; Ferdinand & Verhult, 1995). The YASR-OCS contains the same 8 items as the CBCL-OCS (Nelson et al., 2001), except that items were worded in the first person (Table 2). Using a cut-off of 5 on the CBCL-OCS, 91% of all DSM-detected OCD cases were identified in a clinical sample of children with reasonable specificity (67.2%) (Hudziak et al., 2006). The CBCL-OCS showed also good reliability and validity in several other samples (Cellier et al., 2006; Storch et al., 2006).

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>MZM families</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MZF families</td>
<td>2 twins: 100</td>
<td>1 twin: 50</td>
<td></td>
</tr>
<tr>
<td>DZM families</td>
<td>2 twins: 100</td>
<td>1 twin: 50</td>
<td></td>
</tr>
<tr>
<td>DZF families</td>
<td>2 twins: 100</td>
<td>1 twin: 50</td>
<td></td>
</tr>
<tr>
<td>DOS families</td>
<td>2 twins: 100</td>
<td>1 twin: 50</td>
<td></td>
</tr>
</tbody>
</table>

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 and specificity (true positives/(true positives + false negatives)) and specificity (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 .50 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. (1999). YASR-OCS syndrome can accurately identify persons with OCD.

Because the data exhibited a pronounced right skew, we used a threshold model under the assumption of an underlying continuous liability distribution with the thresholds defining categories (Derks et al., 2004). The thresholds are chosen in such a way that the prevalence or more or less similar in each of the categories. We used three thresholds, because the use of more thresholds had the disadvantage of the presence of empty cells. To correct for multiple testing, we used the familywise error rate for each model in the sequence at a significance level (α) of .01. Genetic analyses were carried out in several steps using the software package Mx (Neale et al., 2006). We first fitted a saturated model in which thresholds and polyphasic correlations between twins, twin-sibling pairs, and sibling-sibling pairs were estimated without any restrictions. 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. 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 of OC symptoms into additive genetic (A), shared environmental (C) and nonshared or individual-specific environment (E). Analysis using all zygosity groups for opposite sex pairs and DZ twin/sib pairs, female MZ twin pairs and DZ twin/sib pairs, DZ opposite sex twin/sib 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 correlation for opposite sex pairs to .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 0.81 (95% CI = 0.75 – 0.88) 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). The best cut-off point of the sensitivity was 82.4% and the specificity was 67.7% when compared to clinical controls.
The results of genetic model fitting are summarized in Table 2. This table describes the data adequately when compared with the fully saturated model (model 1). Next, a model was fitted without the shared environmental effect (model 3). The fit did not get significantly worse. In model 4 we constrained the correlation of the genetic factors for opposite sex twins to be 0.5. This did not give a significant deterioration in fit, which suggests that the same genes account for variation in OC behavior in men and women. In model 5 we constrained the magnitude of the effect of the genetic factors in men and women to be equal. This model just fits the data, suggesting no differences in the influence of genetic and environmental factors between men and women. Fifth, because the genetic correlation for opposite sex pairs could be constrained to 0.5, the genes which account for the genetic influence seem to be the same in both sexes.

Table 2. Twin correlations on YASR-OCS scores by zygosity

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>MZM</th>
<th>DZM</th>
<th>DZFF</th>
<th>DZMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td>0.44</td>
<td>0.02</td>
<td>0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>DZ</td>
<td>0.21</td>
<td>0.13</td>
<td>0.26</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The Psychometric analyses of 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 of 92% and a specificity of 89% for the diagnosis of depression. The major advantage of these two instruments is the performance that they provide investigators and clinicians with two fully comparable screeners 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 (Witnitzer et al., 1992).

The VASROCS is an instrument that seems to effectively deal with the discontinuity in available diagnostic and research tools between children and adolescents on the one hand and adults on the other.

Table 3. Model fitting results for heritability of YASR-OCS scores

<table>
<thead>
<tr>
<th>Number of model</th>
<th>Type of model†</th>
<th>2LL</th>
<th>χ²</th>
<th>df</th>
<th>p</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully saturated model</td>
<td>18477.0</td>
<td>153.7</td>
<td>121</td>
<td>.02</td>
<td>42.527.2</td>
</tr>
<tr>
<td>2</td>
<td>ACE, quantitative and qualitative sex differences allowed</td>
<td>18630.7</td>
<td>121.7</td>
<td>121</td>
<td>.02</td>
<td>42.527.2</td>
</tr>
<tr>
<td>3</td>
<td>AE, quantitative and qualitative sex differences allowed</td>
<td>18630.2</td>
<td>29.0</td>
<td>90</td>
<td>.29</td>
<td>42.489.2</td>
</tr>
<tr>
<td>4</td>
<td>AE, quantitative sex-differences allowed, but no qualitative sex differences</td>
<td>18631.0</td>
<td>1</td>
<td>75</td>
<td>.75</td>
<td>42.470.0</td>
</tr>
<tr>
<td>5</td>
<td>AE, no qualitative and quantitative sex differences allowed</td>
<td>18636.0</td>
<td>5.0</td>
<td>1</td>
<td>43</td>
<td>42.500.0</td>
</tr>
</tbody>
</table>

The limitations of the results of this study should be interpreted in the context of four potential methodological limitations. First, the modest number of cases in each of the groups may contribute to increased error variance. Secondly, the VASROCS 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 VASROCS scores, not clinical measures of DSM-IV OC. Although the VASROCS showed satisfactory criterion validity for DSM-IV OC 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., 2003; Kendler, 2005). A quantitative approach does justice to the fact 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 D-SIM-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 el 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 small amount of assortative is negligible. Jonnal et al. (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated.

**REFERENCES**


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

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-spouse and over 850 parent-spouse families. Correlations of the trait in twin’s sons and daughters, 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. We finally 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-disease disorder 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 risk of anxiety disorder in spouses of patients with an anxiety disorder (Eagles et al., 1987; Low et al., 2007), but several other studies found an increased risk (Tambu, 1991; Zimmermann-Tansella & Lattanzi, 1991; McCleod, 1995; Galbaud du Tast et al., 1998; Dubuis-Stadelmann et al., 2001) with spousal correlations varying between 1. and 3. Only one study mentioned data on marital resemblance for Obsessive-Compulsive Disorder (OCD). Mathews et al. (2007) conducted a linkage study with OCD and found 19 mating pairs with known OCD status for both spouses. In two of these pairs (10%), both members had OCD or clinically significantly Obsessive Compulsive (OC) symptoms which may be an indication that assortative mating exists for OCD.

For depressive disorders, a review and a meta-analysis were conducted by Mathews and Beurs (2001). Twelve of 17 studies reported marital resemblance for depression. Results of the meta-analysis supported these findings, and indicated that marital resemblance occurs in major depression, with odds ratios for the combined data of 2.38. One of the most extensive studies on spousal correlation for psychiatric disorders in a population-based sample was carried out by Maes et al. (1998). Several psychiatric diagnoses were examined, including generalized anxiety disorder, major depressive disorder, panic disorder and phobias. A small degree of assortment with correlations between 1. and 2. was seen within and across psychiatric diagnoses.

Marital resemblance is likely due to a multifactorial process, including phenotypic assortment, social homogamy, and marital interaction (Reynolds et al., 2006). Phenotypic assortment means that partner selection is based directly on the partner’s phenotype; there is a preference for a phenotype like one’s own, resulting in marital resemblance. A variant of the latter, called secondary phenotypic assortment, encompasses partner selection that occurs on the basis of variables that correlate with the phenotype under study, such as demographic variables or personality characteristics. As in several other studies (Galbaud du Tast et al., 1998; Dubuis-Stadelmann et al., 2001; Maes et al. found (1998) that only a small amount of the observed marital resemblance for mental illness could be explained by assortment of correlated variables, such as age, religious attendance and education.

Social homogamy refers to the tendency for individuals to have partners with similar social background. Whereas phenotypic assortment refers to the selection of a partner based on the observed phenotype, which may or may not be influenced by genetic factors, social homogamy refers to assortment based on the social background (Heath & Eaves, 1985; Reynolds et al., 2006). Under social homogamy partner selection takes place within social strata and which are correlated with the phenotype under study. An example of social homogamy was found recently by Reynolds et al. (2006) for tobacco use, implying that one may be socially associated with those among whom tobacco use is common or uncommon due to for example social contacts through one’s family or network of friends.

Marital interaction or shared influences after marriage refers to a process of mutual influences between spouses living together (Penrose, 1944). In addition to the process of initial assortment, spouses may become more similar the longer they are married due to marital influence between spouses or by sharing the same social environment. Contagion is a special case of marital interaction where illness of one partner is a direct consequence of the breakdown of the other (Maes et al., 1998).

For twin and family studies examining psychiatric disorders or traits, it is important to know if marital resemblance is due to non-random mating due to phenotypic assortment will lead to an increase in genetic variance in the offspring generation and to an increase in resemblance among siblings and between parents and offspring (Falconer & Mackay, 1996). Social homogamy refers to the tendency for individuals to have partners with similar social background. Whereas phenotypic assortment refers to the selection of a partner based on the observed phenotype, which may or may not be influenced by genetic factors, social homogamy refers to assortment based on the social background (Heath & Eaves, 1985; Reynolds et al., 2006). Under social homogamy partner selection takes place within social strata and which are correlated with the phenotype under study. An example of social homogamy was found recently by Reynolds et al. (2006) for tobacco use, implying that one may be socially associated with those among whom tobacco use is common or uncommon due to for example social contacts through one’s family or network of friends.

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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 OC, 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 Table 1. Number of complete pairs relationship for 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>Twins-spouse</td>
<td>1416</td>
<td>1441</td>
<td>1407</td>
</tr>
<tr>
<td>Cenain-spouse</td>
<td>1090</td>
<td>1110</td>
<td>1081</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>

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 3340 responses for 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 psychiatric symptoms. Because we have data on the number of attendances and education.

Table 1. Number of complete pairs relationship for OC, anxious and depressive symptoms

<table>
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<td>857</td>
</tr>
</tbody>
</table>
If marital resemblance is due to marital interaction, we expect the \( r_{12} \) to be larger than \( r_{12\text{spouse}} \) as spouses in the young adult sample are 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 duration 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 sympotms, \( r_{12} \) and \( r_{12\text{spouse}} \) were calculated. The highest correlation was found across OC, anxious and depressive symptoms at once, using the conditional path method (Carey, 1996). For this method, the observed matrix of correlations decomposed into five matrices: (1) the matrix of correlations within husbands (Rh); (2) the matrix of correlations within wives (Rw); and (3) the matrix of correlations between the disorder scores of husbands and the disorders of wives (Di). 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 young generation, suggesting absence of marital interaction. This is confirmed by the fact that no significant correlation was found across generations \( r_{12\text{spouse}} > r_{12} \), and the correlations \( r_{12\text{spouse}} > r_{12\text{spouse}} > r_{12\text{spouse}} \) are expected.

If the expected pattern of correlations is similar to those of DZ families for cotwin-spouse and spouse1-spouse2 correlations of MZ families and DZ families show some variety of values across different types of twin pairs, especially when the number of twin pairs is lower (e.g. spouse2-spouse2). Correlations could not be distinguished from each other, making it impossible to distinguish between phenotypic assortment and social homogamy. For all four types of pairings correlations could be constrained to be equal across the five zygosity groups. Spouse similarity is small \( r_{12} \) but significantly \( 0 < r_{12\text{spouse}} < 0.01 \) higher than zero. Similarity among other pairs, i.e., \( r_{12\text{spouse}} > r_{12\text{spouse}} > r_{12\text{spouse}} \), is not significantly different from the correlation in the young generation, suggesting absence of marital interaction. This is confirmed by the fact that no significant correlation was found across generations \( r_{12\text{spouse}} > r_{12\text{spouse}} > r_{12\text{spouse}} \).

To study if marital resemblance occurs primarily within or across OC, anxious and/or depressive symptoms, \( r_{12} \) and \( r_{12\text{spouse}} \) were calculated. The highest correlation was found across OC, anxious and depressive symptoms at once, using the conditional path method (Carey, 1996). For this method, the observed matrix of correlations decomposed into five matrices: (1) the matrix of correlations within husbands (Rh); (2) the matrix of correlations within wives (Rw); and (3) the matrix of correlations between the disorder scores of husbands and the disorders of wives (Di). 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 young generation, suggesting absence of marital interaction. This is confirmed by the fact that no significant correlation was found across generations \( r_{12\text{spouse}} > r_{12\text{spouse}} > r_{12\text{spouse}} \), and the correlations \( r_{12\text{spouse}} > r_{12\text{spouse}} > r_{12\text{spouse}} \) are expected.
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 (CI)</th>
<th>Anxious symptoms (CI)</th>
<th>Depressive symptoms (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouse 1</td>
<td>0.50 (.48 - .52)</td>
<td>0.10 (.04 - .16)</td>
<td>-0.11 (-.19 - -.03)</td>
</tr>
<tr>
<td>Spouse 2</td>
<td>-0.13 (.10 - .17)</td>
<td>-0.04 (-.08 - .01)</td>
<td>0.07 (.02 - .12)</td>
</tr>
<tr>
<td>Parents</td>
<td>-0.50 (-.19 - -.03)</td>
<td>-0.10 (-.13 - -.07)</td>
<td>0.07 (.02 - .12)</td>
</tr>
</tbody>
</table>

DISCUSSION

This study examined the existence and possible cause of marital resemblance for OC, anxious, and depressive symptoms. Several important findings emerged that are relevant 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 (Tamsb, 1991; Zimmerman-Tansela & Lattanzi, 1991; McLeod, 1995; Mues et al., 1998; Galbaud du et al., 1998; Dubuis-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. Eagle et al. (1987) assessed anxiety in a population-based sample of elderly couples aged over 65. They actually found a small, but significant, correlation of .07. 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 previous 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 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 Mues et al. (1998). Results from direct assortment estimations,
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 we are the first study to report on these assessment estimations, replication of these later results are needed.

The present study attempted to test whether social homogamy or phenotypic assortment is the predominant source of psychiatric diseases, if we had information on the spouses of identical and fraternal twins. We found roughly the same pattern of correlations for OC, anxious and depressive symptomatology. Since the correlations are small with confidence intervals overlapping, we were unable to distinguish between social homogamy and phenotypic assortment processes. In the AE model, the bias in small samples is small, depending on the true heritability, amounts to up to 3%, for a marital correlation of r. The downward bias of an ACE model is more substantial. Using a formula to calculate r for phenotypic assortment (Martin, 1978), the bias for an AC model with an estimation of 40% for the proportion of variance explained by A, 20% for A and 40% for E is about 2%. For a marital correlation of r = 0.40, the mean that after correction the proportion of variance explained by A would be 50% and C 10%. In the present research, we found that if phenotypic assortment would completely explain this resemblance, the bias in estimates reported in twin studies on psychiatric diagnoses is likely to be very small. Interestingly, if gene (shared) environment correlation would be present, social homogamy would have consequences for the genetic structure in a population, but as 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. The spurious 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 information of the situation of the patient or discussing the role of the partner in a treatment plan but also to examine if psychiatric symptoms 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 general, the rate of divorce in subjects without interviewed partners is higher. Furthermore psychiatric pathology in divorced partners is increased (Maes et al., 1998; Wade & Careney, 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 = 89.1, 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 resemblance, partners are followed longitudinally, preferably starting shortly after having met their partner.

Third, although the measurements we used are well-known questionnaires showing satisfying psychometric properties, some limitations regarding these measurements have to be mentioned. First, we measured symptoms, no DSM diagnoses. This hampers the usefulness of the current study in clinical practice and comparability with studies based on DSM diagnosis. Nevertheless, findings from the current study are remarkably comparable with the study of Maes et al. (1998), who used DSM-III-R diagnoses. Second, distributions of the measurements used were skewed, which may cause underestimation of correlations. Derks et al. (2004) showed that use a threshold model estimate polygenic correlations could be a solution, but this has the disadvantage of losing power. We therefore chose to use the raw data. Third, the reliability for cross-sectional assessments 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 comorbidity, the question remains if the intercorrelations are caused by comorbidity or by overlapping instruments. Interestingly, Maes et al. (1998) found similar intercorrelations 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.


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 transmission.

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. Shared environmental influences played a relevant role (exceeding 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 of 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 (Boomsma et al., 1995; Nestadt et al., 2000). The resemblance between relatives can be due to genetic transmission, environmental similarities, cultural transmission, assortative mating from one generation to the next, social interactions between family members, or a combination of these mechanisms. When one wants to study causes of familial resemblance within first-degree relatives, such as parents and their offspring, or siblings reared together, it is not possible to disentangle shared genetic from (i.e. family) environmental effects. With a twin design in which data of monozygotic (MZ) and dizygotic (DZ) twins are obtained, the influence of shared environment can be made, since monozygotic twins share all, or nearly all of their DNA, while dizygotic (DZ) twins share only 50% of their segregating genes (Plomin et al., 2002; Boomsma et al., 2002a). Therefore, more resemblance between MZ than between DZ twins is suggestive of genetic influences on familial resemblance.

Although adult twin studies have evolved from case-studies with patients with OCD into large samples of unselected subjects using the whole distribution of OC Symptoms (van Grootheest et al., 2005), no study has used the extended parent-twin design yet. Clifford et al. (1984) examined 419 twin pairs of monozygotic (MZ) and dizygotic (DZ) twins with the Leyton Obses

sion Rating Scale (LORS). The heritability of OCS was estimated to be 47%. Another study using unselected adult twins was published by Jonnal et al. (2000). They examined 527 female twin pairs and carried out a factor analysis on 20 Padua Inventory items. Two major factors were used in the genetic analysis, one factor described the total symptom load and the other described the severity of the symptoms. The factor analysis did not produce any significant findings. Heritabilities of 33% and 26% were estimated for MZ and DZ twins, respectively. Recently, van Grootheest et al. (2007b) obtained data from the Young Adult Self Report Obsessive-Compulsive Sub

scale (YASR-OCS) 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.

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 non-clinical samples, the sample was extended including the control group (6.6 ±5.6; p < .0001 in both comparisons). In table 2 the minimum, maximum and mean scores and SD can be found for the PI-R ABBR for twins, siblings and parents.

Statistical modeling

In the classical twin study, the relative contribution of genes and environment to phenotypic variation is estimated from their respective variances, covariances, or covariances. When DZ twins are alike as MZ twins, phenotypic variation is caused by shared and unique environmental factors. The more similar MZ twins are relative to DZ twins, the more phenotypic variabil

ity is caused by genetic factors. Additive genetic effects (A) represent the addictive effects of alleles (possibly at multiple loci), and are assumed to be perfectly corre

lated in MZ twin pairs, as they have the same DNA se

quence. DZ twins and siblings share on average half of their segregating genes, therefore the genetic correlation

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 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 samples 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 sib

lings 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 ABBR) was included (Cath et al., 2008), derived from the Padua In

ventory-Revised (PI-R), which is a widely used self report inventory on obsessive-compulsive symp

toms. The PI-R is translated into Dutch, revised and validated by Van Oppen et al. (1995). The PI-R ABBR is shown in table 1. To investigate its psychometric qualities psychometric analyses have been conducted in three groups (Cath et al., 2008) derived from an earlier study by van Oppen et al. (1995). Cronbach’s α of the scale was 0.73, which is an indication of good inter

nal consistency. The sensitivity and specificity for the 12 items to detect OC disorder in current psychiatric, when comparing a group of OCD patients with clini

cal controls (Cath et al., 2008). Analyses of Variance (ANOVA) of PI-R ABBR scores revealed a significant main group-between effect (p < .0001). Post-hoc t-tests showed that the mean PI-R ABBR OC score for the OCD group (20.7 ± 8.1) was significantly higher than the control group (6.6 ± 5.6; p < .0001 in both compar

isons). In table 2 the minimum, maximum and mean scores and SD can be found for the PI-R ABBR for twins, siblings and parents.
When I see a train approaching I sometimes think I could throw myself under its wheels. My thoughts constantly go astray, therefore I find it difficult to attend to what is happening around me. In certain situations, I am afraid of losing my self-control and doing embarrassing things. When I start thinking of certain things, I become obsessed with them. I get upset and worried at the sight of knives, daggers and other pointed objects. I feel I have to repeat certain numbers for no reason. Impulses take over, and I cannot get rid of them. I return home to check doors, windows, drawers etc., to make sure they are properly shut. I sometimes have to wash or clean myself dimply because I think I may be dirty or ‘contaminated’. I check and recheck gas and water taps and light switches after turning them off. Unpleasant thoughts come into my mind against my will and I cannot get rid of them. I check, and even if I know I have done so, I have to check again. I return home to check doors, windows, drawers etc., to make sure they are properly shut. I sometimes have to wash or clean myself dimply because I think I may be dirty or ‘contaminated’. I feel I have to repeat certain numbers for no reason. Impulses take over, and I cannot get rid of them. I return home to check doors, windows, drawers etc., to make sure they are properly shut. I sometimes have to wash or clean myself dimply because I think I may be dirty or ‘contaminated’. I check, and even if I know I have done so, I have to check again. I return home to check doors, windows, drawers etc., to make sure they are properly shut. I sometimes have to wash or clean myself dimply because I think I may be dirty or ‘contaminated’. I feel I have to repeat certain numbers for no reason. Impulses take over, and I cannot get rid of them.
women describes 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 without a substantial loss of fit.

The best-fitting model (model 3) estimated the heritability of OC symptoms for men at 1%, the effect of shared environmental factors (C) at less than 1%, shared environmental effects at 27% and non-shared environmental effects at 71% for Binder et al. (2008). 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., parental influences). We could not find evidence for a special twin environment as we could equalize DZM, twin-sibM and sib-sibM correlations, but did find significant evidence for cultural transmission. However, the variation explained by cultural transmission is minimal and the remaining nonshared environmental influence large. This would imply that the shared environmental influences (C) are mainly due to non-parental sources like 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 modelling from their parents (Maes et al., 2006).

As expected we found a significant influence of assortative mating, but because of the low spurious correlation, the bias in estimates caused by these correlations is minimal (van Grootheest et al., 2008). Together with the finding of a minimal effect of cultural transmission, and thus genetic-environmental 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 information for this phenotype. Note that the present design is not suited to uncover genetic-environmental correlations other than resulting form 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 genetic influences phenotype, or an active gene-environment correlation, where individuals seek or create environments correlated with their genetic background.

The results of this study should be interpreted in the context of several potential limitations. First, although the PADUA-ABBR showed a moderately high sensitivity and specificity in diagnosing DSM 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 reflects the end of a normal distribution, while OC symp- toms represent a milder form of the latter (OCD: 1995; van Oord et al., 2003; Kendler, 2005).

Second, the PADUA-ABBR 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). Therefore, we decided to use the continuous scales with the disadvantage of possibly underestimating the twin correlations, resulting in underestimating the genetic proportions and overestimating the nonshared proportions a bit.

If we compare the results of this study to other studies in the field, our findings are consistent with the findings of Cath et al. (2008). The results of this study do not support the hypothesis that the heritability of OC symptoms is high (Kendler, 2005). However, this conclusion is based on the findings of the OCQ-14 (Jonnal et al., 2000) and the OCQ-20 (van Grootheest et al., 1995). The OCQ comprises only general OC symptoms, whereas the OCQ-14 and the OCQ-20 also include subscales for OC rituals. The OCQ-14 and the OCQ-20 were developed for diagnostic purposes and thus do not fully capture the breadth of OC symptoms.

The present study is the first to report on the heritability of OC symptoms in male twins. The results of this study are consistent with the findings of Cath et al. (2008), who found a low heritability of OC symptoms in female twins. The findings of Cath et al. (2008) are also consistent with the findings of van Grootheest et al. (1995), who found no significant contribution of cultural transmission to OC symptoms in twin families.

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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

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 same design, stability of OC behavior and genetic and environmental influences on OC behavior 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 OC 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., 2002a), 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 Child Behavior Checklist Obsessive-Compulsive Scale (CBCL-OCS) (Nielsen et al., 2001; Hudziak et al., 2006) used the CBCL-OCS to determine the prevalence of OC 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 at ages 7, 10 and 12. These heritabilities are in line with those from family studies, indicating that childhood onset OCD is highly familial (Pauls et al., 1995; Nestadt et al., 2008; Delorme et al., 2005; dos Rosario-Campos et al., 2008).

These data provided an epidemiologic perspective on prevalence and genetic architecture of CBCL-OCS, but did not examine stability and its underlying etiology. Knowledge about persistence, resilience, and new onset cases provides a framework to answer key clinical questions such as: If my child meets CBCL-OCS criteria for OCD at age 7, will (s)he continue to have OCD at age 12? If my child does not meet CBCL-OCS criteria at age 7, what are the odds that (s)he will meet these criteria at a Later age? Although genetic and unique environmental influences account for the expression of OC behavior at any given age, it is unknown which factors account for persistence. To date, research on persistence of OCD has concentrated on subjects who are patients. A recent meta-analysis on the long-term outcome of pediatric OCD, mostly adolescents, with 521 participants from 16 different study samples, found a persistence rate of 41% for full OCD and 60% including subthreshold OCD (Stewart et al., 2004). Only two of the study samples in this meta-analysis were community samples (Beng et al., 1989; Vallieu-Ilaude, 1996). To our knowledge, no previous study has investigated persistence of OC or OC symptoms in a community sample of children in a younger age group.

The purpose of the present study was to gain insight into stability of CBCL-OCS scores and the etiology of this stability. Longitudinal data were analyzed from twin families in which both parents had rated OC behavior in 7, 10 and 12 year old twins. 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 environment) and variance that is explained by a unique perception of each parent on the behavior of their child (i.e. unique or rater specific phenotype). The common perception is not confounded by rater bias, e.g. the tendency of an individual rater to consistently over- or underestimate scores (Hewitt et al., 1992), or measure error. The unique phenotype leaves room for specific views of a certain rater, but may include both rater bias and measurement error. We sought answers to the following questions:

1. What is the stability of OC behavior in children over time?
2. To what extent do early cases remit, do new cases emerge, and do other cases persist? 
3. To what extent do genetic or environmental influences account for stability of OC behavior?

METHODS AND MATERIALS

Subjects and procedure

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 Twin 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 - 1990, 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). Parents who 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 64% 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 final study sample consists of 8083 twin 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 543 twin pairs at age 7, 317 pairs at age 10 and 178 pairs at age 12. Maternal ratings were available in 1057, 1272 and 558 twin 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 age 7, 10 and 12. For mother rat- ings, 1348 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 age 10 and 12. For father rat- ings, 1348 twin pairs participated at age 7, 10 and 12, 1367 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 sample attrition on the results at ages 10 and 12 are accounted for by inclusion 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 remaining same-sex twin pairs, zygosity was determined by questionnaire. This was particularly true about phenotyping and frequency of confusion of the twins by family and strangers (Rietveld et al., 2006).

Table 1. Sample sizes (N), means (M) and standard deviations (SD) for CBCL-OCS in 7, 10 and 12-year-old twins by zygosity and raters

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>M</th>
<th>M (SD)</th>
<th>M (SD)</th>
<th>M (SD)</th>
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</thead>
<tbody>
<tr>
<td>Mzm</td>
<td>376</td>
<td>105.9</td>
<td>169.6</td>
<td>88.5</td>
</tr>
<tr>
<td>Dzm</td>
<td>315</td>
<td>109.7</td>
<td>163.2</td>
<td>111.0</td>
</tr>
<tr>
<td>Mzf</td>
<td>376</td>
<td>118.0</td>
<td>181.5</td>
<td>148.2</td>
</tr>
<tr>
<td>Dzf</td>
<td>309</td>
<td>108.6</td>
<td>148.0</td>
<td>103.0</td>
</tr>
</tbody>
</table>

Note: Mzm, monozygotic male; Dzm, dizygotic male; Mzf, monozygotic female; Dzf, dizygotic female. Biochemical markers for gender were used from birth.

Measures

The Child Behavior Checklist (CBCL) (Achenbach 1991, Verhulst et al., 1996) is a widely used ques- tionnaire for parents. It includes 120 items about prob- lem behaviors exhibited by the child over the previous 6 months. The parents respond to a 3-point scale (0 if the item is not true of the child, 1 for sometimes true, and 2 if the item is often true). The characteristics and
psychometric stability of the CBCL have been well established (Achenbach 1991; Verhulst et al., 1996). OC behavior 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 determined OCD 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., 2008).

### STATISTICAL ANALYSES

#### Descriptives and correlations

Means, standard deviations and the effects of sex, rater and zygosity 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-twin longitudinal correlations (phenotypic stability of CBCL-OCS), within person-inter parent correla-
tions (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 age 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 cross-rater correlations) are used to investigate the under-
lying developmental patterns of the distinct common and rater specific variance components.

#### Genetic Modeling

In the classical twin design the relative contribu-
tions of genetic and environmental factors to individ-
ual 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 en-
vironmental (E) factors (Boomsma et al., 2002b). Addi-
tive 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 depend on zygosity, 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 per-
ceded by both parents (the 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 consid-
ered 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 raters must have been assessing a “real” but unique aspect of the child’s behavior. Error and/or unreliability (the unique or rater-specific phenotype). In this model, the unique or rater-specific factors correlate 1.0 in both MZ and DZ twins.

#### RESULTS

#### Descriptive statistics

Table 1 summarizes the means and standard devi-
ations for the CBCL-OCS by age and sex in mothers and fathers. Mothers reported significantly more OC symp-
toms than fathers for both boys and girls, except for female DZ twins at age 12 ($\chi^2(1) = 50$, p = .048).

No significant differences between boys and girls. No differences between zygosity groups were found with the exception of age 7. At that age, DZ female twins had a mean score of 7.8, while DZ male twins had a mean score of 4.6, 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-off 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 identify 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 the same result (not shown) as for mothers, using a cutoff of 5.
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 3. Pheno typic correlations for mother and father ratings. Correlations for boys and girls are reported below and above diagonal respectively.

Table 4. Within age twin correlations (diagonal) and across-age twin correlations (off-diagonal) by sex and zygosity for mother and father ratings. Correlations for boys and girls are reported below and above diagonal respectively.

Table 5. Cross-twin cross-rater correlations within age (diagonal) and across age (off-diagonal) by sex and zygosity. Correlations for boys and girls are reported below and above diagonal respectively.

Genetic Modeling

Rater (Dis)agreement of OC Behavior

Table 6 gives the percentages of the genetic, shared and non-shared environmental contributions to the variances (diagonal) and covariances across time (off-diagonal) of the CBCL-OCS for the common phenotype and the rater-specific phenotype based on the longitudinal analyses for boys (below diagonal) and girls (above diagonal). In table 6, common and unique variance or common and unique covariance add up to 100%. There were no influences from C on rater-specific ratings, ($\Delta^2 = 0$). The influence of additive genes (A) was significant. The influence of additive genes (A) was significant for both the common and the rater-specific phenotype.

Table 7 gives the percentages of variance explained by genetic influences (A), environmental influences shared by twins (C) and non-shared environment (E). These are given for the total variance (diagonal), shared cells and total covariance (i.e. stability, off-diagonal).
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%.

<table>
<thead>
<tr>
<th>Age</th>
<th>A</th>
<th>C</th>
<th>E</th>
<th>A</th>
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<td>42</td>
<td>13</td>
<td>7</td>
<td>65</td>
<td>42</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Age</th>
<th>A</th>
<th>C</th>
<th>E</th>
<th>A</th>
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DISCUSSION

This is the first longitudinal twin study of stability of OCS in children from ages 7 to 12. It has focused on stability of childhood OB behavior and on the underlying etiology of this stability. By using both paternal and maternal ratings with large sample sizes we could examine differences between mothers and fathers in the ratings of their children, identify that aspect of the phenotype that both parents agree upon, and identify possible rater bias. Several important findings emerged that are relevant to both clinical practice and future research.

What is the stability of OB behavior in children over time?

In comparison with other phenotypes, OB behavior showed a moderate degree of stability of .50. Bartels et al. (2004b) found a mean phenotypic correlation over time of about .60 for internalizing problem behavior. To what extent do early cases remit, do new cases emerge, and do others persist? To what extent do early cases remit, do new cases emerge, and do others persist? To what extent do early cases remit, do new cases emerge, and do others persist? To what extent do early cases remit, do new cases emerge, and do others persist?

What does the stability of OB behavior indicate about the potential for treatment?

This is conform Stewart et al. (2004), who found sex to be a significant predictor of persistence in OCD. If sex differences in prevalence of pediatric OCD are reported by others, boys outnumber girls, but this is mostly due 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 symptoms are present and may persist into adolescence.

To what extent do early cases remit, do new cases emerge, and do others persist?

When we analyzed categorical stability, we found that very few children who meet cutpoint criteria at one age will meet it at the next. We found evidence of persistence to be rare and emergence of new cases and resilience being more common. These data are consistent with those of others who indicate that many children with OCD remit or recover (Stewart et al., 2004). However, these data, taken together with the stability data provided by the quantitative analyses, also point to the weakness of using cutpoint approaches in phenotypes that appear to be quantitatively distributed. Children who initially scored at or above the cutpoint (5) and scored just below the cutpoint at a later age would categorically represent a remitted case and quantitatively be considered a typical child. However, all cases in table 2 who scored above the cutpoint at age 7 and scored lower than 5 at age 10, on average 50% had a CBCL-OCS score at age 10 of 5 or 4. When looking at interrater correlation across mothers and fathers using quantitative approaches, the degree of agreement is simply computed without concern for the cutpoint. Such approaches lead to increased power to test for agreement and disagreement.

We found neither sex differences in prevalence of CBCL-OCS (Hudziak et al., 2006), in OCD persistence. This is conform Stewart et al. (2004), who found sex to be a significant predictor of persistence in OCD. If sex differences in prevalence of pediatric OCD are reported by others, boys outnumber girls, but this is mostly due 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 symptoms are present and may persist into adolescence.

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In particular, fathers seem to add little extra information on stability of OC behavior. One might conclude that mothers are the mainstay of assessment for a long term 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 was found and kurtosis. Derks et al. (2004) showed that skewness in the data lead to biases in parameter estimates, i.e. underestimation of the shared environmental estimates and overestimation of the non-shared environmental estimates. One approach to deal with this problem is using a likelihood threshold model (Lynch & Walsh, 1998). For the long-term design of our study, however, a liability threshold model is practically not feasible.

Second, the genetic and environmental contribution report are for CRCL-OCs, not for clinical measures of DSM OCD. Although we have performed prior studies (Nelson et al., 2001; Hooft et al., 2006), replicated by others (Geller et al., 2006, Stochr et al., 2006), to demonstrate the validity, specificity, sensitivity and predictive power of the CRCL-OCs in DSM-IV OCD, it remains possible that the CRCL-OCs may over-identify in cases of general population samples. However, as we have shown, the quantifiable approach may be useful to identify children at risk for, but not yet expressing, DSM OCD.

Third, despite the fact that we used both maternal and paternal ratings, reliance on parental reports is still a limitation not easily corrected in children ages 7 to 12. Younghusband et al. (1991) data in this sample when they become adolescents may reveal age-specific effects as to be expected in candidate gene studies.

Fourth, one assumption underlying most twin studies is that the environmental and genetic latent factors show a continuous, normal distribution. Such distributions are implied to be hypotheses with no specific predictions for which small individual effects are found in the literature. Kendler et al. (2005) compared this assumption for self ratings of depression and found very little or no evidence of non-normality. It implies that there were no evidence that partici- pants with high depressive score may be qualitatively distinct. Although it is likely that this is also the case for OC symptoms/behavior, a psychiatric disease closely related to depression, we did not test whether the latent underlying factors are continuous.

Fifth, the findings of this analysis are predicted on the assumptions of the method used. These assumptions include absence of assortative mating and the assumption of environmental assumption (EEA). The EEA states that environmental influences are shared to the same extent by MZ and DZ twins. Meas et al. (1998) found that significant but moderate primary associations exist for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of association is negligible. Jonnal et al. (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated.

Implications

Our study has implications for clinical inter-vention. First our data, consistent with those of others, points to the fact that OC behavior is not an unstable condition for which remission from ‘clinical deficiency’ is a relatively common phenomenon. These data allow a clinician to have diagnostic optimism when a parent 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 the phenotype structure. Put simply, this finding argues strongly for changing the environment in children so that obses- sions and compulsions will diminish (e.g. move kids out of the room), for example by involving family members in the treatment of OC (Renshaw et al. 2005).

Furthermore, this study has implications for meas-urement of environmental influences. In traditional heritability analyses, combining father and mother data adds extra information, suggesting that researchers studying children’s behavior problems in a cross-sectional design 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 lon- gitudinal research with multiple rating on different phenotypes are necessary to see if this is only the case for OC behavior within a clinical setting this could mean that both rating parents 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 term view.

Lastly, this research has implications for molecu- lar genetic research. Within the common phenotype of OC behaviour the same genes influence OC behaviour throughout life and ontogeny. It suggests that one may pool data from children of different ages together in link- age-analyses, obtaining an increase of power, and that no age-specific effects are to be expected in candidate gene studies.

REFERENCES


CHAPTER 8
Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at age 12, 14 and 16

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 ObsessiveCompulsive (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, girls had more OC symptoms. At all ages, genetic factors 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 Symptom Disorder (OCS) a distinction should be made between symptoms expressed as a result of a disease process, or part of a disorder such as a neurodevelopmental disorder or autistic spectrum disorder (Delorme et al., 2005; Chabane et al., 2005). Early age of onset of OCD is associated with tic disorder (Swedo 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 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 etiologic 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. It is important to recognize that 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 Grootenhuis 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-compulsive symptoms. This factor is estimated to be .92 for OCD and .64 for OCs for siblings of OCD probands and the morbidity risk for OCD in family members of OCD subjects with early-onset of OCD is .69. The YASR-OCS makes use of the same 8 items and showed a Cronbach's alpha of .67 within the current adolescent population (all ages taken together). Both the YASR-OCS and YASR-OCS have the same format as the CBCL-OCS (Nelson et al., 2001), except that YASR and YASR-OCS are worded in the first person. The CBCL-OCS showed high sensitivity and moderate specificity in predicting DSM-IV diagnosis of OCD in children and adolescents in several studies (Nelson et al., 2001).

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?

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) (Boomsma et al., 2006; Bartels et al., 2007). We analyzed data from twin pairs who reported on their behavior with the Dutch Twin Reference Obsessive Compulsive Scale when they were 4, 7, 10, 12, 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 polymorphism 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., 2000).

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., 2001), and then tested on self-report data in the Young Adult Self Report, the YASR-OCS (van Grootenhuis et al., 2007b). The YASR-OCS measures from 8 items: 2 for 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:

<table>
<thead>
<tr>
<th>YSR Item no</th>
<th>YSR Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>I am afraid I might think or do something bad</td>
</tr>
<tr>
<td>32</td>
<td>I feel I have to be perfect</td>
</tr>
<tr>
<td>52</td>
<td>I feel too guilty</td>
</tr>
<tr>
<td>66</td>
<td>I repeat certain acts over and over</td>
</tr>
<tr>
<td>84</td>
<td>I do things other people think are strange</td>
</tr>
<tr>
<td>85</td>
<td>I have thoughts that other people would think are strange</td>
</tr>
<tr>
<td>112</td>
<td>I worry a lot</td>
</tr>
</tbody>
</table>

The American sample showed a heritability of 55%. Small but significant shared environmental influences were seen at age 12 in the Dutch children. Significant sex differences in heritabilities were only seen in the USA data. Bolton et al. (2007) assessed 854 6-year old British twin pairs by maternal informant diagnostic interviews using DSM-IV criteria. The heritability estimate was at 47% for sub-threshold OCD. The study lacked the statistical power to distinguish between shared genetic and environmental factors to explain the familial aggregation. Lastly, follow-up studies by Hudziak et al. (2004) study the genetic and environmental etiology of preadolescent childhood and another peak in adult life. The results of early age at onset of OCD is associated with familial factors contributed signifi- cantly (.50) for boys and for girls was found. Stability of OC behav- ior was influenced by genetic factors, by environmental factors shared by children growing up in the same family, and by non-shared environmental factors. Shared environ- ment was observed to be important especially at age 12.
### 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 environmental influences not shared by members of a family (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.

The relative importance of each component is obtained by inspecting the twin correlations. MZ correlations twice as high as DZ correlations indicate additive genetic influences, while MZ and DZ correlations higher than half the MZ correlations design environmental influences in addition to genetic influences. MZ correlations as high as DZ correlations indicate only shared environmental influences and no genetic sources of variance.

### 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(1)=21.6, p = .04). However, at ages 14 and 16, the thresholds were significantly lower for girls (χ²(3)=43.94, p < .001) and χ²(3)=42.37, p < .001) reported by girls compared to boys on the YSR-OCS at the age of 14 and 16.

Polytrophic twin correlations are presented in table 3 as a function of sex. It seems evident that environmental factors seem to be of importance, because MZ correlations are less than twice the DZ correlations. Except for boys at age 16, with MZ correlations smaller than twice the DZ correlations, at age 14 and 16 MZ correlations are clearly about twice the DZ correlations, indicating the influence of genetic factors, but not of shared environment. The twin correlations in opposite-sex twin pairs were not attenuated compared to the correlations in same-sex dizygotic twin pairs (all p-values > .05) at three different ages. This means that there is no indication for sex-specific genes influencing variance in YSR-OCS scores.

Model-fitting results are given in table 4. Starting from the saturated threshold model, the full ACE model with sex differences in variance components fits the data well at all ages (all p-values > .05). From the full model we constrained the estimates for additive genetic, shared environmental and non-shared environmental factors to be equal across the sexes. At all ages this model did not worsen the fit (all p-values > .05), meaning that the relative effects of these components were the same in boys and girls.

At age 12, the ACE model without sex differences gave a standardized estimate of .27 for genetic variance and .18 for shared environmental variance. We fitted both an AE and a CE model. Both models fit the data, although the AE model (χ²(1)=2.16, p = .15) fitted slightly better than the CE model (χ²(1)=3.5, p = .06). A closer look at the AIC fit index showed that the ACE model without sex differences fit the data the best, suggesting that both genetic and shared influences play a role in individual differences in OC symptoms, regardless of sex.

In 1997, Neale and Cardon (1997) showed that genetic and environmental factors play a role in individual differences in OC symptoms, regardless of sex. In 1998, ages 14 and 16 the estimates of the shared environmental variance were zero. An AE model was the best fitting model for the data. Individual differences

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

<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>Cohrnbah's alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al., 2003</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>79.3% 84.9% (depending on percentile scores)</td>
<td>72.8% 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 Nelson et al.)</td>
<td>See Nelson et al.</td>
<td>92% (using a cut-off of 5)</td>
<td>67% (using a cut-off of 5)</td>
<td>See Nelson et al.</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>

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

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Age 12</th>
<th>Age 14</th>
<th>Age 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete twin pairs</td>
<td>Complete twin pairs</td>
<td>Complete twin pairs</td>
<td>Complete twin pairs</td>
</tr>
<tr>
<td>MZM</td>
<td>140</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>DZM</td>
<td>118</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>MZF</td>
<td>162</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>DZF</td>
<td>124</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>DOS</td>
<td>162</td>
<td>21</td>
<td>172</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Sample</th>
<th>Type of model</th>
<th>-2LL</th>
<th>AIC</th>
<th>Compared with model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>Girls</td>
<td>a²</td>
<td>e²</td>
<td>a²</td>
</tr>
<tr>
<td>Age 12</td>
<td>Full saturated</td>
<td>3935.9</td>
<td>26.0</td>
<td>57.0</td>
</tr>
<tr>
<td></td>
<td>ACE sex</td>
<td>3954.8</td>
<td>15.3</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>3958.0</td>
<td>3.2</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>3960.5</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>3960.5</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>3936.0</td>
<td>3.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>3943.4</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>4932.4</td>
<td>12.3</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>4935.7</td>
<td>12.3</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>4941.6</td>
<td>3.2</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>4936.9</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>5246.2</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>5246.0</td>
<td>4.9</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>5262.7</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>5262.7</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>ACE no sex</td>
<td>5262.7</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Notes

- Age 12
- Age 14
- Age 16
- Full saturated
- ACE sex
- ACE no sex
- Full saturated
- ACE sex
- ACE no sex
- Full saturated
- ACE sex
- ACE no sex
es in OC symptoms were explained by additive genetic influences (57% and 54% at age 14 and 16 respectively) and non-shared environmental effects (43% and 46% at age 14 and 16 respectively). Next we tested if genetic and non-shared environmental influences were of the same magnitude for adolescents at 14 and 16 years of age. At both ages genetic influences accounted for 55% of the variation in OC symptoms and non-shared environmental influences were estimated to account for 45% (g2) = 0.253, p = 0.61.

**DISCUSSION**

To our knowledge, this is the first twin study of OCs in adolescents, revealing that individual differences in OCs across adolescence are heritable, with shared environmental influences only playing a role at the beginning of adolescence. No sex differences in heritability estimates or 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 OC 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 clinical samples with OCD, where boys are often twice as frequent as girls (Boomsma et al., 2007).

To our knowledge, this is the first twin study of OCs in adolescence across puberty, with shared environmental influences only playing a role at the beginning of adolescence. No sex differences in heritability estimates or 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 OC 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 clinical samples with OCD, where boys are often twice as frequent as girls (Boomsma et al., 2007).

**REFERENCES**


van den Oord et al. (2003), Kendler, 2005). Since the current twin analyses are based on a liability threshold model, it should make no difference if the studied variable is dimensional, as long as it reflects the same underlying liability as the categorical diagnosis (Reichborn-Kjennerud et al., 2007).

Second, the use of twin models requires several assumptions, including the absence of assortative mating, the equal environment assumption to be important (ap self reports. Van Grootheest paper. Note that the study of Hudziak who used essentially the same sample as the current study of OCs in adolescents is in line with a recent study using the YASR-OCS within childhood (van Grootheest et al., 2007), a well-known stressful event (Sriram, 2003). When leaving the old school to enter the new, children leave their old peer group to build up a new one, and therefore rely more on family life than before. Considering the demands in this transitional period, families may differ in their ability to effectively deal with stress. Gene-environment interaction could affect twin similarity in either direction depending on whether both twins are exposed to the specific environmental factor in question. Questioning our knowledge, gene-environment interaction and/or correlation have yet to be demonstrated for the phenotype studied.

Thirdly, the 8-item YSR-OCS is robust to examine OC symptom dimensions. More and more evidence is coming out that OCD or OCS appears to encompass at least four consistent and temporally stable symptom dimensions (Mataix-Cols et al., 2005). By considering these OC symptom dimensions as quantitatively continuous and 45% in adult samples with obsessive-compulsive phenotype, dimensional approach could provide a more powerful approach for the detection of genes or environmental risk factors that contribute to OC behavior (van Grootheest et al., 2005). We recently found evidence for specific genetic and environmental factors underlying the Contamination subscale of the Y-BOCS (van Grootheest et al., 2008a), and scoring the potential value of OC symptom dimensions in this field of research (Leckman et al., 2007).

In sum, the present study suggests that heritability estimates of OC 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 OC symptoms. Sex differences in scores on OC symptoms were found, with girls scoring higher than boys on OC symptoms at age 14. **Future studies will focus on the age period from adolescence to adulthood. The current study underscores the importance of conducting more research to OC symptoms in the adolescent period.**
CHAPTER 9
Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register

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 (VASR-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 analyzed 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 .39 and .61 for subsequent 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 chronic and lifelong with waxing and waning symptom severity (Goodwin et al., 1969). More recent studies on the course of OCD have found that OCD is a chronic illness with low rates of remission (Rasmussen & Tasang, 1986; Eisen et al., 1999; Alosno et al., 2001), while some other studies showed less pessimistic findings with conclusions that about 50% of patients remit (Or et al., 2005; Angst et al., 2004) followed 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., 2002b; Boomsma et al., 2006). Since 1991, every two to three years twins and their families have received a survey mail containing questions about health, personality and lifestyle. For the present study, we included OC data of adolescent and adult twins from wave 1991, 1995, 1997 and 2002. Table 1 gives an overview of the complete and incomplete twin pairs included in our study, presented by sex and by time-point and zygosity. The total sample consists of twins from 418 different families. Four hundred and forty-nine twin pairs participated at 1991 and 58 at time-point 1995, 102 twin pairs participated twice; 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 effect 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, 25.5 (SD 9.8) in 1997 and 33.0 (SD 13.5) in 2002.

Zygosity of the twins was determined using eye color similarity and the frequency of confusion of the twins by family and strangers. Of 869 same sex twin pairs, zygosity information was available from DNA polymorphisms. The agreement between zygosity information from the questionnaire and DNA data was 97% (Willemsen et al., 2000).

Measures

At wave 1991, 1995 and 1997, OC symptoms were measured with the Young Adult Self Report Obsessive-Compulsive Subscale (VASR-OCS) (van Goothest et al., 2007b). At wave 2002, OC symptoms were measured with the Padua Inventory abbreviated (PADUA ABBR) (van Goothest et al., 2007b). The Boy's Achenbach System of Empirically Based Assessment (BASC-2) (Achenbach, 1991) is a 41 item self-report instrument that measures OC items from the YASR, and is similar to the CBCL-YSR. The agreement between zygosity information from the questionnaire and DNA data was 97% (Willemsen et al., 2000).

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

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Complete twin pairs</th>
<th>Incomplete twin pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZM</td>
<td>272</td>
<td>275</td>
</tr>
<tr>
<td>DZM</td>
<td>231</td>
<td>123</td>
</tr>
<tr>
<td>MZF</td>
<td>380</td>
<td>342</td>
</tr>
<tr>
<td>DZF</td>
<td>280</td>
<td>258</td>
</tr>
<tr>
<td>DOS</td>
<td>473</td>
<td>453</td>
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</tbody>
</table>

MZM, monogygotic males; MZF, monogygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, opposite sex pair.

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<tbody>
<tr>
<td>MZM</td>
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<td>19.7</td>
<td>19.8</td>
<td>20.4</td>
<td>2.6</td>
<td>3.1</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>DDM</td>
<td>17.6</td>
<td>19.7</td>
<td>19.8</td>
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<td>3.0</td>
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</tr>
<tr>
<td>MZF</td>
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<td>19.7</td>
<td>19.8</td>
<td>20.4</td>
<td>2.6</td>
<td>3.1</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>DZF</td>
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<td>19.7</td>
<td>19.8</td>
<td>20.4</td>
<td>2.6</td>
<td>3.1</td>
<td>3.0</td>
<td>2.8</td>
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Correlations decrease with increasing distances between time-points (Boomsma & Molenberghs, 1997). Figure 1 represents the simplex model, because of space limits only for 3 time-points. It includes causal pathways or transmission effects (β) in figure 1) between genetic (A) or environmental (C or E) latent factors that influence the trait at different occasions. As a result, genetic or environmental factors (A, C or E) at a particular time-point are influenced by factors preceding that time-point. Furthermore, the model includes innovations (ε in figure 1) (Neale & Cardon, 1992). The innovation is that part of the latent factor that is not caused by a latent factor at a preceding occasion. At the first occasion the first latent factor cannot be explained by factors associated with an earlier time-point, and therefore this factor itself is regarded as an innovation (van Beijsterveldt et al., 2003). In a genetic study, the genetic innovations represent the expression of a new set of genes.

The simplex model is also able to distinguish the non-shared environmental variance in measurement error (ε in figure 1) and “real” non-shared environmental innovations (εe in figure 1). There is an important conceptual distinction between innovations of latent variables and measurement errors of observed variables. The innovations are the part of the latent variable at a time that is not caused by the latent variable at time t-1, but are part of every subsequent observed variable, t+1. In contrast, the random errors of measurement are terms that do not influence subsequent observed variables (Cornes et al., 2007). In figure 1, the diamond shows the loadings of the observed phenotype on the latent factors. In the current study, these loadings were set to unity, so that the scaling of the latent factors is identical to the scaling of the phenotype. The variance of all measurement error terms was constrained to be equal in order for the model to be identified. Because at occasion 4, a different questionnaire was used with larger variance than in the first three occasions, the variance of measurement errors could not be constrained to be equal. We therefore constrained the first measurement error term to be equal and fixed measurement error term at occasion 4 to zero. This means that for time-point 4, the measurement error is included in the innovation at time-point 4.

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- en by a specific developmental hypothesis. The model is a saturated unconstrained model and it decomposes a covariance matrix into genetic and non-genetic covariance 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 YASR-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 (χ²(8.74)=2.8, p<.01). At that time-point DZ men scored higher on the VAS-OCS than MZ men. Significant sex differences were seen at time-point 1991, 1995 and 1997 with women scoring higher on the YASR-OCS than men (all p<.01). At time-point 2002, women seem to score higher on the PI-R ABBR, but this was non-significant (χ²(4.87)=2.0, p<.01). The sex pattern is also seen for the variances, significant variance differences between men and women for the first three time-points (all p<.01) and a non-significant difference for the last time-point (χ²(4.04)=1.0, p=.48).

Table 3 shows the within-person phenotypic correlations over time for men and women. OC behavior was moderately stable with correlations between .39 and .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>0.48</td>
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</table>

Correlations for men and women are reported below and above diagonal respectively.
over 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-point 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 suggests that both genes and non-shared environmental influences explain individual differences in OC symptoms. Only at time-point 2002 and only in men, the DZ correlations are close to the MZ correlation, suggesting the influence of shared environment at that time-point. Cross-twin-cross-time-point correlations represent the correlations 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 between first-born and second-born twins are constrained to be equal whereas correlations between second-born and first-born twins. As can be seen, for almost all cross-correlations the MZ correlations are higher than DZ correlations, indicating the influence of genes on covariance of OC symptoms across time-points.

Genetic analyses

Table 5 displays the results of model fitting analyses conducted to test which model best described the data. The simplex model fitted very well against the Cholesky analyses, indicating the influence of genetic factors on covariance relations. The MZ correlations are higher than DZ correlations in both men and women. The mean square root (RMSE) of the model without sex differences. The fit of the model was compared with the model without sex differences. The fit of the model without sex differences deteriorated significantly (model 4 in Table 5), because of covariance differences between men and women. This means that the AE simplex model with sex differences is the best fitting model (bold in Table 5).

Figure 2 shows the unstandardized estimates of the final model. These estimates can be used to compute the relative contributions of A and E to the time-point specific total variances and stability coefficients. The genetic contribution to OC symptoms at each time-point consisted of genetic influences novel to that time-point (=innovation effect, italics in figure 2), plus the genetic influences that were already present at a previous time-point (=transmission effect, bold in figure 2). The standardized innovation effect is achieved by dividing the genetic variance at time-point t by the total variance for men and women. The squares represent the observed variances at each time-point (OC1, OC5, OC an OC02). The circular representation indicates the genetic factors to the stability were small. The correlations in Table 7 indicate the degree of overlap between genetic and environmental influences at one age and influences at subsequent time-points. The additive genetic correlations are estimated between 0.63 and 0.82 for men between the first three time-points with correlations of 0.39 and 0.63 between the first three time-points and the last time-point. For women, the correlations varied between 0.80 and 0.90 between the first three time-points, and 0.49 and 0.61 for the last time-point. These high genetic correlations suggest that there is a high overlap between time-points of the same genetic influence in adulthood using the same scale, but somewhat lower between two different measures. This last finding was already reflected in the high genetic innovation at the last time-point in Figure 2.

The simplex model fitted very well against the Cholesky analyses, indicating the influence of genetic factors on covariance relations. The MZ correlations are higher than DZ correlations in both men and women. The mean square root (RMSE) of the model without sex differences. The fit of the model was compared with the model without sex differences. The fit of the model without sex differences deteriorated significantly (model 4 in Table 5), because of covariance differences between men and women. This means that the AE simplex model with sex differences is the best fitting model (bold in Table 5).

Figure 2: Unstandardized estimates of the simplex model for OC symptoms at four time-points for men (left) and women (right)
D I S C U S S I O N
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 not 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 variance explained 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., 1994). Stoessel & Skog, 1999; Steketee et al., 1999; Angst et al., 2004; Reddy et al., 2005). These studies suggested a relatively favourable 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 lifetime.

Interestingly, in our paper examining stability for OCs in children (van Grootheest et al., 2001), 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 in OC symptoms or behavioral problems at the highest in children, and low in 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 of 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 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 time, as every questionnaire has its merits and demerits and captures other pieces of information about the OC phenotype.

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 in account the small amount 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 trait, with the PI-R ABBR capturing some extra information.

Third, both the VASR-OCS and PI-R ABBR showcept 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 time, as every questionnaire has its merits and demerits and captures other pieces of information about the OC phenotype.

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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. (2004) found small, but significant assortative mating for OC symptoms but concluded that the bias in assortative mating is not substantial. The small amount of assortative mating is negligible. Jonnal et al. 2003) 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 specific 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 high heritability across the life span, which implies that in general the same genes influence OC symptoms over time.
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 monozygotic 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, childhood, current medical conditions and lifestyle, birth complications and early 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 birth weight in the discordant 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.

Obsessive-Compulsive Disorder (OCD) is characterized by anxious, intrusive, and anxiety-provoking intrusive thoughts, mostly in combination with repetitive distressing and anxiety-provoking actions. In the current study a twin design was used to study environmental factors that might protect against or exacerbate OC behavior. The aim of this explorative study was to replicate and extend the information from previous studies on both unique and shared environmental influences that might protect against or exacerbate OC behavior. Unique environmental factors were studied using within discordant MZ twin pair comparisons, whereas between-discordant MZ pairs were compared. Perinatal risk factors, such as prolonged labour and low birth weight, were found to be related to OCD in girls. Further, measures of anxiety, depression and personality were used to compare the parents of the concordant and discordant twin pairs, with the following reasoning: concordance between MZ twin pairs on OC behavior most likely results from genetic similarity between the twins of a pair. Thus, the contrasts between twin pairs who are concordant high and low reflect differences in genetic vulnerability to OC behavior. As a consequence, the parent scores on OC symptomatology and on neuroticism (the latter characteristics are known to be related to OC symptoms) are expected to reflect these differences in genetic vulnerability and therefore to be highest in the parents of the concordant high MZ pairs, to be intermediate in the parents of the discordant MZ pairs and to be low in the parents of the concordant low MZ pairs.

Finally, longitudinal measures of psychopathology were studied to investigate age at onset of OC symptoms, sex differences and age differences between concordant and discordant groups. Family studies have suggested that lower age at onset is associated with higher familiality, possibly reflecting higher genetic load (De Lorme et al., 2005). We hypothesized that the concordant high MZ twin pairs, in whom the OC symptoms are more severe, are more likely to have a lower age at onset than the high scoring twins of the discordant group in whom unique environmental factors might be more important.
I return home to check doors, windows, drawers etc., to make sure they are properly shut. In certain situations, I am afraid of losing my self-control and doing embarrassing things. I check and recheck gas and water taps and light switches after turning them off. I sometimes have to wash or clean myself dimply because I think I may be dirty or ‘contaminated’. I feel obliged to follow a particular order in dressing, undressing and washing myself. When I start thinking of certain things, I become obsessed with them. Unpleasant thoughts come into my mind against my will and I cannot get rid of them. Rumination

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

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<thead>
<tr>
<th>Original Factor</th>
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<tr>
<td>Checking</td>
<td>Precision</td>
</tr>
<tr>
<td>Precision</td>
<td>Impulses</td>
</tr>
<tr>
<td>Ruminating</td>
<td>Checking</td>
</tr>
<tr>
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</tr>
<tr>
<td>Washing</td>
<td>Impulses</td>
</tr>
<tr>
<td>Impulses</td>
<td>Washing</td>
</tr>
</tbody>
</table>

Rumination

On alcohol and smoking behavior, respondents were questioned about their consumption ever, in the past year and past month, as well as the number of cigarettes per week or gram of alcohol per day, respectively. Alcohol dependence was assessed using 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 (Schookwerkens Inventarisslijtlijst = SHEL) (van der Velde et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of self or a significant other; divorce/break-up of a relationship; traffic accident; violent or sexual assault or rape, and robbery. Response categories are: never experienced; 0–6 months ago; 6–12 months ago; 1–5 years ago, and more than five years ago.

Data on anxiety and depression were available at most time points between wave 1 and 6, and were assessed with the Spielberg State-Trait Anxiety Inventory, (Spielberger, et al., 1979; Van der Ploeg, 1979), and the Young Adult Self report, anxious-depressed subscale (Achenbach, 2000, Verhulst et al., 1997). Questionnaires between waves 1 and 4 (between 1991 and 1997) also contained the 8-item OC symptom subscale of the VASR (Nelson et al., 2001; Geller et al., 2006). Neuroticism, somatic complaints and extraversion were measured with the Amsterdamse Biografische Vragenlijst (ABV: Amsterdam Biographical Questionnaire) (Wilde et al., 1964). The ABV neuroticism and extraversion scores are very similar to the Eysenck Personality Questionnaire neuroticism and extraversion subscales (Eysenck and Eysenck, 1964), and contain answer categories: yes/no/don’t know. The satisfaction with life scale and the subjective happiness scale (Lewis and Joseph, 1995), a combined 10-item scale with scoring possibilities between 1 and 10 were taken, and the Rosenberg self-efficacy scale, a 10-item scale scoring between 1 and 4 (Rosenberg, 1965; Helsing, 1982). Socio Economic Status (SES) in 2002 was assessed as per the complexity of the work, ranging from low skilled (1) to complex control group (n=272) and a clinical OCD group (n=120), for an extensive description of the study groups (see van Oppen et al., 1995). Cronbach’s ρ of the scale was 0.73, which is an indication of good inter- and intraclass reliability. Analyses of Variance (ANOVA) of PI-R ABBR scores within the 5 groups revealed a significant main-between-group effect (p < .0001). Post-hoc t-tests showed that the mean PI-R ABBR score for the OCD group (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 < .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 carried out. ROC analyses use the association between sensitivity and specificity to derive an Area Under the Curve (AUC), which indicates how well a measure differentiates between OC cases (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 78% (95% CI = 73 - 83). When compared with the population controls, the AUC was 93% (95% CI = 90 - 95). At the best cut-off point of 16 (i.e., maximum difference between sensitivity and 1-specificity), the sensitivity, the specificity, the PPV, the NPV and the positive likelihood ratio was 74 with a specificity of .72, when compared with clinical controls. If the adult twins, 2672 twins, their family members and – in some instances - their spouses (a total of 9950 individuals) returned the survey. Monozygotic twin pairs were selected at random out 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 considered to be discordant when one twin scored >17 (in the clinical range), and his/her MZ twin sibling scored < 7 (popula- tion control range). Between 2000 and 2002, 24 pairs participated in waves 2, 3 pairs in 4, 3 pairs in 5, and 4 pairs in all six waves.

Measures and instruments

The NTR survey contains a broad range of longitudinal measurements taken at six time points between 1992-2002, as well as cross-sectional measure- ments. Information is obtained on life events, perinatal adversities, physical and mental health, lifestyle factors such as smoking and drug behavior, and on demographic variables such as, relationships, number of children, level of education, living situation, and work status. Since this is an ex- ploratory study, all available information was taken into account. The religiosity was assessed by asking whether the respondent had had a religious upbringing (yes/no), the person’s current religion, and whether the respondent currently was an active church member.

Within-discordant pair differences in concordant high pairs low pairs were calculated using paired t-tests (t-tests on alcohol and smoking behavior, respondents were questioned about their consumption ever, in the past year and past month, as well as the number of ciga- rettes per week or gram of alcohol per day, respectively. Alcohol dependence was assessed using 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 (Schookwerkens Inventarisslijtlijst = SHEL) (van der Velde et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of self or a significant other; divorce/break-up of a relationship; traffic accident; violent or sexual assault or rape, and robbery. Response categories are: never experienced; 0–6 months ago; 6–12 months ago; 1–5 years ago, and more than five years ago.

Statistical analyses

Within pair analyses. Within discordant pair differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests on alcohol and smoking behavior, respondents were questioned about their consumption ever, in the past year and past month, as well as the number of ciga- rettes per week or gram of alcohol per day, respectively. Alcohol dependence was assessed using 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 (Schookwerkens Inventarisslijtlijst = SHEL) (van der Velde et al., 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of self or a significant other; divorce/break-up of a relationship; traffic accident; violent or sexual assault or rape, and robbery. Response categories are: never experienced; 0–6 months ago; 6–12 months ago; 1–5 years ago, and more than five years ago.

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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., carcinogenic 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 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).

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 the high-group twin who had experienced sexual abuse between 1 and 5 years ago.

Longitudinal data

YASR-OC subscale scores, taken in 1997, 1999 and 1997, revealed significant differences between high and low-scoring twins of the discordant pairs in 1997 (p=0.007). Further, scale scores between 1997-2002 revealed significant within-pair differences on the YASR anxious-depression 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.

BELOW-PAIR ANALYSES OF CONCORDANT AND DISCORDANT PAIRS

Seventeen MZ twin pairs were included who were concordant high on OC behavior, of whom 14 pairs were female. Their mean age was 30.0 years (SD II.3 years), mean PI-R ABBR OC scores were 23.7 (SD 6.7). Thirty-four MZ twin pairs were included who were concordant low on OC behavior, of whom 28 pairs were female. Their mean age was 30.0 years (SD III.3 years), mean PI-R ABBR OC scores were 3.8 (SD 2.2).

Health and lifestyle characteristics (table 4)

The concordant group generally experienced the best health, with the discordant group scoring intermediate between high and low concordant groups. Members of the discordant group more often had a spouse than both concordant groups, 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 dismissed 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).
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 PI-R-ABBR (p's < 0.001), the YASR anxious-depressed scale (p's < 0.001), ABV neuroticism (p = 0.001 in high comparison; p = n.s. between high and discordant twin pairs), somatic complaints (p's < 0.001 and 0.003), and STAI-trait anxiety (p < 0.001). Further, the concordant high group had lower scores on ABV extraversion (p < 0.001), satisfaction with life (p's between 0.01 and 0.001), happiness (p < 0.001 and 0.008) and self-efficacy (p < 0.01) than the concordant low and discordant groups.

Shared environment influences (table 5)

Between-group analyses revealed that the discordant group had the lowest rate of cesarean sections (p's < 0.05 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 = non significant in all comparisons). There were no between-pair differences in the occurrence of parental death. The concordant 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 parents 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 < 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).

Parent data (Table 6)

Parent data were available for 66 persons; the 34 parents of concordant low twin pairs had a mean age of 53.6 years (SD 5.9), a PI-R ABBR mean score of 5.2 (SD 3.8); 9 parents of concordant high twin pairs had a mean age of 51.6 years (SD 2.5), and a PI-R ABBR mean score of 11.7 (SD 3.8); and 23 parents of discordant twin pairs had a mean age of 57.5 years (SD 6.9) and a

### Table 5. Between twin-pair comparisons: comparison of common environment characteristics (after correction for interrelatedness)

<table>
<thead>
<tr>
<th></th>
<th>Concordant low twin pairs Mean (SD)</th>
<th>Concordant high twin pairs Mean (SD)</th>
<th>Discordant twin pairs Mean (SD)</th>
<th>Low-high p-value</th>
<th>Low-discount p-value</th>
<th>High-discount p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarian section (yes)</td>
<td>N=5-pairs</td>
<td>n=5-pairs</td>
<td>n=4-pairs</td>
<td>n.s.</td>
<td>0.008</td>
<td>0.000</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2650 (876)</td>
<td>2685 (795)</td>
<td>2109 (736)</td>
<td>n.s.</td>
<td>0.004</td>
<td>0.009</td>
</tr>
<tr>
<td>Religious upbringing yes</td>
<td>N=45 (67%)</td>
<td>N=16 (47%)</td>
<td>N=34 (69%)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education level father* (1-13)</td>
<td>7.5 (4.8)</td>
<td>5.5 (3.7)</td>
<td>5.7 (3.5)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</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>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Death mother (0-2) yes</td>
<td>n=2 (2%)</td>
<td>n=3 (10%)</td>
<td>n=4 (8%)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Death father (0-2)</td>
<td>n=12 (39%)</td>
<td>n=7 (24%)</td>
<td>n=6 (12%)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</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>
<td>n.s.</td>
<td>n.s.</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>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>N parents drinking (ever; yes)**</td>
<td>91%</td>
<td>100%</td>
<td>74%</td>
<td>0.06</td>
<td>n.s.</td>
<td>0.04</td>
</tr>
<tr>
<td>N drinks/wk parents (2-7)**</td>
<td>3.5 (4-drinks/wk)</td>
<td>2.7 (3-drinks/wk)</td>
<td>2.3 (2-drinks/wk)</td>
<td>0.03</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
| N parents smoking ever (yes)** | 71% | 89% | 48% | 0.04 | n.s. | 0.06 

*Signified by two child-born parents. **Direct parent data. SD, Standard deviation. n.s., not significant.
**Table 6. Between-pairs comparisons of psychological scales**

<table>
<thead>
<tr>
<th></th>
<th>Means Comparison</th>
<th>p-value</th>
<th>Means Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parents concordant low</strong></td>
<td><strong>Parents concordant high</strong></td>
<td><strong>Parents discordant</strong></td>
<td><strong>High-low</strong></td>
<td><strong>Low-disorder</strong></td>
</tr>
<tr>
<td>PI-R ABBR OC scale</td>
<td>5.2 (3.8)</td>
<td>11.7 (3.8)</td>
<td>9.9 (3.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>YASR anxious depression scale</td>
<td>4.5 (3.5)</td>
<td>11.7 (4.2)</td>
<td>7.7 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI-R ABBR OC scale</td>
<td>53.4 (37.5)</td>
<td>64.9 (32.9)</td>
<td>62.4 (31.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>AVB examination</td>
<td>36.6 (24.5)</td>
<td>79.2 (24.5)</td>
<td>62.7 (17.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVB somatic complaints</td>
<td>16.3 (4.5)</td>
<td>21.2 (6.6)</td>
<td>26.9 (2.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>STAI-trait</td>
<td>29.5 (6.7)</td>
<td>44.1 (7.1)</td>
<td>47.7 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Satisfaction with life</td>
<td>25.5 (10.5)</td>
<td>38.6 (9.5)</td>
<td>25.5 (7.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Happiness</td>
<td>23.3 (5.5)</td>
<td>26.0 (6.9)</td>
<td>15.1 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>32.1 (3.8)</td>
<td>28.0 (4.2)</td>
<td>25.3 (5.6)</td>
<td>&lt;0.001</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 discordant scored higher between the parents discordant twins of the concordant low and high pairs on anxious depression, satisfaction with life, happiness and self-efficacy scales. On somatic complaints and extraversion they showed higher scores than the other groups. On the PI-R ABBR, 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 unique environmental factors associated with OC symptoms. Although the discordant pairs were genetically identical, were raised at the same time in the same family, and were born at the same time in the same hospital, they experienced different environmental factors in their lives. The twins differed almost on several measures across time. The twins who scored low on OC symptoms reported to have experienced somatic medical health contacts, and lowest scores on OC symptoms, anxiety and depression, neuroticism, and somatic complaints. Further, they reported to be more extraver, more satisfied with life, happier and more self-efficient, with the discordant pairs scoring between the low and high pairs.

**Sources of variation**

There were no between differences in rates of parental death or death of a sibling, nor in frequency of relationship termination between the parents, levels of alcohol consumption, stressful life events, and no discordant twin pairs were born through caesarean section, as opposed to 8 concordant pairs. This is remarkable in light of the fact that in general, caesarean section is carried out more often in multiple pregnancies, especially when one suspects low birth weight in the foetuses (Colla et al., 2001). Although it might be a chance finding, one can speculate that – since caesarean section is intended to decrease perinatal adversities – the discordant group of this sample has been ‘under treated’, providing an additional negative environmental factor to explain between-group differences.

Finally, between-twin pair comparisons on unique life events revealed an elevated rate of disintegration in the discordant twins compared to concordant twins. Children with low birth weight appeared to be more vulnerable to negative environmental factors than normal birth weight children possibly in association with lower IQ levels (Hochberg et al., 2000; Teuscher et al., 2002). Children with low birth weight are more prone to a variety of health problems during childhood. This may explain why children with low birth weight had higher scores on anxiety and depression, and most of all on OC symptoms. The most striking unique environmental factor in this study was a high level of education of the parents, as a measure of socio-economic status, a risk factor reported in OCD was not found to be associated with OC symptoms in this study, although the parents of the twins who were concordant low on OC symptoms were more educated. Apparently, different problem behavior is associated with different environmental risk factors. Deficits in encoding complex information and subsequent memory impairments have been reported in OCD (Buhlmann et al., 2000; Deckerbach et al., 2008). These deficits might be unique to the MZ twin discordant pairs compared to the MZ twin concordant pairs.

**Conclusions**

Though the findings of this explorative study on the relationship between OC symptoms and environmental factors need to be interpreted with caution, we can conclude that OC symptoms may be influenced by environmental factors associated with OC symptoms. Further, the current findings suggest that OC symptoms may be related to negative environmental factors, such as maternal psychological stress, alcohol and drug abuse, depression, anxiety, and low birth weight. This suggests that OC symptoms might be related to adverse life events and postnatal medical health contacts.
study operate? Do they add to genetic risk factors, are and at which age are they most harmful? 2) Along

tomatology have been identified. Two crucial questions

diators of OC symptomatology. Environmental factors, leaving some questions unanswered,

a mild correction of type I errors (Perneger, 1998). Therefore, we decided to compromise by only applying II errors by correction of type I errors was undesirable.

ry nature of this study, an increase in the odds of type ed for type I errors. However, considering the explorato

sult of lack of power to detect within-pair differences. Alternatively we could have relaxed the stringent sele

some of the negative outcomes might in fact be the re

ly, especially in the within-discordant pair comparisons,

Limitations

First, sample size is small, although we sampled from 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 re

Second, considering the large number of tests relative to the small sample size, we only modestly correct for type I errors. However, considering the exploratory

nature of this study, an increase in the odds of 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).

Finally, the database used in this study was not primarily designed to specifically inquire about envi

mental factors, leaving some questions unanswered, especially with respect to protective environmental me

diators of OC symptomatology. In conclusion, this study has been a first attempt to identify characteristics of the environment associated with OC symptoms using a twin study design. Some

important environmental factors involved in OC symp

tomatology have been identified. Two crucial questions to be addressed in future studies are: 1) what is the

differential impact of the various environmental media
tors on OC symptoms, and under which circumstanc
es and at which age are they most harmful? 2) Along

which lines do the environmental factors found in this study operate? Do they add to genetic risk factors, are they causal in themselves, or do they operate through

gene-environment interaction? Future studies are needed to study the differential effects of environment and genes on phenotype, on endophenotypes, and to elucidate the nature of the interplay between genes and environment.


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 can be divided into at least four consistent dimensions. Obsessive-Compulsive Symptoms (OCS) are influenced by genetic components, but it is unknown to what extent these symptom dimensions are heritable. The phenotypic heterogeneity also raises the question to what extent the symptom dimensions are influenced by specific or shared genetic factors.

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, namely, Ruminating, Checking, and Rumination, were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

Results 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 (65%) and environmental factors (64%). Only the Contamination dimension was influenced by specific genes and seemed to be a relatively independent dimension.

Conclusions 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. Use of the Contamination dimension could therefore provide a powerful approach for the detection of genetic susceptibility loci that contribute to OCS.

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). There is no current consensus on the concept adopted 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 studies and the search for vulnerability genes (Miguel et al., 2005).

Obsessive-Compulsive Symptoms (OCS) are the use of OC symptoms in a family study, allowing one to investigate the genetic and environmental factors underlying different OC symptom dimensions. The most heritable symptom dimensions may be useful as a refined phenotype for further linkage or association studies. In this study we present multivariate analyses of the OCS data described by Jonnal et al. (2000). Instead of heritability of the classic obsessive-compulsive symptom category as a whole, we report on our results from multivariate 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, 2000). 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 a set of 10 dichotomous poly-morphisms. 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. Instead of data of a non-clinical sample, we used data of a non-clinical sample. The Padua Inventory (Pi) was developed by Sanavio (1988) to obtain the most important and frequent types of obsessional complaints. From this original 60-item Pi, a 41-item, the Padua Inventory Revised (Pi-R) (Van Oppen et al., 1995) and a 39-item version, the Padua Inventory-Washington State University Revision (Pi-HSUR), have been developed by examining the factorial structure of the Pi and deleting items that were poor or impure measures of these factors. The Pi-R was the first study on Pi items that used also data of OCD patients, instead of data of a non-clinical sample, i.e., OCD patients, instead of data of a non-clinical sample. The revised version contains all items of the Pi-R and is still frequently used in research. The 41 items of the Pi-R form five subscales or symptom dimensions, represented by a factorial analysis of symptoms found in OCs: Impulses (or Aggressive/Harm Obsessions), Washing (or Contamination), Checking, Rumination, and Precision (Van Oppen et al., 1995; Denys et al., 2000). The 20 items used in the current study did not contain any Precision items. Van Oppen et al. (1995) reported good to excellent internal consistency for the full scale (range = .89 - .92), and the subscales (range = .66 - .89) in a group of patients with OCD, patients with other anxiety disorders, and a general population sample. OCD patients scored highest, followed by full Pi-R and the subscales, than patients with other anxiety disorders and general population controls (Van Oppen et al., 1995). Van Oppen et al. (1995) also found that the factorial structure of the Pi-R is invariant across the OCD patient group, the anxiety patient group and the general population group. In other words, they found the same factorial structure in OCD patients and general population controls.
Impulsions or Aggressiveness (table I). Inspection of the items included in these four factors suggested that the components represented (1) Rumination, (2) Contamination, (3) Impulses or Aggressiveness, and which you cannot get rid of?

Who sometimes feels a need to break or damage things for no reason?

Who invents doubts and problems about most of the things you do?

Who has to do things several times before thinking they are done properly?

Who after doing something carefully, still has the impression it is either done badly or is not finished?

Who has to wash their hands more often and longer than necessary?

Who has to do things several times before thinking they are done properly?

Who after doing something carefully, still has the impression it is either done badly or is not finished?

Who sometimes feels a need to break or damage things for no reason?

Who invents doubts and problems about most of the things you do?

Who has to do things several times before thinking they are done properly?

Who after doing something carefully, still has the impression it is either done badly or is not finished?

Who has to wash their hands more often and longer than necessary?

Who avoids using public toilets because of fear of disease and contamination?

Who sometimes has to wash or clean yourself because you think you may be dirty or "contaminated"?

Who when looking down from a bridge or very high window, feel an impulse to throw yourself into space?

Who when a brain aggregates, sometimes thinks of throwing yourself under the wheels?

Who, while driving, sometimes feels an impulse to drive the car into someone or something?

Who checks and rechecks gas burners, water faucets, and light switches after turning them off?

Who has to return home to check doors, windows, and drawers etc., so make sure they are properly shut?

Who has to keep on checking forms, documents, checks etc. in detail to make sure they have been filled out correctly?

The numbers represent the factor loadings on the four factors and bold numbers are the primary loadings on that factor.

Table 1. Results of factor analysis of 17 Padua Inventory items used in present study

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rumination</th>
<th>Contamination</th>
<th>Impulses</th>
<th>Checking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who after doing something carefully, still has the impression it is either done badly or is not finished?</td>
<td>1.000*</td>
<td>.083</td>
<td>-.246</td>
<td>-.111</td>
</tr>
<tr>
<td>Who has to wash their hands more often and longer than necessary?</td>
<td>.687</td>
<td>1.07</td>
<td>-.101</td>
<td>.203</td>
</tr>
<tr>
<td>Who sometimes feels a need to break or damage things for no reason?</td>
<td>.646</td>
<td>.069</td>
<td>.113</td>
<td>.150</td>
</tr>
<tr>
<td>Who has to do things several times before thinking they are done properly?</td>
<td>.562</td>
<td>-.148</td>
<td>.231</td>
<td>.089</td>
</tr>
<tr>
<td>Who avoids using public toilets because of fear of disease and contamination?</td>
<td>.832</td>
<td>.050</td>
<td>.087</td>
<td>-.234</td>
</tr>
<tr>
<td>Who sometimes has to wash or clean yourself because you think you may be dirty or “contaminated”?</td>
<td>.000</td>
<td>.750</td>
<td>.047</td>
<td>.184</td>
</tr>
<tr>
<td>Who who checks and rechecks gas burners, water faucets, and light switches after turning them off?</td>
<td>.030</td>
<td>.689</td>
<td>.038</td>
<td>.173</td>
</tr>
<tr>
<td>Who sometimes feels a need to throw something away in a fit of rage?</td>
<td>.025</td>
<td>.582</td>
<td>.015</td>
<td>.373</td>
</tr>
<tr>
<td>Who, while driving, sometimes feels an impulse to drive the car into someone or something?</td>
<td>.108</td>
<td>.474</td>
<td>.043</td>
<td>.341</td>
</tr>
<tr>
<td>Who, who when looking down from a bridge or very high window, feel an impulse to throw yourself into space?</td>
<td>-.240</td>
<td>-.210</td>
<td>-.964</td>
<td>.341</td>
</tr>
<tr>
<td>Who when a brain aggregates, sometimes thinks of throwing yourself under the wheels?</td>
<td>-.156</td>
<td>.238</td>
<td>.940</td>
<td>-.259</td>
</tr>
<tr>
<td>Who, while driving, sometimes feels an impulse to drive the car into someone or something?</td>
<td>.110</td>
<td>-.063</td>
<td>.795</td>
<td>-.104</td>
</tr>
<tr>
<td>Who checks and rechecks gas burners, water faucets, and light switches after turning them off?</td>
<td>.308</td>
<td>.061</td>
<td>.418</td>
<td>-.066</td>
</tr>
<tr>
<td>Who sometimes feels a need to throw something away in a fit of rage?</td>
<td>.054</td>
<td>.050</td>
<td>.003</td>
<td>.799</td>
</tr>
<tr>
<td>Who has to return home to check doors, windows, and drawers etc., so make sure they are properly shut?</td>
<td>.220</td>
<td>.046</td>
<td>.064</td>
<td>.695</td>
</tr>
</tbody>
</table>

The numbers represent the factor loadings on the four factors and bold numbers are the primary loadings on that factor.
The common pathway method 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 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 (Rumination, Contamination, and Checking) is constrained to be 1. The proportions, the square of the parameter estimates of figure 1, of genetic and environmental influences from the best fitting common pathway model 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 (χ2(1) = 1.4, p = .23), though worse than the AE model. Dropping both A and C resulted in a significantly worse fit (χ2(2) = 13.8, p = .00). The latent OC behavior phenotype explained more than half of the variation (56%) andChecking (69%), but in the Contamination dimension, only 25% of the variation of the Contamination dimension is explained by specific factors, with 33% explained by genetic factors. The shared environmental factor explained 0% of the variance and could be dropped without any worsening of the fit and is therefore not shown in figure 1. For both Rumination and Checking dimensions, genetic and shared environmental specific factors could be dropped without a significant decline in fit (χ2(2) = 33, p = .77, and χ2(2) = 2.42, p = .30, respectively). Twenty-five percent of shared familial factors do not play a role in these two OC dimensions.

Thus this is the first twin study to investigate genetic and environmental effects on different dimensions within in OC symptoms in a population-based sample. We first completed a factor analysis on 17 PI-R items to search for distinguishing OC dimensions. We then performed multivariate twin analyses of three OC dimensions.

Of the dimensions Rumination, Contamination, and Checking, the Rumination and Checking dimensions, genetic and nonshared environmental factors. Third, besides genes for the broad OC behavior phenotype, specific genetic influences are also seen for Contamination dimension, explaining a fair amount of its variation. The structure of the factor with the PI-R items we found is similar to that found in the prodromal and 42% by nonshared environmental factors. The shared environmental factor explained 33% of the variance and could be dropped without any worsening of the fit and is therefore not shown in figure 1. For both Rumination and Checking dimensions, genetic and shared environmental specific factors could be dropped without a significant decline in fit (χ2(2) = 33, p = .77, and χ2(2) = 2.42, p = .30, respectively). Twenty-five percent of shared familial factors do not play a role in these two OC dimensions.

**Table 1.** Factor loadings for PI-R items on Rumination, Contamination, and Checking.

<table>
<thead>
<tr>
<th>Item</th>
<th>Rumination</th>
<th>Contamination</th>
<th>Checking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.49</td>
<td>0.30</td>
<td>0.43</td>
</tr>
<tr>
<td>2</td>
<td>0.38</td>
<td>0.22</td>
<td>0.45</td>
</tr>
<tr>
<td>3</td>
<td>0.35</td>
<td>0.28</td>
<td>0.46</td>
</tr>
<tr>
<td>4</td>
<td>0.32</td>
<td>0.27</td>
<td>0.47</td>
</tr>
<tr>
<td>5</td>
<td>0.30</td>
<td>0.26</td>
<td>0.47</td>
</tr>
</tbody>
</table>

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. The specific OC dimensions are influenced by genes and nonshared environmental factors. This corresponds well with clinical presentations of OC symptoms from multiple dimensions, with usually one or two dimensions appearing more prominent.
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 Grootheest 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 assortative exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assortative 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 the use of a threshold model. 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 assortative exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assortative is negligible. Jonnal et al. (2000) tested the EEA for OC symptoms in the current sample and concluded that the EEA was not violated.

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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, indicating that both genetic and environmental factors have contributed to 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 access to treatment. Differences between people in the liability to develop OCD are caused by a combination of genetic and environmental factors. Effective treatments exist, either pharmaco- therapy or cognitive behavior therapy. In chapter 3, all known published twin studies on OCD/OCS have been described and over 70 years of twin research of OCD/ OCS was presented. Four different approaches to twin studies of OCD/OCS were recognized. These approaches include (1) case-studies of twins with OCD from the old literature, (2) twin studies of OCD using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, (3) twin studies of OCD using a dimensional approach, comparing resemblances in monozygotic and dizygotic twins, and (4) twin studies of OCD using a dimensional approach, analyzing the data with Structural Equation Modeling. It was concluded that only the studies using the last method have convincingly shown that obsessive-compulsive symptoms are heritable with genetic effects 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 comprehensive data is needed to provide conclusive evidence, including a closer look at sex-differences, issues of phenotypic assortment and cultural transmission lies in longitudinal studies. That is exactly what I have done in this thesis.

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

In chapter 4 the genetic and environmental influences on OC symptoms were investigated in a large population based twin-family study. The OC scale of the YASR, based on the CBCL-OCS, developed by the group of Hudziak (Nelson et al., 2001; Hudziak et al., 2006) was used. The YASR-OCS contains the same 8 items as the CBCL-OCS, except that items are worded in the first person. At the best cut-off point of 7, the sensitivity and specificity of the YASR-OCS was 82.4% and 69.7% respectively, when compared to child psychiatric patients in the Cornbach’s coefficient of .69. YASR-OCS data were available in 5893 mono- and dizygotic twins, and 1304 singletons and additional siblings. The design allows for testing phenotypic assortment and cultural transmission, as well as genetic and non-shared environmental factors contributing significantly to the variance of OC symptoms in men and women. In males, shared environmental influences played a relative large role (27%) with a small role for genetic factors (1%). Significant influence of cultural transmission was only found for men, but was non-shared environmental and non-shared factors, while OC symptoms explained 71% of the variance of OC symptoms. For women, the heritability was estimated at 37% and non-shared environmental explained 43%, while total variance explained by individual differences was 83% in OC symptoms. No evidence for a special twin environment was seen, cultural transmission, from parents to twins was 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-child pairs. Marital resemblance between people in the liability to develop OCD are caused by a combination of genetic and environmental factors. Effective treatments exist, either pharmaco- therapy or cognitive behavior therapy. In chapter 3, all known published twin studies on OCD/OCS have been described and over 70 years of twin research of OCD/ OCS was presented. Four different approaches to twin studies of OCD/OCS were recognized. These approaches include (1) case-studies of twins with OCD from the old literature, (2) twin studies of OCD using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, (3) twin studies of OCD using a dimensional approach, comparing resemblances in monozygotic and dizygotic twins, and (4) twin studies of OCD using a dimensional approach, analyzing the data with Structural Equation Modeling. It was concluded that only the studies using the last method have convincingly shown that obsessive-compulsive symptoms are heritable with genetic effects 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 comprehensive data is needed to provide conclusive evidence, including a closer look at sex-differences, issues of phenotypic assortment and cultural transmission lies in longitudinal studies. That is exactly what I have done in this thesis.

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The findings of a longitudinal study in adults tend to support the hypothesis that OC behavior is influenced by factors that are shared by relatives of the same phenotype. The study found that the concordance of high scores between twins is higher than between unrelated pairs, suggesting a genetic influence. However, the between-pair comparisons revealed that environmental factors, including family and peer influences, also play a significant role. The genetic and environmental influences on OC behavior vary across different ages and stages of development, as evidenced by the differences in concordance and discordance rates between twins.

The study also investigated the impact of environmental factors on OC behavior, including the role of peer pressure and social support. The results suggested that peer influence is a significant factor in the development of OC symptoms, particularly among adolescents and young adults. The study highlighted the importance of understanding the complex interplay between genetic and environmental factors in the development of OC symptoms.

In conclusion, the study provided valuable insights into the genetic and environmental factors that influence OC behavior across different stages of development. The findings underscore the need for further research to dissect the genetic and environmental influences on OC behavior and to develop targeted interventions to prevent and treat OC symptoms.
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 1990 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: Rumination, Contamination, and Checking. These OC dimensions were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

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

In Part IV we focused both on the environmental factors which play a role in Obsessive Compulsive symptoms and on symptom dimensions within OC symptoms. The discordant MZ twin design is intriguing. Why is there a difference in a trait, while we know that the genome sequence is in general the same within a MZ twin pair? That 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/OCDD. At this moment, there is no literature within the psychiatric literature of statistical sound studies of environmental factors in OC phenomenology.

In addition to the study of chapter ten, we recently conducted an mMRI 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-BOCS and the Padua Inventory), would be analysed in the same manner as described in our study to answer questions like: Which dimensions have specific genes and environment? Are there any sex differences? Is there any difference in heritabilities of specific symptom dimensions? When we are able to follow this group of twins in a longitudinal way, we also can answer questions like: Are dimensions stable over time? Are these sex-differences in stability? Is stability caused by genes or environment?
REFERENCES


In dit proefschrift, getiteld ‘Obsessie. De genetische en omgevingsarchitectuur van obsessieve-compulsieve symptomen’, is met behulp van tweelingonderzoek onderzocht hoe de herkomst van deze symptomen beïnvloed wordt door genetische factoren en/of omgevingsinvloeden.

**Obsessieve-compulsieve stoornis**

Een obsessieve-compulsieve stoornis (OCS) is een complexe psychiatrische stoornis, gekenmerkt door obsessies of dwanggedachten en compulsies of dwanghandelingen. Obsessies zijn steeds terugkerende en hardnekkige gedachten, beelden of impulsen die als onverdiend of onredelijk worden beoordeeld. Obsessies veroorzaken angst of spanning, die meer geneutraliseerd moeten worden door het uitvoeren van compulsies. Compulsies zijn herhaalde gedragingen of objecten die mensen gebruiken om de angst te beïnvloeden of om te vermijden dat deze zorgen vaak een ritueel karakter of moeten uitgevoerd worden volgens strikte regels. Veel voorkomende dwanghandelingen zijn was- sen, controleren, tellen en verzamelen. De diagnose OCS wordt gesteld als obsessies en compulsies meer dan één uur per dag in beslag nemen en duidelijk hinder geven in het dagelijks leven. Als dwanggedachten of handelingen minder dan een uur per dag inimmen, maar wel kunnen hen hinder geven of wanneer ze meer dan een uur optreden maar zonder hinder, spreekt men van ‘subthreshold’ OCS. OCS komt bij ongeveer 1% van de Nederlanders voor en is daarmee een relatief frequente oorzaak van volwassenen tweelingstudies en wordt veroorzaakt door culturele transmissie. Deze conclusie geldt ook voor angst en depressieve symptomen.

**DEEL II. ERFELIJKHEID, SELECTIEVE PARTNERKEuze EN CULTUREELLE TRANSMissIE**

In hoofdstuk 4 worden de erfelijkheidschattingen van OCS symptomen onderzocht in een groot familie onderzoek bij tweelingen. De Young Adult Self Report (YASR-OCS), een vragenlijst met 8 OCS vragen, werd gebruikt om de OCS symptomen te meten. De schaal werd eerst gevalideerd en liet bevredigende eigenschappen zien met een sensitiviteit en specificiteit van respectievelijk 82.4 en 69.7%. Van 5939 een- en twee-eige tweelingen waren ingevuld OC vragenlijsten beschikbaar. Naar deze tweelingen werd de YASR-OCS ingevuld bij kinderen, met erfelijkheidschatten varierend van 45% tot 65%. Bij volwassenen werden erfelijkheidschatten gevonden van 27% tot 47%, maar een groot-schalige tweelingsexperiment naar OCS ontbreekt nog.

**Hoofdstuk 2** geeft in een kort bestek een overzicht van wat OCS is, de epidemiologie, de stand van zaken op neurobiologisch en genetisch gebied en de be- handingsmogelijkheden.

Hoofdstuk 3 geeft een literatuuroverzicht van meer dan 20 publiceerde tweelingstudies die ge- dicht de helft zijn van hun genen delen. Dit laatste geldt ook voor de gemiddelde man terwijl twee-eige of dizygote (DZ) tweelingen gemiddeld de helft van hun genen delen. Dit laatste geldt ook voor twee-eige van kinderen, met erfelijkheidschatten varieerende van 45% tot 65%. Bij volwassenen werden erfelijkheidschatten gevonden van 27% tot 47%, maar een groot-schalige tweelingsexperiment naar OCS ontbreekt nog. De correlaties gekeken bij vaak kleine groepen tweelingen, de *viertel fase* kenmerkt zich door gebruik van een dini- mensioenele benadering en moderne analysemethoden bij grote groepen tweelingen met daardoorwijkelijke schat- tingen van de erfelijkheidspercentages. Geconcludeerd wordt dat er geen aanwijzing bestaat dat genetische factoren van groot belang zijn bij OCS bij kinderen, met erfelijkheidschatten varierend van 45% tot 65%. Bij volwassenen worden erfelijkheidschatten gevonden van 27% tot 47%, maar een groot-schalige tweelingsexperiment naar OCS ontbreekt nog.

De correlaties bestaat uit vier delen. Hieronder volgt per deel een samenvatting van de bijbehorende hoofd- stukken.

**DEEL I. INTRODUCTIE IN OCS, OC SYMPTOMEN EN TWEELINGSTUDIES**

**Hoofdstuk 2** geeft een kort bestek bij een over- zicht van wat OCS is, de epidemiologie, de stand van zaken op neurobiologisch en genetisch gebied en de be- handingsmogelijkheden.

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**Hoofdstuk 4** geeft een samenvatting van de bijbehorende hoofdstukken.
relatief hoge correlatie bij mannelijk twee-eeige tweelingen. Gezien het feit dat de groep mannelijke twee-eeige 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 persistente, 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 er steeds naar vader- als moederbeoordelingen te kijken kon 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 (16%). Deels van deze stabiliteit is de stabiliteit aanwezig omdat er genen zijn die de ene tweeling wel heeft beleefd en de andere niet. Of de concreet hoge correlatie over de tijd gevonden tussen OC symptomen van 50. Dit duidt op een redelijke stabielte van OC symptomen. Deze stabielte werd veroorzaakt door invloeden van zowel genen (ruwweg 35%) als omgeving (16%).

**DEEL IV. OMGEVINGSFACHTEN EN SYMPTOMDIMENSIONEN VAN OC SYMPTOMEN**

In hoofdstuk 10 is onderzocht welke omgevingsfactoren bij kinderen en nader te onderzoeken in hoeverre deze omgevingsfactoren beïnvloed worden gemaakt van overeenkomst tussen deze beoordelingen waarmee een hoge mate van betrouwbaarheid werd verkregen.


Het is nog maar relatief kort geleden dat genetische oorzaken voor OC's niet tot sprake kwamen in de spreekkamer van de psychiater. Sterker nog, oorzaken werden vooral in omgevingsfactoren gezocht, bijvoorbeeld in de voedselvoeding van ouders. Dit proefschrift laat zien dat, zowel tijdens de kindertijd als volwassenentijd, genetische als wel omgevingsfactoren van cruciaal belang zijn voor het ontstaan van OC's.
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:

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Curriculum Vitae

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).