Genetic and Environmental Contributions Underlying Stability in Childhood Obsessive-Compulsive Behavior

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

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

Results: *OC behavior assessed by the CBCL-OCS showed a moderate stability with phenotypic correlations of around .50 for boys and for girls. Stability of OC behavior was influenced by genetic factors, by environmental factors shared by children growing up in the same family, and by non-shared environmental factors. Stability for OCS was lower when categorical data were analyzed than when quantitative definitions were used.*

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

Key Words: Genetics, obsessive-compulsive behavior, pediatric OCD, rater bias, stability, twins

Given how common and impairing obsessive-compulsive disorder (OCD) is in children (Piacentini et al 2003), a better understanding of the etiology and course of OCD is important. One of the factors that limits a clear understanding of the etiology and development of pediatric OCD is the scarcity 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) (Nelson et al 2001). Hudziak et al (2006) used the CBCL-OCS to determine the prevalence of OCD in US and Dutch population twin samples. They found higher prevalence rates than previously reported. Genetic contributions accounted for at least 50% of individual differences in CBCL-OCS scores in children at ages 7, 10, and 12 (Hudziak et al 2004). 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 2000; Delorme et al 2005; do Rosario-Campos et al 2005).

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 symptoms 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 (Berg et al 1989; Valleni-Basile et al 1996). To our knowledge, no previous study has investigated persistence of OCD 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 phenotype) and variance that is explained by a unique perception of each parent on the behavior of their child (i.e., unique or rater specific phenotype). The common perception is not confounded by rater bias, that is, the tendency of an individual rater to consistently over- or underestimate scores (Hewitt et al 1992), or measurement 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

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Received January 11, 2006; revised May 24, 2006; accepted May 31, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.05.035

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 birth-cohorts 1986–1996, 10-year-old twin pairs from cohorts 1986–1993 and 12-year-old twin pairs from cohorts 1986–1990. Both parents were asked to complete a Child Behavior Checklist (CBCL) (Achenbach 1991). 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 again 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 total 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 5433 twin pairs at age 7, 3172 pairs at age 10 and 1787 pairs at age 12. Maternal ratings were available for 1857, 1217 and 558 twin pairs at ages 7, 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 ratings, 1852 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 ratings, 1338 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 dropout 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 (< 1 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 items about physical similarity and frequency of confusion of the twins by family and strangers (Rietveld et al 2000).

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 Rater

	Mother Ratings			Father Ratings		
	N	M	SD	N	M	SD
			7-Year-Olds			
mzm	1215	.84	1.23	927	.60	.98
dzm	1230	.99	1.42	940	.77	1.20
mzf	1394	.91	1.36	1061	.67	1.11
dzf	1156	1.08	1.55	856	.75	1.21
dos mf	1186	.88	1.38	912	.66	1.08
dos fm	1109	.90	1.31	829	.65	1.05
			10-Year-Olds			
mzm	745	.89	1.27	573	.70	1.05
dzm	680	1.11	1.68	487	.76	1.19
mzf	907	1.05	1.47	666	.78	1.21
dzf	655	1.16	1.66	484	.87	1.41
dos mf	730	.98	1.53	535	.73	1.20
dos fm	672	.99	1.46	501	.74	1.11
			12-Year-Olds			
mzm	422	.86	1.41	329	.64	1.15
dzm	378	1.01	1.69	284	.85	1.39
mzf	494	.92	1.27	385	.65	1.03
dzf	351	.88	1.39	280	.86	1.47
dos mf	370	.89	1.45	288	.62	1.10
dos fm	330	.76	1.20	261	.60	1.04

Mzm, monozygotic male; dzm, dizygotic male; mzf, monozygotic female; dzf, dizygotic female; dos mf, dizygotic opposite-sex twin pairs with male first-born; dos fm, dizygotic opposite-sex twin pairs with female first-born.

Measures

The Child Behavior Checklist (CBCL) (Achenbach 1991; Verhulst et al 1996) is a widely used questionnaire for parents. It includes 120 items about problem behaviors exhibited by the child over the previous 6 months. The parents respond on 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-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 2006).

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-person longitudinal correlations (phenotypic stability of CBCL-OCS), within person inter-parent correlations (parental agreement), twin correlations (cross-sectional twin 1—twin 2 correlations) and, cross-twin-cross-age correlations (e.g., twin 1 at age 7 with twin 2 at age 10). Further, to take rater differences into account, cross-rater twin correlations within 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 underlying developmental patterns of the distinct common and rater specific variance components.

Genetic Modeling. In the classical twin design, the relative contributions of genetic and environmental factors to individual differences in OCS scores can be inferred from the different levels of genetic relatedness between MZ and DZ twins. Indivi-

dual differences may be due to additive genetic (A), shared environmental (C) or non-shared environmental (E) factors (Boomsma et al 2002b). Additive genetic factors are correlated 1.0 in MZ twins, since MZ twins are genetically identical. For DZ twins, the additive genetic factors are correlated .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 twins, we used a psychometric model (see Figure 1) (Bartels et al 2003; Bartels et al 2004a; Hewitt et al 1992) and expanded this model to longitudinal data. The psychometric model allows the parental ratings to be influenced by aspects of the child's behavior perceived commonly by both parents (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 considered as independent of rater bias and unreliability of the ratings. Unique perceptions of the child's behavior can arise if the child behaves differentially towards the parents or if the parents observe the child 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 do not cause systematic effects and cannot mimic genetic influences. The shared environmental effects on the unique phenotype may be confounded by rater bias, such as using normative standards or response styles. Because rater bias is independent of zygosity, it mimics shared environmental effects. A further advantage of the longitudinal psychometric model is that genuine unique non-shared environmental effects can be distinguished from random measurement error. Random errors of measurement are age specific and are unlikely to contribute to the correlations across time in non-shared environmental effects.

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

We tested whether the model could be simplified by dropping one or more latent factors. The rater-specific non-shared environmental (E) factor was never dropped from the model, because in addition to non-shared environmental experiences, this factor includes measurement error. The models were fitted to raw data with Mx (Neale et al 2003), by the method of raw maximum likelihood estimation. This allowed the use of all twin data, whether or not there were missing parental ratings at certain time points. Goodness-of-fit was assessed by likelihood-ratio chi-square tests. These tests compare the differences between -2-log likelihood of a full model with a restricted nested model. This difference is distributed as an X^2, and the degrees of freedom (*df*) for this test are equal to the difference between the number of estimated parameters in the full model and that in the restricted model. A large X^2 value in comparison to the number of *df* suggests that the simpler model does not fit the data as appropriately as the more complex model. More technical details of genetic model-fitting analyses are reviewed elsewhere (Neale and Cardon 1992).

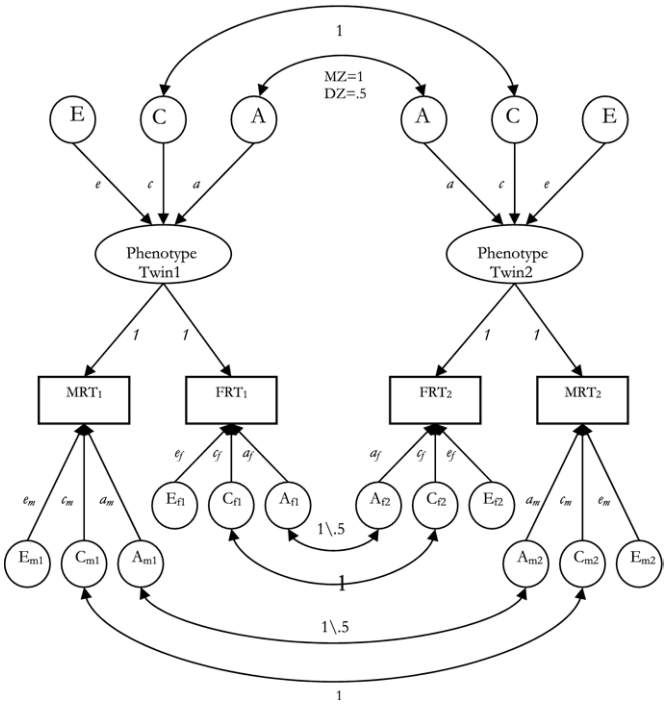

Figure 1. The psychometric model for multiple raters. A, genetic contribution; C, shared contribution; E, non-shared contribution; MR, mother rating; FR, father rating.

Results

Descriptive Statistics

Table 1 summarizes the means and standard deviations for the CBCL-OCS by age and sex in mother and father reports. Mothers reported significantly more OC symptoms than fathers for both boys and girls, except for female DZ twins at age 12 ($\Delta\chi^2(1) = .50$, $p = .48$). No significant differences were seen between boys and girls. No differences between zygosity groups were found with the exception of age 7. At that age, DZ female twins had significantly ($\Delta\chi^2(1) = 7.78$, $p < .01$) more OC-symptoms than MZ female twins according to mother ratings and DZ male twins had higher means than MZ male twins according to father ratings ($\Delta\chi^2(1) = 9.65$, $p < .01$).

Persistence of Cases of OCD

Figure 2 shows persistence of cases with a CBCL-OCS score of 5 or higher. It is clear that the stability of cases meeting cutpoint 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 4 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

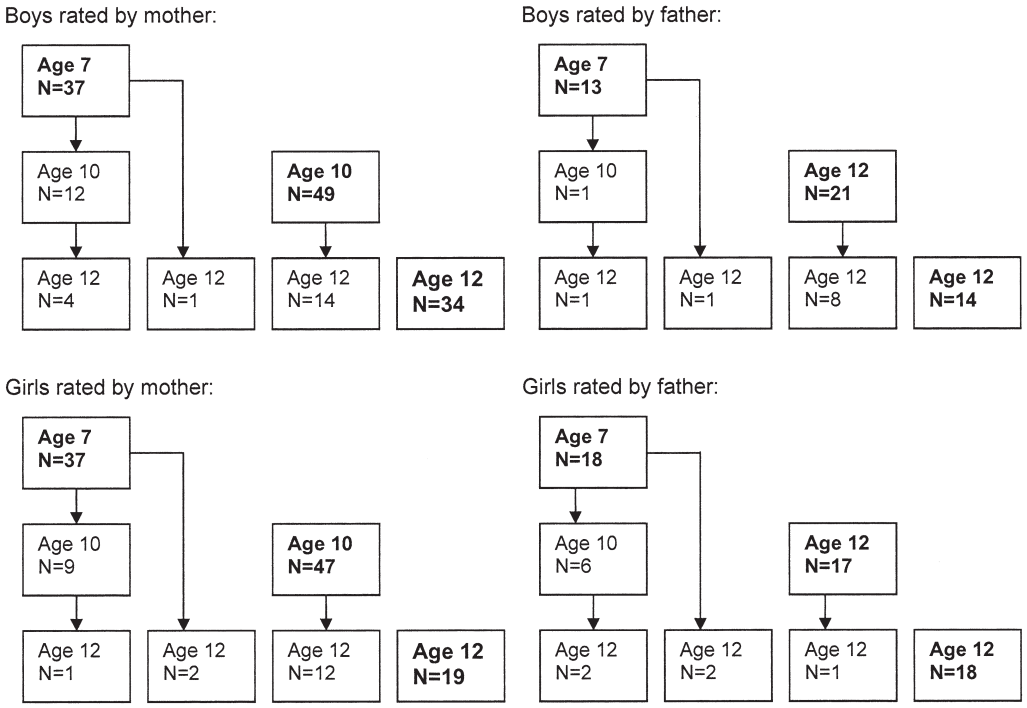

Figure 2. Cases with Score of 5 or Higher on the CBCL-OCS at Different Ages. Bold faced numbers show the number of new cases of OCD at that specific age. Non-bold numbers show the cases which persist at a specific age. For example, boys rated by mother: of the 37 cases at age 7, 12 cases persisted at age 10 of which 4 persisted at age 12. The case from age 7 which showed up at age 12, had a score lower than 5 at age 10.

4 for fathers gave almost exactly the same pattern (not shown) as for mothers, using a cutoff of 5.

Correlations

Table 2 contains the within-person phenotypic correlations over time. These correlations provide an indication of the stability of the expression of CBLC-OCS, irrespective of possible changes in group means. Both boys and girls displayed a comparable degree of stability of about .50 from ages 7 to 10 and from ages 10 to 12 for both mother and father ratings. Within-person inter-parent correlations were comparable over the distinct zygosity groups and at the distinct ages (not shown). The correlations ranged between .48 and .73 with an average of .58.

Table 3 presents cross-sectional twin correlations (diagonal) for MZ and DZ pairs. MZ correlations are higher than DZ correlations, suggesting genetic influences. MZ correlations were lower than one, which suggests influences of non-shared environment. Further, shared environmental influences were implied by the fact that the MZ correlations are less than twice the DZ correlations.

Twin correlations over time (cross-twin-cross-age correlations) are given on the off-diagonal of Table 4. These correlations are informative with respect to the proportion of longitudinal covariance explained by genes and environment for CBCL-OCS over time. Across-age MZ correlations were higher than DZ correlations, with a larger difference for mother ratings, suggesting that additive genetic effects are more important in phenotypic stability of mother ratings compared to father ratings.

Table 4 shows the cross-twin-cross-rater correlations within age (diagonal) and across age (off-diagonal). The cross-twin-cross-rater correlations give a first indication of the involvement

Table 2. Phenotypic Correlations for Mother and Father Ratings

	Mother Ratings			Father Ratings		
Age	7	10	12	7	10	12
7	1	.55	.47	1	.53	.44
10	.55	1	.58	.51	1	.52
12	.43	.58	1	.44	.54	1

Correlations for boys and girls are reported below and above diagonal respectively.

Table 3. Within Age Twin Correlations (Diagonal) and Across-Age Twin Correlations (Off-Diagonal) by Sex and Zygosity for Mother and Father Ratings

		Mother Ratings of the Oldest			Father Ratings of the Oldest		
	Age	7	10	12	7	10	12
				MZ			
Youngest	7	.56/.56	.30	.26	.58/.56	.37	.25
	10	.38	.59/.53	.36	.31	.51/.49	.32
	12	.27	.32	.55/.52	.24	.31	.43/.50
				DZ			
	7	.29/.29	.18	.13	.32/.29	.20	.19
	10	.22	.34/.32	.20	.22	.31/.33	.31
	12	.21	.21	.28/.35	.21	.20	.29/.39
				DOS[a]			
	7	.28/.34	.23	.12	.30/.34	.20	.14
	10	.19	.35/.34	.13	.18	.28/.32	.32
	12	.20	.27	.39/.25	.09	.16	.26/.39

Correlations for boys and girls are reported below and above diagonal respectively. On diagonal, correlations for boys are reported on the left and for girls on the right.

[a]Dizygotic opposite-sex twin pairs with male first-born below diagonal; Dizygotic opposite-sex twin pairs with female first-born above diagonal.

of genes and environmental factors on the common parental view. At all ages, the within age MZ cross-rater correlations were larger than the DZ cross-rater correlations and suggested genetic influences on the common parental phenotype (diagonal). Especially at older ages, the DZ cross-rater twin correlations seemed to be larger than expected on the basis of genetic influences alone, and therefore shared environmental influences seemed to contribute to the common parental phenotype. For each age, the cross-twin-cross-rater correlations were lower than the within rater twin correlations (Table 3, diagonal). The differences indicate the part that is unique to a particular rater (i.e., the unique or rater-specific phenotype). A same pattern of higher MZ than DZ correlations is seen for the cross-rater-cross-age twin correlations (off-diagonal), indicating genetic influences on the stability of the common parental phenotype. The differences with the within rater twin correlations over time (Table 4, off-diagonal) were quite small, which means a relatively small influence of the unique or rater-specific phenotype on stability compared to the larger influence of the common phenotype.

Genetic Modeling

Rater (Dis)agreement of OC Behavior. Table 5 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, ($\Delta\chi^2(24) = 11.89$, $p = .98$). The influence of common family environment (C) on the common phenotype was significant. The influence of additive genes (A) was significant for both the common and the rater-specific phenotype.

As can be seen in Table 6, for mother ratings at age 7, the variance explained by the total common phenotype explained almost half of the total variation, and this is decreasing to roughly 30% at the age of 10 and 12. The remaining variation was rater specific. For father ratings, the total common phenotype explained almost 60% of the variance at age 7 and 40% of the variance at age 12. In other words, parental agreement decreased when children grew older.

For stability (off-diagonal covariances), we see the same pattern with a decrease in parental agreement when children grew older. For example, the total covariance of the common phenotype varied between 65 and 81% between age 7 and 10 for mother ratings for both girls and boys and between 51% and 62% between age 10 and 12 for both boys and girls for father ratings. The rater-specific phenotype explains the rest of the covariance and became more important with increasing age.

Underlying Resources of Stability of OC Behavior. Table 6 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; shaded cells) and total covariance (i.e., stability; off-diagonal) of the CBCL-OCS, the common phenotype and rater-specific phenotype have been added together.

For boys, analyses of the covariance showed that stability could be largely explained by additive genetic influences, 51% (57 + 54 + 43/3) for mother ratings and 35% (44 + 43 + 19/3) for father ratings, on average. The differences for father and mother ratings are mainly explained by the fact that fathers do not add any unique additive genetic information on stability (see Table 5), while mothers do, especially for boys. For girls, stability could be explained by additive genetic influences of 34% for mother ratings and 28% by father ratings. For girls, genetic,

Table 4. Cross-Twin-Cross-Rater Correlations within Age (Diagonal) and Across Age (Off-Diagonal) by Sex and Zygosity

		Mother Ratings of the Oldest		
	Age	7	10	12
		MZ		
Father Ratings of the Youngest	7	.31/.30	.25	.20
	10	.21	.30/.27	.21
	12	.21	.25	.27/.24
		DZ		
	7	.15/.12	.13	.11
	10	.13	.17/.18	.16
	12	.17	.13	.15/.15
		DOS[a]		
	7	.12/.15	.12	.08
	10	.11	.14/.12	.13
	12	.09	.11	.16/.11

Correlations for boys and girls are reported below and above diagonal respectively. On diagonal, correlations for boys are reported on the left and for girls on the right.

[a]Dizygotic opposite-sex twin pairs with male first-born below diagonal; Dizygotic opposite-sex twin pairs with female first-born above diagonal.

Table 5. Percentages of the Genetic (A), Shared (C) and Non-Shared (E) Environmental Contributions to the Total Variances (Diagonal; Boldface) 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 or Left on Diagonal) and Girls (above Diagonal or Right on Diagonal)

		Mother Ratings			Father Ratings		
	Age	7	10	12	7	10	12
Total common phenotype	7	46/42	67	78	59/56	77	100
	10	65	30/32	52	81	42/42	62
	12	82	42	30/36	98	51	39/44
A_c[a]	7	**26/21**	30	27	**33/28**	34	35
	10	35	**15/12**	14	44	**21/16**	16
	12	36	16	**4/3**	43	19	**5/4**
C_c[b]	7	**10/11**	18	39	**13/15**	21	50
	10	13	**6/9**	30	16	**8/12**	36
	12	38	22	**26/31**	46	27	**33/38**
E_c[c]	7	**10/10**	19	12	**13/13**	22	15
	10	17	**9/11**	8	21	**13/14**	10
	12	8	4	**0/2**	9	5	**1/2**
Total unique phenotype	7	54/58	33	22	41/44	23	0
	10	35	70/68	48	19	58/58	38
	12	18	58	70/64	2	49	61/56
A_u[d]	7	**27/28**	10	0	**26/26**	0	0
	10	22	**43/34**	22	0	**27/26**	0
	12	18	27	**31/29**	0	0	**12/26**
E_u[e]	7	**27/30**	23	22	**15/18**	23	0
	10	13	**27/34**	26	19	**31/32**	38
	12	0	31	**39/35**	2	49	**49/30**

Note that common and unique phenotype add up to 100%.
[a]Additive genetic influence on the common phenotype.
[b]Shared environmental influence on the common phenotype.
[c]Non-shared environmental influence on the common phenotype.
[d]Additive genetic influence on the unique phenotype.
[e]Non-shared environmental influence on the unique phenotype.

Table 6. Percentages of the Genetic (A), Shared (C) and Non-Shared (E) Environmental Contributions to the Total Variance (Diagonal; Boldface) and Total Covariance (Off-Diagonal) of the CBCL-OCS for Boys (below Diagonal or Left on Diagonal) and Girls (above Diagonal or Right on Diagonal)

		Mother Ratings			Father Ratings		
	Age	7	10	12	7	10	12
A	7	**53/49**	40	27	**59/46**	34	35
	10	57	**58/46**	36	44	**48/42**	16
	12	54	43	**35/32**	43	19	**17/30**
C	7	**10/11**	18	39	**13/15**	21	50
	10	13	**6/9**	30	16	**8/12**	36
	12	38	22	**26/31**	46	27	**33/38**
E	7	**37/41**	42	34	**28/31**	45	15
	10	30	**33/45**	34	40	**44/46**	48
	12	8	35	**39/37**	11	54	**50/32**

Common phenotype and unique/rater-specific phenotype have been added together.

shared environmental and non-shared environmental influences explained each for a third of the stability of OC behavior.

Same or Different Genes Across Ages? Analyses of the covariance similarly assessed by both parents (the common phenotype) showed that stability could be partly explained by common additive genetic influences, 43% of the covariance on average for boys and 35% for girls (not shown). Interestingly, a closer look on the parameter estimates in Mx revealed that the genetic influences seen on the common phenotype at ages 10 and 12 are transmitted from age 7, so one underlying set of genes can be considered to be of importance for OC behavior between age 7 and 12.

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 OC behavior and on the underlying etiology of this stability. By using both maternal and paternal 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 OC Behavior in Children Over Time?

In comparison with other phenotypes, OC 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 and Rietveld et al (2004) showed a high stability of .70 for attention problems for children in the same age-range. Our result seems to be in line with the result of Stewart et al (2004). They found a persistence rate of OCD of 26% within two community studies included in their meta-analysis, with adolescents only. Thus, having OC behavior as a child does not automatically imply OC behaviour for the rest of your life. This is also in line with the notion that the prevalence of OCD in children is similar to prevalence rates in adults, which means, as only one-third to one-half of adults with OCD develop the disorder in childhood (Pauls et al 1995), a considerable proportion of youth with OCD becomes subsyndromal (Stewart et al 2004).

We found no sex differences in prevalence (Hudziak et al 2006) and persistence of CBCL-OCS. This conforms to Stewart et al (2004), who found sex to be a non significant predictor of persistence in OCD. If sex differences in prevalence of pediatric OCD are reported by others, which is mostly done in clinical samples (Geller et al 1998; Eichstedt and Arnold 2001), boys outnumber girls. This may imply that girls with OCS 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, with 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 of 5 and scored just below the cutpoint at a later age would categorically represent a remitted case and quantitatively be considered highly stable. For example, 50% of all cases in Table 2 who scored above the cutpoint at age 7 and scored lower than 5 at age 10 had a CBCL-OCS score of 3 or 4 at age 10. When looking at inter-rater correlations 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.

To What Extent Do Genetic or Environmental Influences Account for Stability of OC Behavior?

When using the more informative quantitative approach, we showed that, in boys, stability of OC behavior of ratings of both fathers and mothers is mainly due to additive genetic factors, especially for mother ratings. For girls, genetic and both shared and non-shared environmental influences are equally important in explaining stability of OC symptoms throughout childhood. For stability, the rater-specific phenotype was, in general, of less importance than the common phenotype. In particular, fathers seem to add little extra information on stability of OC behavior. One might conclude that mothers are better aware of 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 data show high skewness and kurtosis. Derks and colleagues (Derks et al 2004) showed that skewness in the data lead to biases in parameter estimates, that is, underestimation of the shared environmental estimates and overestimation of the non-shared environmental estimates. One approach to deal with this problem is using a liability threshold model (Lynch and Walsh 1998). For the longitudinal design of the present study, however, a liability threshold model is practically not feasible.

Second, the genetic and environmental contributions presented in this report are for CBCL-OCS scores, not for clinical measures of DSM OCD. Although we have performed prior studies (Nelson et al 2001; Hudziak et al 2006), replicated by others (Geller et al 2006, Storch et al 2006), to demonstrate the validity, specificity, sensitivity and predictive power of the CBCL-OCS in relation to DSM-IV OCD, it remains possible that the CBCL-OCS may over-identify cases in general population sam-

ples. However, as we have shown, the quantitative 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. Collection of Youth Self Report (YSR) (Achenbach 1991) data in this sample when they become adolescents will be valuable in order to test the stability and change in OCS behavior across adolescents and young adults, where self-reports become the mainstay of assessment. As a result, we currently aim to collect YSR data on these twins as they reach adolescence and young adulthood.

Fourth, one assumption underlying most twin designs is that the genetic and environmental latent factors show a continuous, normal distribution. Such distributions are implied if a large number of loci and environmental contributions, each with small individual effects, are present (Kendler, 2005). Van den Oord and colleagues (Van den Oord et al 2003) tested this assumption for self-ratings of depression and found very little or no evidence of non-normality. This implies that there was no evidence that participants with high depressive score may be qualitatively distinct. Although it is likely that 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 predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). The EEA states that environmental influences are shared to the same extent by MZ and DZ twins. Maes et al (1998) found that significant but moderate primary assortment exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assortment 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 intervention. First, our data, consistent with those of others, points to the fact that CBCL-OCS is a relatively unstable condition for which remission from 'clinical deviance' is a relatively common phenomenon. These data allow a clinician to have prognostic 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 and Wells 2005) to positively affect OC behavior, our data point out the contribution of shared and unshared environment to phenotypic stability. Put simply, this finding argues strongly for changing the environment in children such that obsessions and compulsions will diminish (e.g., move kids out of the deviant group), for example by involving family members in the treatment of OCD (Renshaw et al 2005).

Furthermore, this study has implications for measurement of behaviour problems. For cross-sectional heritability analyses, combining father and mother data adds extra information, suggesting that researchers studying children's behaviour 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 longitudinal studies with multiple raters for different phenotypes are necessary to see if this is only the case for OC behavior. Within a clinical setting, this could mean that interviewing 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 molecular genetic research. Within the common phenotype of OC behaviour, the same genes influence OC behaviour throughout at age 7, 10, and 12. It suggests that one may pool data from children of different ages together in linkage-analyses, obtaining an increase of power, and that no age-specific effects are to be expected in candidate gene studies.

This research was supported by ZonMw (Grant number 920-03-268), NWO (Grant number 400-03-330), and the National Institute of Mental Health (NIMH, RO1, MH58799-03). MB is financially supported by NWO (Veni; Grant number 451-04-034).

We are grateful to the parents of the twins for their participation.

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