

# Genetic and Environmental Contributions to the Child Behavior Checklist Obsessive-Compulsive Scale

## A Cross-cultural Twin Study

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**Context:** We have reported elsewhere on the development of an 8-item Obsessive-Compulsive Scale (OCS) contained in the Child Behavior Checklist (CBCL) to identify children who meet criteria for *DSM-IV* obsessive-compulsive disorder. Twin studies of obsessive-compulsive disorder have indicated a significant genetic component to its expression.

**Objective:** To determine the relative contributions of genetic and environmental influences on childhood obsessive-compulsive behavior using the CBCL OCS in twin samples.

**Design:** The CBCL data were received by survey of twins in the Netherlands Twin Registry (NTR) and the Missouri Twin Study (USA/MOTWIN).

**Setting:** General community twin samples.

**Participants:** Participants were 4246 twin pairs aged 7 years, 2841 aged 10 years, and 1562 aged 12 years (who also participated in the study at 7 and 10 years of age) from the NTR and 1461 mixed-age twin pairs (average age, approximately 9 years) from the USA/MOTWIN.

**Main Outcome Measures:** Model fitting to test for genetic and environmental influences, sex differences, and sibling interaction/rater contrast effects on the CBCL OCS.

**Results:** In each case, the best-fitting model was one that indicated significant additive genetic influences (range, 45%-58%; 95% confidence interval [CI], 45%-61%), and unique environmental influences (range, 42%-55%; 95% CI, 39%-55%), with shared environmental influences in the NTR sample aged 12 years (16%). Sex differences were seen in the mixed-age USA/MOTWIN model, but not in the NTR samples. No evidence of dominance, sibling interaction, or rater-contrast effects was seen. These data were relatively consistent across age and cultures.

**Conclusions:** The CBCL OCS is influenced by genetic factors (approximately 55%) and unique environmental factors (approximately 45%) in the younger sample, with common environmental influences only at 12 years of age. These effects do not vary with differences in sex or sibling interaction/rater contrast effects. Our data reveal higher genetic influences for obsessive-compulsive behavior and do not demonstrate genetic differences across sex.

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**O**BSESSIVE-COMPULSIVE DISORDER (OCD) is common in children and adults. It is associated with serious impairment and, in many cases, has a lifelong course. Studies on prevalence indicate that the lifetime rates of OCD in adolescents range from 1.9% to 4.1%,<sup>1-6</sup> with a higher prevalence in girls than in boys.<sup>7</sup> The wide variability in prevalence rates may be due to differences in the populations sampled and the methods used for assessment. Nonetheless, the prevalence of OCD in children and adolescents may be higher than originally thought. Other reports<sup>8</sup> (including unpublished data March 2003: J.J.H., R.R.A., C.S., C.E.M.v.B., E.C.N., G. L. Hanna, MD, D.I.B., and R.D.T.)

have described our development of an 8-item Obsessive-Compulsive Scale (OCS) contained in the Child Behavior Checklist (CBCL) that is useful in identifying children aged 7 to 12 years who meet criteria for *DSM-IV* OCD (**Table 1**). Using a summed score of 5 (the borderline clinical range, >95th percentile based on the CBCL normative sample), the CBCL OCS demonstrated high sensitivity (92%), moderate specificity (67%), high negative predictive value (90%), and moderate positive predictive value (73%) in subjects who had been diagnosed as having *DSM-IV* OCD by board-certified psychiatrists. Using a higher 98% clinical range, which corresponds to a score of 6, the sensitivity of the test was 79%; specificity was 78.1%; positive pre-

**Table 1. Items Used for the OCS**

CBCL Item No.	CBCL Item	CBCL Syndrome on Which Item Is Scored
9	Can't get his or her mind off certain thoughts; obsessions	Thought problems
31	Feels he or she might think or do something bad	Anxious/depressed
32	Feels he or she has to be perfect	Anxious/depressed
52	Feels too guilty	Anxious/depressed
66	Repeats certain acts over and over; compulsions	Thought problems
84	Strange behavior	Thought problems
85	Strange ideas	Thought problems
112	Worries	Anxious/depressed

Abbreviations: CBCL, Child Behavior Checklist; OCS, Obsessive-Compulsive Scale.

dictive value was 77.8%; and negative predictive value was 79.4%. In 4 large twin samples (1 in the United States and 3 in the Netherlands), the percentage of participants with CBCL OCS scores in the borderline clinical range was 2.4% to 4.3%, with 1.4% to 3.8% in the clinical range (**Table 2**).

The purpose of the present study was to extend our previous work and determine the contributions of environment, genes, sex, and age to the expression of CBCL OCS and, by extension, childhood OCD.

#### PREVIOUS GENETIC STUDIES OF OCD

The estimation of genetic and environmental influences on a disorder typically includes twin, family, adoption, and molecular genetic approaches. Tsuang et al<sup>9</sup> argued that although our molecular genetic techniques have advanced to the point that identifying genetic variants that contribute to the development of a phenotype is now a trivial laboratory exercise, the development of phenotypic identification strategies that refine diagnoses for molecular genetic investigations remain problematic. This is especially true in childhood OCD, where relatively few genetic studies have been performed. Family and twin studies of OCD are rare relative to the studies of other psychiatric disorders. Of the OCD studies, many have used small samples that were generally derived from highly comorbid clinical populations, with a resultant reduction in the generalizability of the results.<sup>10</sup> Despite these limitations, the belief that OCD is influenced by genetic factors is widely held; in fact, initial reports on the genetic contributions to OCD are more than 60 years old.<sup>11</sup>

#### FAMILY STUDIES

Family studies to date have revealed conflicting results. The percentage of affected first-degree relatives of patients with OCD has ranged from being indistinguishable from control subjects<sup>12</sup> to 30%,<sup>13</sup> with several estimates between.<sup>14-18</sup> Many OCD studies include patients with other disorders such as Tourette syndrome and other tic disorders. These studies have reported rates of OCD as high as 26% among first-degree relatives of patients with Tourette syndrome, a familial condition known to have significant genetic influences.<sup>19,20</sup> A recent meta-

**Table 2. Percentage of Whole Sample Meeting CBCL OCS Cut Points**

Study Sample*	Percentage of Sample			
	Boys		Girls	
	OCS Score $\geq 5$	OCS Score $\geq 6$	OCS Score $\geq 5$	OCS Score $\geq 6$
NTR-7	2.4	1.1	2.4	1.1
NTR-10	3.6	1.8	3.1	1.8
NTR-12	3.1	2.1	1.9	0.8
MOTWIN/USA, age 7-11 y	6.6	3.8	3.5	1.6

Abbreviations: CBCL, Child Behavior Checklist; USA/MOTWIN, Missouri Twin Study; NTR, the Netherlands Twin Registry; OCS, Obsessive-Compulsive Scale.

\*NTR numbers indicate age (in years) of children at the time of data sampling.

analysis<sup>21</sup> demonstrated an unadjusted aggregate risk of 8.2% in first-degree relatives of patients with OCD vs 2% in relatives of controls. In summary, published family studies support the contention that OCD, alone or comorbid, is a condition that is influenced by genetic factors.

#### TWIN STUDIES

Twin studies have also demonstrated genetic influences on OCD. Monozygotic (MZ) twins have been shown to have a concordance rate for OCD as high as 70% to 80%, compared with 22% to 47% among dizygotic (DZ) twins.<sup>22,23</sup> Heritability estimates have been calculated in the range of 26% to 33%.<sup>10,24</sup> However, Hettrema et al<sup>21</sup> were unable to find any twin studies of adequate size without ascertainment bias to meet their criterion for inclusion, although they noted that published twin studies had found consistent evidence of genetic contributions to obsessions and compulsions.

#### MOLECULAR GENETIC STUDIES

Most molecular genetic studies of OCD have focused on the monoamine pathway genes. Numerous molecular genetic studies have aimed to determine the relative contributions of different candidate genes to the pathophysiology of OCD. The catechol *O*-methyltransferase (*COMT*) gene,<sup>25-28</sup> the serotonin 2 $\beta$  receptor (*5HT2B*) gene,<sup>29,30</sup> the serotonin transporter gene,<sup>31,32</sup> the serotonin 2 $\alpha$  receptor (*5HT2A*) gene,<sup>33,34</sup> and the 7 repeat of the dopamine D<sub>4</sub> receptor (*DRD4*) gene,<sup>35</sup> among others, have all been implicated in OCD or OCD-like phenotypes, some perhaps in a sex-specific<sup>36</sup> or a population-specific<sup>27,37</sup> fashion. Other reports have shown the contrary.<sup>38-40</sup> In each of these studies, the authors considered the results preliminary and called for studies on much larger populations and more refined samples to clearly understand the contribution of individual gene variations to the etiology of OCD.

#### SUMMARY

In aggregate, family, twin, and molecular genetics studies support the premise that OCD or features of OCD are influenced by genetic factors. Most of these studies did

**Table 3. Numbers and Ages of Twin Pairs**

Zygoty/Sex	Study Samples*							
	USA/MOTWIN		NTR-7		NTR-10		NTR-12	
	No.	Age, y, Mean (SD)	No.	Age, y, Mean (SD)	No.	Age, y, Mean (SD)	No.	Age, y, Mean (SD)
MZ/M	300	9.4 (1.6)	760	7.5 (0.5)	506	10.2 (0.4)	277	12.1 (0.3)
DZ/M	280	9.5 (1.6)	651	7.5 (0.4)	443	10.2 (0.4)	233	12.1 (0.3)
MZ/F	242	9.0 (1.2)	822	7.5 (0.5)	593	10.2 (0.4)	330	12.1 (0.3)
DZ/F	204	8.8 (1.2)	634	7.5 (0.5)	429	10.2 (0.4)	240	12.1 (0.4)
DOS	435	9.4 (1.6)	1379	7.5 (0.4)	870	10.2 (0.4)	482	12.1 (0.4)
<b>Total</b>	<b>1461</b>		<b>4246</b>		<b>2841</b>		<b>1562</b>	

Abbreviations: DOS, dizygotic opposite sex; DZ, dizygotic; USA/MOTWIN, Missouri Twin Study; MZ, monozygotic; NTR, the Netherlands Twin Registry.  
 \*NTR numbers indicate age (in years) of children at the time of data sampling.

not control for sex, age, referral bias, or comorbidity. Thus, confusion remains about the best way to conceptualize and refine the OCD phenotype for genetic analysis.

### AIMS OF THE PRESENT STUDY

There were multiple aims of this study. The first was to determine the genetic and environmental contributions to CBCL OCS scores. The second was to determine whether evidence of sex-genetic interactions existed. The third was to determine whether the age of the child contributed to the genetic/environmental influences on CBCL OCS scores by analyzing these data in samples of twins aged 7, 10, and 12 years and a mixed sample of twins aged 8 to 12 years. Finally, the study assessed cultural differences by determining whether the genetic/environmental contributions differed by country (the Netherlands vs the United States).

## METHODS

### SUBJECTS AND PROCEDURE

#### The Netherlands Twin Registry

The study was part of an ongoing twin-family study of health-related characteristics, personality, and behavior in the Netherlands. The subjects were all part of the Netherlands Twin Registry (NTR).<sup>41</sup> At present, the NTR has data on more than 25 000 twin pairs from ages 3 to 30 years. For this study, we assessed a sample of Dutch twin pairs whose parents reported on their behavior when they were 7, 10, and 12 years of age (NTR-7, NTR-10, and NTR-12 samples, respectively). The total sample with CBCL data available in the NTR at these age groups at the time of the study included 4484, 2905, and 1664 twin pairs aged 7, 10, and 12 years, respectively. Of these, 238, 64, and 102 twin pairs, respectively, were excluded owing to missing data, leaving a total of 4246, 2841, and 1562 twin pairs available for analysis at ages 7, 10, and 12 years, respectively. The socioeconomic status of the parents of the twins was somewhat higher than the level in the general Dutch population.<sup>42</sup>

The assessment procedures at ages 7, 10, and 12 years have been described elsewhere.<sup>41</sup> Parents received a CBCL by mail. Parents who did not return the forms within 2 months received a reminder. Those who did not respond after 4 months were called by the NTR research assistant. This procedure resulted in an average continued participation rate of 80% from 7 to 10 and 10 to 12 years of age.

Zygoty were determined by means of DNA analyses of blood group polymorphisms for 634 same-sex twin pairs. For the remaining twins, zygoty was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers. The classification of zygoty was based on a discriminant analysis, relating the questionnaire items to zygoty based on blood/DNA typing. According to this analysis, the zygoty was correctly classified by questionnaire in nearly 95% of the cases.<sup>43</sup>

#### Missouri Twin Study Sample

To apply this screening tool to a large sample of twins with different ages and mixed ethnicity, we selected twins from an ongoing project, the Missouri Twin Study (USA/MOTWIN). This sample has been described previously.<sup>44</sup> Briefly, an attempt was made to contact parents of all twins born in Missouri from 1975 to 1991 to invite them to participate. They were paid \$5 for completing survey materials. At the time that the genetic analyses were performed, data on 1461 of 1565 twin pairs who were sent CBCLs were used. One hundred four pairs were excluded because 1 or more of the 8 items of the CBCL OCS were missing. The CBCL OCS scores from each of these remaining twin pairs were computed.

Zygoty was determined by means of questionnaire items as for the NTR samples, with assignment based on a latent class approach. In a comparison of genotypic determination of 121 twin pairs, only 1 pair was misassigned using this method.<sup>45</sup>

**Table 3** provides a description of the numbers of twin pairs by sex and zygoty for the 4 samples. There was a small but statistically significant difference in age, with girls slightly younger; however, there was no statistical age difference by zygoty group. Although the USA/MOTWIN sample was ethnically mixed (85% European American, 13.4% African American, and <1% Hispanic, Asian, or Native American), the NTR samples consisted primarily of children of European descent. The NTR-10 sample was a subset of the NTR-7 sample studied 3 years later, and the NTR-12 sample was a subset of the NTR-10 sample.

### MEASURES

The CBCL is a widely used questionnaire for parents to respond to 118 problem behaviors exhibited by their child during the previous 6 months. The parent responds along a 3-point scale with the code of 0 if the item is not true of the child, 1 for sometimes true, and 2 for often true. The characteristics and psychometric stability of the CBCL have been well established.<sup>46</sup> The analyses performed herein used the 1991 version of the CBCL, but the same items can be scored on the more recent 2001 version.<sup>47</sup>

The CBCL OCS was developed using factor analysis on 11 CBCL items that were thought to likely predict OCD.<sup>8</sup> Using a 1-factor model, 8 items were retained and were shown to have good internal consistency (Cronbach  $\alpha = .84$ ). Those items retained are shown in Table 1, along with their CBCL item number. A numerical value for the CBCL OCS is created by adding the scores on these 8 items (0, 1, or 2 for each), thus limiting the scale to a range of 0 to 16. The CBCL OCS was tested to determine prevalence, specificity, and sensitivity.<sup>9</sup>

## DATA ANALYSES

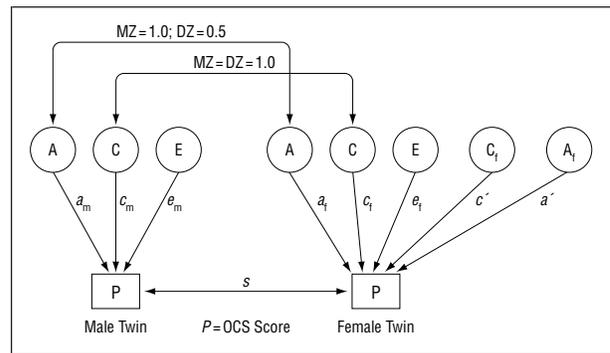
### Differences in Means

Means, variances, and twin correlations were calculated using Mx.<sup>48</sup> Differences in mean scores and variances between sex and zygosity were tested by means of likelihood ratio  $\chi^2$  tests. These tests were performed taking into account the dependency that exists between scores of the twins. Because the CBCL OCS score was not normally distributed, the data were square root transformed to approximate a normal distribution.

### Models

Genetic and environmental influences on CBCL OCS scores were computed using structural equation modeling. The relative contributions of genetic and environmental factors to individual differences in CBCL OCS scores can be inferred from the different level of genetic relatedness of MZ and DZ twins.<sup>49</sup> The **Figure** summarizes the fundamental univariate genetic model that underlies our analyses. The variance may be due to additive genetic factors (A), common or shared environment factors (C), or nonshared environment effects (E). We also tested for dominance genetic effects (D), which correlate at 1.0 in MZ twins and 0.25 in DZ twins. Estimating D and C at the same time is not possible in a design using only MZ and DZ twins reared together. Using D instead of C in the models did not contribute to a better fit; thus, D was not examined further. The genetic factors are correlated at 1.0 in MZ twins, as they are genetically identical. For DZ twins, the additive genetic factors are correlated at 0.5, because DZ twins share on average half of their genes. The environment shared by a twin pair is assumed not to depend on zygosity, and thus shared environmental factors correlate at 1.0 in both MZ and DZ twins. The E term is by definition uncorrelated. All uncorrelated error is also absorbed in the E term. The parameters  $a$ ,  $c$ , and  $e$  are loadings of the observed phenotype on the latent factors A, C, and E and indicate the degree of relations between the latent factors and the observed phenotype. The proportion of the variance accounted for by genetic and environmental influences is calculated by squaring the parameters  $a$ ,  $c$ , and  $e$  and dividing them by the total variance ( $a^2 + c^2 + e^2$ ). In addition, in the univariate model, the effects of sibling interaction (path  $s$ ) are also considered. Sibling interaction reflects the effect of the behavior of one twin on the behavior of the other twin. The interaction effect may also be due to bias in parental reports when parents rate their children's behavior in comparison with each other. Whether the sibling interaction effects are a function of rater contrast or of real sibling interaction cannot be tested with the current data, but would need information from more than 1 informant. The AE model with sibling interaction was tested and did not lead to a better fit than the AE model without sibling interaction, and it was not examined further.

The Figure extends the latent variable component of the model by allowing for genotype  $\times$  sex interaction effects (illustrated for the case of unlike-sex sibling pairs). This may take the form of sex differences in the magnitude of genetic or environmental influences (paths  $a_m$ ,  $c_m$ , and  $e_m$  vs  $a_f$ ,  $c_f$ , and  $e_f$ ) or



Sex-genetic model. Additive genetic factors are correlated at 0.5 in dizygotic (DZ) twins, because DZ twins share on average half of their genes, and at 1.0 in monozygotic (MZ) twins. The parameters  $a$ ,  $c$ , and  $e$  are loadings of the observed phenotype (P) on the latent additive genetic factors (A), common or shared environment factors (C), and nonshared environment effects (E) and indicate the degree of relations between the latent factors and the observed P. The proportion of the variance accounted for by genetic and environmental influences is calculated by squaring the parameters  $a$ ,  $c$ , and  $e$  and dividing them by the total variance ( $a^2 + c^2 + e^2$ ). In addition, in the univariate model, the effects of sibling interaction (path  $s$ ) are also considered. Genotype  $\times$  sex interaction effects (illustrated for the case of unlike-sex sibling pairs) may take the form of sex differences in the magnitude of genetic or environmental influences (paths  $a_m$ ,  $c_m$ , and  $e_m$  vs  $a_f$ ,  $c_f$ , and  $e_f$ ) or the form of an additional genetic or common environmental influence on only 1 of the unlike-sex sibling pairs (paths  $a'$  and  $c'$ ). OCS indicates Obsessive-Compulsive Scale.

the form of an additional genetic or common environmental influence on only 1 of the unlike-sex sibling pairs (paths  $a'$  and  $c'$ ). These analyses allowed us to test for sex differences on CBCL OCS scores.

### Model Fitting

To estimate the genetic and environmental contributions, the data for twins 1 and 2 were summarized into  $2 \times 2$  covariance matrices, computed by PRELIS scientific software.<sup>50</sup> All model fitting was performed with Mx,<sup>48</sup> a statistical software package designed for conducting genetic analyses with an approach that is standard in structural equation modeling.<sup>51</sup> The basic model tested was an ACE model. The significance of the A and C factors was tested by dropping each of these variance components one at a time and using the  $\chi^2$  difference test. The  $\chi^2$  statistic was computed by subtracting the  $\chi^2$  statistic for the full model from that for a reduced model. The degrees of freedom for this test are equal to the differences between the degrees of freedom for the full and the reduced model. If the  $\chi^2$  statistic is significant, this means that the variance component makes a significant contribution to the fit of the full model, because removing it significantly worsens the fit of the model. In addition, the Akaike information criterion, a goodness-of-fit index that considers the rule of parsimony, was calculated. A smaller Akaike information criterion indicates a better fit. We also computed likelihood-based 95% confidence intervals (CIs) for each parameter.<sup>48,52</sup> More technical details of genetic model-fitting analyses are reviewed elsewhere.<sup>49</sup>

## RESULTS

The square root-transformed mean CBCL OCS scores and variances across sex and zygosity are presented in **Table 4**. Raw CBCL OCS scores were quite similar across age and country. The homogeneity of the variance across sex was tested with Mx<sup>48</sup> and revealed significant sex differences for CBCL OCS scores in all 3 samples. In the

**Table 4. Estimated Square Root–Transformed CBCL OCS Scores**

Zygoty/Sex	Study Samples*							
	USA/MOTWIN		NTR-7		NTR-10		NTR-12	
	Mean	Variance	Mean	Variance	Mean	Variance	Mean	Variance
MZ/M	0.71	0.64	0.55	0.45	0.62	0.51	0.57	0.75
DZ/M	0.80	0.66	0.63	0.54	0.70	0.60	0.61	0.74
MZ/F	0.64	0.55	0.63	0.51	0.69	0.54	0.60	0.71
DZ/F	0.64	0.54	0.66	0.51	0.71	0.57	0.59	0.71
DOS/M	0.80	0.75	0.55	0.49	0.63	0.57	0.54	0.70
DOS/F	0.65	0.56	0.60	0.48	0.65	0.52	0.54	0.65

Abbreviations: CBCL, Child Behavior Checklist; DOS, dizygotic opposite sex; DZ, dizygotic; USA/MOTWIN, Missouri Twin Study; MZ, monozygotic; NTR, the Netherlands Twin Registry; OCS, Obsessive-Compulsive Scale.

\*NTR numbers indicate age (in years) of children at the time of data sampling.

**Table 5. Observed Variance-Covariance Matrix for the Square Root–Transformed CBCL OCS Scores\***

Zygoty/Sex	Study Samples*							
	USA/MOTWIN		NTR-7		NTR-10		NTR-12	
	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ/M								
Twin 1	0.66		0.46		0.51		0.53	
Twin 2	0.33	0.612	0.25	0.45	0.30	0.51	0.30	0.54
DZ/M								
Twin 1	0.70		0.54		0.60		0.53	
Twin 2	0.22	0.61	0.164	0.54	0.21	0.60	0.15	0.49
MZ/F								
Twin 1	0.58		0.51		0.55		0.50	
Twin 2	0.25	0.508	0.29	0.52	0.30	0.54	0.25	0.51
DZ/F								
Twin 1	0.60		0.54		0.59		0.50	
Twin 2	0.05	0.438	0.11	0.48	0.12	0.54	0.20	0.50
DOS								
Twin 1	0.75		0.49		0.57		0.50	
Twin 2	0.21	0.559	0.15	0.48	0.18	0.52	0.15	0.43

Abbreviations: See Table 4.

\*Data are coefficients.

†NTR numbers indicate age (in years) of children at the time of data sampling.

USA/MOTWIN sample, boys had higher scores; in both Dutch samples, girls had higher scores. The variance and covariance matrices for all zygosity groups are given in **Table 5**. There were no differences in the means, variances, and covariances across the 5 zygosity groups for the USA/MOTWIN sample and the NTR-10 or NTR-12 samples. In the NTR-7 sample, the means and the variances of the DZ twins were larger than for MZ twins ( $\Delta c_8^2=21.18$ ). As shown in Table 5, although significant, these differences were very small.

The twin correlations for the CBCL OCS score are shown in **Table 6**. Analysis of twin correlations yielded evidence of the influence of genetic and environmental factors. In all 3 samples, MZ correlations were larger than DZ correlations, indicating the influences of genes. The MZ and DZ correlations were not different across sex, with 1 exception. The female DZ correlation was lower than the male DZ correlation in all samples, but only significantly so in the USA/MOTWIN sample. In the remaining samples, the magnitude of genetic and environ-

mental effects was equal across sex. In addition, the DZ opposite-sex correlations equaled the same-sex male correlations in all 3 samples, suggesting that the same genes and environmental influences play a role for boys and girls.

A summary of the model-fitting results is given in **Table 7**. The  $c^2$  statistic indicates the goodness of fit, and smaller  $c^2$  statistics indicate better agreement of the observed data with the model. First, we computed a model for each sample that allowed the variance components to differ between boys and girls. In the second set of models, A, C, and E parameters were constrained to be equal across sex. These constrained models were compared with the unconstrained models, and the best-fitting models were selected. These results showed no deterioration in fit in the 2 Dutch samples when the parameters were constrained to be the same across sex. In the USA/MOTWIN sample, this resulted in a worsening of the fit ( $\Delta c_3^2=16.85$ ). This sex difference was probably due to differences in total variance between boys and girls seen in

this sample only. Next, the significance of the C factor was tested by dropping it from the models and calculating change in the goodness of fit. Dropping C from the model did not lead to a deterioration of the fit in any of the samples except for the NTR-12, meaning that the AE was the best model for all 3 of the other samples, with an ACE model being the best fit for the NTR-12 sample only.

### SUMMARY OF MODEL FITTING

The best-fitting model for 3 samples included A and E contributions (Table 7), with C contributions evident in the NTR-12 sample. There were no sex effects in the Dutch samples, although there were minor sex effects in the USA/MOTWIN sample, likely due to underlying differences in the means and variances of the CBCL OCS score in this mixed-aged sample. Across age groups and cultures, the additive genetic influence of the CBCL OCS varied from 45% to 58% (95% CI, 45%-61%). The E factors (which conspire to make members of a twin pair different) ranged from 42% to 55% (95% CI, 39%-55%). In the NTR-12 only, the magnitude of the shared environmental influences was about 16%.

### COMMENT

With these results, we extend our previous work on the CBCL OCS by revealing that scores on this proposed scale for assessing childhood OCD are highly heritable and influenced by additive genetic and unique environmental factors in younger children, with common environmental influences appearing to play a role beginning at 12 years of age. The magnitude and type of the genetic and environmental influences were surprisingly stable across age, sex, and culture within the younger group, but may differ as the children enter puberty, given the differences reported herein at 12 years of age.

The magnitude of the genetic contribution for each sample is larger than previous estimates,<sup>10,24</sup> which fell in the range of 26% to 33%. There are several reasons for this difference. First, restriction of range introduced by examining genetic effects on OCD in clinical samples may have attenuated previous estimated genetic contributions. Clinical cases are often more severe, with higher rates of comorbid illness that may be influenced by environmental factors that, in concert with genetic risks, may lead to the expression of OCD (eg, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections<sup>53</sup>). We also used a continuous CBCL OCS score rather than the dichotomous *DSM-IV* diagnoses used by others. Previous studies have observed high rates of subclinical OCD symptoms in family members of OCD probands. By using CBCL OCS scores, we may have better characterized the underlying trait.

Second, the environmental contributions for each of the younger samples are of the unique or unshared type. There are a variety of propositions about which unique environmental contributions may lead to the expression of OCD, including the presence of autoimmune processes. The unique environmental contribution found in all 3 samples may explain earlier reports of genetic-environmental interaction leading to the expression of

**Table 6. Twin Correlations for Transformed CBCL OCS Syndrome**

Zygosity/Sex	Study Samples*			
	USA/MOTWIN	NTR-7	NTR-10	NTR-12
MZ/M	0.51	0.55	0.59	0.57
DZ/M	0.34	0.31	0.35	0.30
MZ/F	0.46	0.57	0.54	0.50
DZ/F	0.10	0.21	0.22	0.40
DOS	0.32	0.30	0.33	0.33

Abbreviations: See Table 4.

\*NTR numbers indicate age (in years) of children at the time of data sampling.

OCD. We did not directly test for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in our samples. Other possibilities include differences in parenting, school, activities, etc, as well as error that is part of the E term in structural equation modeling.

Third, although we did not test for developmental factors (these data will be reported later once our samples are large enough to follow up children across key developmental periods), it is important to note the similarity of the genetic/environmental contributions to CBCL OCS scores within and across the young age groups. Collapsing twin pairs aged 8 to 12 years into the same analyses (ie, the USA/MOTWIN sample), and therefore introducing a possible developmental bias into the analyses, had no effect on the magnitude of the genetic or environmental contributions, with the possible exception of inflating the contribution of sex. However, looking only at the cross-sectional analysis at 12 years of age, shared environmental influences first appear. This may mean that investigation of these same twins in adolescence (a topic for further study) may help reveal why sex differences change after puberty and why other genetic studies have shown lower estimates of OCD.

Fourth, no sex-genetic differences were apparent in most of these models, except in the USA/MOTWIN group. This may be due to the inclusion of children who are mostly younger than 12 years. Previous work on the epidemiology of OCD in children has shown that the prevalence of OCD in children increases markedly after 13 years of age<sup>54</sup> and that a shift in prevalence from affecting boys more frequently at a young age to affecting women more frequently in adulthood likely occurs after 18 years of age.<sup>55</sup> In our study, we see little, if any, sex difference affecting the heritability of the CBCL OCS scores up to 12 years of age. Future research will be directed at the adolescent period to determine whether sex effects increase during this time of life.

Finally, in studies of psychopathology, there have been notable differences between the European and US psychiatric communities. These include, but are not limited to, differences in how schizophrenia vs bipolar affective disorders were conceptualized in the 1950s and 1960s, leading to markedly different rates of both disorders across continents.<sup>56</sup> More recently, there have been differences in how children with symptoms of inatten-

**Table 7. Model-Fitting Results for Square Root–Transformed CBCL OCS Scores\***

Study Sample, Model†	$\chi^2$	df	P Value	AIC	Parameter Estimates‡						Compared With Model No.	$\Delta\chi^2$ ( $\Delta df$ )
					Male			Female				
					$a^2$	$c^2$	$e^2$	$a^2$	$c^2$	$e^2$		
USA/MOTWIN												
ACE sex	18.811	9	.027	0.811	38	16	46	40	4	56		
ACE no sex	35.66	12	.000	11.660	44	6	50	44	6	50	1	16.849 (3)*
<b>AE sex</b>	<b>21.403</b>	<b>11</b>	<b>.029</b>	<b>-0.597</b>	<b>55</b>		<b>45</b>	<b>45</b>		<b>55</b>	<b>1</b>	<b>2.592 (2)</b>
NTR-7												
ACE sex	17.847	9	.037	-0.153	57	0	43	55	0	45		
ACE no sex	18.617	12	.098	-5.383	56	0	44	56	0	44	1	0.77 (3)
<b>AE no sex</b>	<b>18.617</b>	<b>13</b>	<b>.135</b>	<b>-7.383</b>	<b>56</b>		<b>44</b>	<b>56</b>		<b>44</b>	<b>2</b>	<b>0.000 (1)</b>
NTR-10												
ACE sex	12.026	9	.212	-5.974	57	5	38	51	2	47		
ACE no sex	18.079	12	.113	-5.921	55	0	45	55	0	45	1	6.053 (3)
<b>AE no sex</b>	<b>18.276</b>	<b>13</b>	<b>.147</b>	<b>-7.724</b>	<b>58</b>		<b>42</b>	<b>58</b>		<b>42</b>	<b>2</b>	<b>0.197 (1)</b>
NTR-12												
ACE sex	5.940	9	.746	-12.060	44	11	44	21	27	52		
<b>ACE no sex</b>	<b>10.395</b>	<b>12</b>	<b>.581</b>	<b>13.605</b>	<b>36</b>	<b>16</b>	<b>48</b>	<b>36</b>	<b>16</b>	<b>48</b>	<b>1</b>	<b>4.455 (3)</b>
AE no sex	17.052	13	.197	-8.948	54		46	54		46	2	6.657 (1)

Abbreviations: See Table 4; ACE sex, model contains additive genetic (A), common environmental (C), and unique environmental (E) parameters with male and female estimates allowed to differ; ACE no sex, model contains ACE parameters but male and female estimates are constrained to be equal; AE sex, model contains AE parameters with male and female estimates allowed to differ; AE no sex, model contains AE parameters but male and female estimates are constrained to be equal; AIC, Akaike information criterion.

\*Boldface type represents the best-fitting model for that sample.

†NTR numbers indicate age (in years) of children at the time of data sampling.

‡The parameters  $a$ ,  $c$ , and  $e$  are loadings of the observed phenotype on the latent factors A, C, and E and indicate the degree of relations between the latent factors and the observed phenotype. The proportion of the variance accounted for by genetic and environmental influences is calculated by squaring the parameters  $a$ ,  $c$ , and  $e$  and dividing them by the total variance.

tion, hyperactivity, and impulsivity were characterized across the two continents. In England, the *International Classification of Diseases, Eighth Revision*, described hyperkinetic conduct disorder, whereas in the United States during the same time period, the era of attention-deficit/hyperactivity disorder was born.<sup>57</sup> These across-continent differences led to different diagnostic paradigms, different prevalences, and different treatment approaches. Our data on the CBCL OCS provide a nice contrast. In our previous work, using normative data with the same instrument in the Netherlands and the United States, we were able to compute rates of the prevalence of CBCL OCS in both cultures independent of bias that may emerge by imposing standards of one culture on another (unpublished data March 2003: J.J.H., R.R.A., C.S., C.E.M.v.B., E.C.N., G.L. Hanna, MD, D.I.B., and R.D.T.) We then tested for genetic contributions to a continuous distribution of CBCL OCS scores across both cultures, and essentially found the same results. Whether these results apply to clinically diagnosed OCD can only be determined by future studies; however, the similarity across age, sex, and culture supports the premise that deviance on the CBCL OCS represents a prevalent syndrome and that scores on the CBCL OCS are stable across ages and cultures with a significant genetic component.

These similar genetic and prevalence data raise another dilemma. Estimates of the prevalence of attention-deficit/hyperactivity disorder in the United States range from 3% to 5% in general population studies and are somewhat higher in twin studies.<sup>58</sup> Attention-deficit/hyperactivity disorder is the second most common disorder seen in US child psychiatry clinics and the most com-

mon psychiatric disorder treated by pediatricians.<sup>59</sup> If OCD is nearly as common as attention-deficit/hyperactivity disorder, with prevalence rates in the range of 2% to 4% according to our studies, and is highly stable across age and culture, why are so few children identified and treated for this diagnosis? Although our data cannot directly answer this question, one possible explanation has to do with the difficulty in screening for and thus diagnosing OCD when using existing OCD diagnostic instruments. Furthermore, the psychopathology measured by deviance on the OCS may not be impairing enough to parents or teachers to lead to early identification and referral. As March and colleagues<sup>60</sup> have demonstrated, the obsessional and compulsive characteristics of children with OCD are often not viewed as pathologic by parents or teachers. In fact, many parents become so familiar with their children's symptom complex that they lose the ability to discriminate what is normal vs pathologic. Finally, with the high and stable heritability estimates that have emerged in this study, together with the family study data that indicate OCD is highly familial,<sup>12-18</sup> it is also possible that children with OCD are not being identified as having an illness, because their parents have a similar or the same malady. These questions can be answered only by extending this research to a twin/family design. In such a study, twins with deviant scores on the OCS could be enrolled in a twin/family design to test for endophenotypic, genetic, and environmental contributions to this disorder. The prevalence and genetic data that have emerged from our studies suggest that such research should be performed soon, as it is likely that most children with this illness are not being identified, are not receiving treatment, and are suffering in private.

The genetic and environmental contributions presented in this report reflect CBCL OCS scores, not clinical measures of *DSM-IV* OCD. Although we have performed prior studies 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 overidentify or underidentify cases in general population samples. One specific set of cases that may be underrepresented is the population of children who may have an alternative manifestation of OCD associated with tics. No item in the CBCL OCS assesses tics. Prospective studies of the CBCL OCS or similar measures with more traditional end-point clinical assessments are needed to address this issue. The cutoffs used for the CBCL OCS were 92% sensitive but only 67% specific, resulting in many false-positive findings. The CBCL OCS cut points could be changed, (eg, a score of 7 instead of 6 for 10-year-old children), and the scale will become less sensitive and more specific. Higher cut points may be needed for gene-finding expeditions where false-positive findings are less acceptable.

A further limitation is the fact that parent ratings of the same twins were included at 7, 10, and 12 years of age. Although this provides us a window on the genetic and environmental contributions to CBCL OCS at specific ages, it could also introduce an ascertainment bias (ie, why do specific parents participate at each wave and others do not?). A long-term aim of this work is to test developmental stability and change when our sample sizes are large enough to allow for such analyses. An additional limitation is the reliance on parental report, given the secrecy that is inherent to children's OCD symptoms.<sup>61</sup> Although youth self-report may be of questionable value, as these children move into adolescence a reassessment of the CBCL OCS using youth-self report will be important.

These data support the contention that childhood obsessive compulsive behavior is prevalent, influenced by both genetic and environmental factors, and affects children of both genders across the 7- to 12-year age range. The findings provide a strategy for using quantitative, gender, and developmentally sensitive screening approaches to identify children at risk for this common and impairing disorder. Future studies using self-reports from children and adolescents may reveal more sensitive and specific ways to screen for OCD across the lifespan of an individual.

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