Chapter 8

GENETIC AND ENVIRONMENTAL INFLUENCES ON ANXIOUS/DEPRESSION

A Longitudinal Study in 3- to 12-Year-Old Children

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Pathways of developmental psychopathology have long been of interest to scientists, clinicians, and patients. To date it is unclear why some children are never affected by psychopathological illness, why others become ill and re-

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cover, and why still others are impaired across their entire lives. Questions about stability and change over time for common childhood psychopathological conditions must be answered to provide diagnostic, therapeutic, and prognostic guidance to families of children who suffer from these disorders. Anxious/depression (A/D) in childhood, the focus of this chapter, has been poorly studied from a developmental point of view. Studies beginning in early childhood and progressing into adolescence and adulthood are rare.

Unlike some other common child psychiatric disorders (e.g., attention-deficit/hyperactivity disorder [ADHD], autism, conduct disorders), it can be said with certainty that all children experience anxiety. Indeed, it is a normal aspect of development. Severe anxiety, or an anxiety disorder, is thought to occur in over 20% of humans across their lifetime (Greenberg et al. 1999). The relative cost of the morbidity of anxiety is estimated to be approximately 44 billion dollars in the United States annually (Greenberg et al. 1999). Given the prevalence of anxiety disorders, it is surprising that little work has been done on the developmental stability and change across childhood.

Certain disorders, such as ADHD, originally were conceptualized as "going away with puberty." Through careful research it has now become clear that the majority of individuals who have ADHD in childhood still manifest both symptoms and impairment associated with this condition in adulthood (Castellanos et al. 2006; Manuzza et al. 2003). Similarly, pessimism surrounds the perception about the developmental prognosis of oppositional defiant disorder and conduct disorder. It has been repeatedly estimated that 50% of children with oppositional defiant disorder will go on to develop conduct disorder, and 50% of those will go onto develop antisocial personality disorder (Robins 1996). Children with autism and pervasive developmental disorders are predicted to suffer from lifelong impairments associated with these conditions (Rutter 2005).

Anxiety disorders are thought to be stable, but little is known about the stability of early childhood anxiety across development, with avoidance and shyness giving way to generalized anxiety and social anxiety and then later adult anxiety disorders (Kagan et al. 1999).

Major depressive disorder presents a bit more baffling target. Little is known about the developmental outcomes of major depressive disorder. Some have reported that major depressive disorder in childhood places a child at greater risk for later affective disorders, both unipolar and bipolar (Geller et al. 1996). Others argue that major depressive disorder, even in children, is an episodic, and in some cases even seasonal, condition (Klein et al. 2002, 2006). It is difficult to fully understand why so little is known about the developmental stability of major depressive disorder in children. Part of the explanation may well be due to taxonomic problems, including developmental, sex, and informant issues that affect studies of this type.

It is widely accepted that different genetic factors affect core neurodevelopment processes such as neuronal genesis, synaptogenesis, myelination, and apoptosis. As such, it should be axiomatic that the genetic influences on brain development will have similar and sentinel influences on children's behavioral and emotional problems (such as A/D) and that these influences may vary in their relative importance depending on the age of the child. The influence of environmental factors may also vary with the age and sex of the child. This statement applies not only to the magnitude of these influences (i.e., percentage of variation explained by environmental effects) but also to the type of environmental influence. The influence of the family environment (often referred to as "shared" or "common" environment), which includes the effects of parental education, socioeconomic status of the family, and rearing practices, may depend on the age or sex of the child. For example, it is now well established that as children grow older, the large initial influence of shared family environment disappears, whereas the influence of genetic factors on cognitive abilities increases (Bartels et al. 2002; Posthuma et al. 2002; Rietveld et al. 2003). For childhood psychopathology such changes in genetic and environmental influences across development are much less clear than for cognitive abilities. It has been argued that until confounds (or modifiers), such as phenotypic assessment and rater bias, and interactions between genes and age and between genes and sex can be addressed, the full impact of molecular genetic studies will not be realized (Rutter and Silberg 2002).

Questions regarding age, sex, rater bias, and development can be addressed in twin studies, but only if the samples are large enough, if the phenotypic information is collected from multiple raters, and if the sample is followed across development. Our group has previously reported on the development of both internalizing and externalizing behavioral problems in young children, as well as on aggressive behavior, attention problems, juvenile bipolar disorder, and obsessive-compulsive disorder in a large sample of Dutch twin pairs registered since birth with the Netherlands Twin Register (NTR) (Bartels et al. 2003, 2007; Boomsma et al. 2006; van Beijsterveldt et al. 2003; van Grootheest et al. 2007; van der Valk et al. 2003). Longitudinal parental ratings of these phenotypes were studied using structural equation modeling approaches. The longitudinal modeling allowed the assessment of correlations between phenotypes at one age and subsequent ages (stability), and the participation of twins allowed the decomposition of those correlations into a genetic part and an environmental part. Furthermore, these studies have allowed the evaluation of the impact of age, sex, and information on estimates of environmental and genetic influences (heritability) on these phenotypes. For all phenotypes, the results have implications for clinical medicine. For example, the correlations between aggres-

sive behavior scores at age 3 and at age 7 years are low, but between ages 7 and 10 years, and between ages 10 and 12 years, the correlations are quite high. Such findings demonstrate that early measures of aggressive behavior do not necessarily correlate highly with later measures. However, the correlations from age 7 years forward are highly predictive of later aggression problems. Furthermore, we found, for example, that for internalizing behavior problems there are no sex differences in the magnitude of the variance components and there is a decrease in heritability with an increase in shared environment across age. For externalizing behavior problems, sex differences in the magnitude of genetic and environmental effects are found at ages 10 and 12 years. Furthermore, an increase in the influence of additive genetic influences is observed between ages 3 and 7 years. For attention problems, a constant and rather high influence of genetic factors was found between ages 3 and 12 years. The remaining variance is attributable to nonshared environmental influences.

For A/D, in a previous article, we analyzed maternal and paternal ratings *cross-sectionally* at ages 3, 5, 7, 10, and 12 years. Data were available for more than 9,025 twin pairs at age 3 years and for more than 2,300 pairs at age 12 years (Boomsma et al. 2005). Multivariate genetic models were used to test for rater-independent and rater-specific assessments of A/D. The agreement between parental A/D ratings was between 0.5 and 0.7, with somewhat higher correlations for the youngest group. Disagreement in ratings between the parents was not merely the result of unreliability or rater bias. Both parents provided unique information from their own perspective on the behavior of their children. Heritability estimates for rater-independent A/D were high in 3-year-olds (76%) and decreased in size as children grew up (60% at age 5, 67% at age 7, 53% at age 10 [60% in boys], and 48% at age 12 years). The decrease in genetic influences was accompanied by an increase in the influence of the shared family environment (absent at ages 3 and 7, 16% at age 5, 20% at age 10 [5% in boys], and 18% at age 12 years). Significant influences of genetic and shared environmental factors were found for the unique parental views. At all ages, the contribution of shared environmental factors to variation in rater-specific views was higher for fathers' ratings. Also, at all ages except age 12 years, the heritability estimates for the rater-specific phenotype were higher for mothers' (59% at age 3 and decreasing to 27% at age 12 years) than for fathers' ratings (between 14% and 29%).

The aim of this chapter is to take the analyses of the A/D data one step further and to assess the *stability* of A/D between ages 3 and 12 years in a genetically informative sample. We assess whether stability in A/D depends on the sex of the child and to what extent the stability in A/D is explained by stable genetic and/or environmental factors. A/D in 3- to 12-year-old children was assessed with the Child Behavior Checklist (CBCL) (Achenbach

et al. 2003). The A/D syndrome contains items with features of both anxiety and depression. A/D is highly related to both the Somatic Complaints and Withdrawn Behavior syndromes of the CBCL, which are also highly predictive of either childhood anxiety (Somatic Complaints) or childhood depression (Withdrawn Behavior). The choice of the phenotype CBCL-A/D is consistent with the work of others who have demonstrated the high rates of co-occurrence between anxiety and depressive disorders (Gorman 1996–1997). Twin and family studies indicate shared vulnerabilities (Boomsma et al. 2000; Kendler et al. 1992, 2006; Ninan and Berger 2001) for anxiety and depression in adults. Ratings on CBCL-A/D were obtained from both parents of the twins to assess rater bias. The relative contributions of genetic and non-genetic factors were estimated conditional on age and sex of the children. The stability of A/D was modeled as a function of stable genetic and environmental influences. Environmental influences were separated into influences unique to each child and influences shared by children growing up in the same family. A large number of twin pairs (at age 3 years: N=9,346 pairs) participated.

METHODS

Sample

The data in this chapter come from a large ongoing longitudinal study that examines the genetic and environmental influences on the development of behavioral and emotional problems in families with 3- to 12-year-old twins. The families are volunteer members of the Netherlands Twin Registry, established by the Department of Biological Psychology at the Free University in Amsterdam (Bartels et al. 2007; Boomsma et al. 2002, 2006). From 1987 onward the NTR has recruited families with twins a few weeks or months after birth. Currently 40%–50% of all multiple births are registered by the NTR. For this study, we included data of 3- and 5-year-old twin pairs from cohorts 1986–1997, of 7-year-old twin pairs from cohorts 1986–1996, of 10-year-old twin pairs from cohorts 1986–1993, and of 12-year-old twin pairs from birth cohort 1986–1990. Both parents of twin pairs were asked to complete questionnaires about problem behaviors for the eldest and youngest twin at ages 3, 5, 7, 10, and 12 years. Because of funding problems, the questionnaire for 3-year-olds was not sent to the fathers of twins born between May 1989 and November 1991. Two months after the questionnaire was mailed out, a reminder was sent to the nonresponders. After 4 months those who still had not responded were telephoned, if resources for telephone follow-up were available at the time. This procedure resulted in a response rate (at least one parental questionnaire returned) of 77% at

age 3 years. From ages 3 to 7, ages 7 to 10, and ages 10 to 12 years, the continued participation was 80%. Nonresponders also include twin families who changed addresses. Some families who did not participate at one age entered the study again at subsequent ages. Families in which one of the twins had a disease or handicap that interfered severely with normal daily functioning (about 2%) were excluded.

Table 8–1 describes the number of twin pairs by sex and zygosity at each age. The smaller sample size for the higher ages reflects the fact that this is an ongoing longitudinal study in which we add newborn twins annually. Thus, only families with twins born in 1986–1991 could have completed all surveys. A total of 1,513 families have completed all questionnaires. For 3,065, 5,353, and 7,516 twin families, there were data for respectively four, three, and two time points. The sample size was always smaller for father data, with an average response of 76%.

In order to test whether attrition has an effect on A/D, scores were compared between continuing and noncontinuing participants. At age 7 years A/D scores were somewhat larger in the noncontinuing group compared with the continuing group ($F_{1,4061}=6.426$; $P=0.011$). For all other ages, the means of the anxiety scores did not differ between the continuing and noncontinuing group.

Zygosity determination was based on blood/DNA polymorphisms and on questionnaires. For 854 same-sex twin pairs, zygosity was based on blood group ($n=436$ pairs) or DNA polymorphisms ($n=418$ pairs). For the remaining twins, zygosity was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers (Goldsmith 1991; Rietveld et al. 2000) obtained at ages 3, 5, 7, 10, and 12 years. The classification of zygosity was based on a discriminant analysis, relating the questionnaire items to zygosity based on blood/DNA typing in a group of same-sex twin pairs. According to this analysis, the zygosity was correctly classified by questionnaire in nearly 95% of the cases. If a discrepancy in zygosity status appeared across ages, then the most frequent zygosity status was used.

Instruments

At age 3 years, problem behavior was measured with the CBCL/2–3, a questionnaire comprising 100 items that describe specific behavioral, emotional, and social problems. Parents were asked to rate the behavior that the child displayed currently or in the past 2 months on a 3-point scale: 0 if the problem item was not true, 1 if the item was somewhat or sometimes true, and 2 if it was very true or often true. The A/D scale is based on factor analyses of data from several Dutch population samples (see Koot et al. 1997)

TABLE 8–1. Number of families with at least one parental report on Anxious/Depression at ages 3, 5, 7, 10, and 12 years

	3 years, *n*	5 years, *n*	7 years, *n*	10 years, *n*	12 years, *n*
Monozygotic, male	1,478	1,495	1,239	771	437
Dizygotic, male	1,576	1,561	1,248	693	384
Monozygotic, female	1,711	1,757	1,423	926	503
Dizygotic, female	1,463	1,453	1,166	672	356
Dizygotic, opposite sex, male and female	1,602	1,539	1,211	746	379
Dizygotic, opposite sex, female and male	1,516	1,450	1,133	691	344
Total	9,346	9,225	7,420	4,499	2,403

Note. Only twin pairs with known zygosity are included.

and is compatible with the syndrome scale as developed by Achenbach (1991). The A/D scale derived from the CBCL/2–3 contains 9 items. Anxiety at age 5 years was measured with a shortened version of the Devereux Child Behavior (DCB) Rating Scale (Spivack and Spotts 1966) that consisted of 42 items (van Beijsterveldt et al. 2004). Parents were asked to rate the behavior of their child in the last 2 months. Items were scored on a 5-point scale, with 1 = never and 5 = very frequently. The anxiety scale included 6 items. At ages 7, 10, and 12 years, A/D behavior was measured with the CBCL/4–18 (Achenbach 1991; Verhulst et al. 1996), a questionnaire of 113 items developed to measure problem behavior in 4- to 18-year-old children. Again parents were asked to rate the behavior of the child in the preceding 2 months on a 3-point scale. The A/D scale derived from the CBCL/4–18 contained 14 items. Table 8–2 summarizes the means and standard deviations for A/D at each age (average scores of mother and father).

STATISTICAL ANALYSES

Phenotypic Stability

Correlations across time within individuals (phenotypic stability coefficients) and twin cross-correlations were calculated by using the statistical software program Mx (Neale et al. 1997). To test for sex differences in correlation structure, the stability coefficients were constrained to be equal across boys and girls, and the fit of this model was compared with the fit of the previous model.

Next, twin cross-correlations (i.e., the correlation of first-born twin at time 1, with the second-born twin at time 2 and vice versa) were calculated. For each age and zygosity group, cross-correlations between oldest youngest and youngest oldest twins were constrained to be the same. The cross-correlations provide a first indication of the importance of genetic and environmental influences on the stability of a trait. If cross-correlations are higher for monozygotic (MZ) than for dizygotic (DZ) twin pairs, then genetic factors influence the stability of the trait.

Genetic Analyses

The essence of genetic model fitting is the decomposition of the observed variance in a univariate or multivariate phenotype (here A/D measured at multiple time points) due to additive genetic effects (A), shared or common environment effects (C), and nonshared environment (E) factors. A represents the additive effects of alleles at multiple loci; C represents common environment effects shared by children growing up in the same family such

TABLE 8–2. Means and standard deviation (SD) for untransformed Child Behavior Checklist (CBCL) Anxious/Depression (at ages 3, 7, 10, and 12 years) and Devereux Child Behavior (DCB) Anxiety (age 5 years): average scores from mother and father

	3 years		5 years		7 years		10 years		12 years	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Monozygotic, male	3.43	2.8	10.69	2.9	1.88	2.3	2.39	2.7	2.00	2.6
Dizygotic, male	3.45	2.9	10.99	3.0	2.22	2.5	2.55	3.0	2.16	2.8
Monozygotic, female	3.71	2.9	11.29	3.0	2.05	2.4	2.43	2.9	2.30	2.6
Dizygotic, female	3.71	2.9	11.38	3.1	2.31	2.5	2.54	3.0	2.20	2.7
Dizygotic, opposite sex, males	3.53	2.9	10.75	3.0	1.85	2.4	2.23	2.9	1.89	2.6
Dizygotic, opposite sex, females	2.98	2.8	10.96	3.0	2.00	2.4	2.30	2.8	2.05	2.6
Males	3.49	2.9	10.81	3.0	1.99	2.4	2.39	2.8	2.02	2.7
Females	3.48	2.9	11.21	3.0	2.12	2.4	2.42	2.9	2.20	2.6

as parental rearing practices, parental income, or socioeconomic status; and E represents all nonshared environmental influences, including measurement error. In model fitting of twin data the influences of A, C, and E are inferred through their effects on the covariances of relatives. The twin design compares the resemblance of MZ twins with DZ twins. MZ twins are nearly always genetically identical, and DZ twins share, on average, 50% of their segregating genes. If genetic variation affects trait variation, the phenotypic resemblance should be larger for MZ twins. If the degree of resemblance of traits is the same in MZ and DZ twins, shared environment mainly determines trait variation. Nonshared environmental effects are a source of phenotypic differences. The same reasoning applies to the analysis of multivariate and longitudinal data: if cross-correlations in MZ twins are higher than those in DZ twins, the covariance between traits is caused by genetic covariance. Application of longitudinal developmental models to the MZ and DZ data allows inferences about the underlying genetic and environmental effects of stability and change to be drawn (Boomsma and Molenaar 1987; Boomsma et al. 1989).

In the first series of longitudinal genetic analyses, we examined which developmental model give the best description of the developmental pattern. For these first series of analyses, the mean of the mother and father A/D ratings were used. If a value was missing for one of the parents, then the value was replaced by the rating of the other parent. By using the mean of the parental ratings, it is assumed that mothers and fathers rate the same underlying phenotype with a shared common understanding of the behavioral descriptions. Next, we combined the rater bias model with the longitudinal model and analyzed all available longitudinal maternal and paternal ratings.

Model Selection

To explore the influence of genetic and environmental factors over time, we started the longitudinal analyses with a triangular, or Cholesky, decomposition. A *Cholesky decomposition* is a fully saturated model in which the number of estimated parameters is equal to the number of independent variances and covariances. For each latent structure (A, C, and E) the number of factors is equal to the number of time points. The first factor influences all phenotypes at all five ages. The second factor influences the phenotype at the subsequent age plus all later ages. The following three factors operate in the same manner, with every factor starting one time point later. The model does not make any strong developmental assumptions, but it provides a general description of the contribution of genetic and environmental factors to developmental processes of stability and change. From the Cholesky

decomposition the genetic and environmental correlations between the A/D ratings across time can be obtained (as well as the heritabilities and other parameters at each time point). Next, we fitted two developmental models to the data that explicitly take into account the nature of developmental processes. The first approach is called a *common factor model.* This model contains one latent genetic (environmental) factor that accounts for the covariance among the five time points. The impact of a genetic (environmental) factor on A/D is the same at each age. To account for new influences, an age-specific factor is included for each age. The second model is called a *simplex model*, and in this model the latent factors that influence A/D scores at successive ages are causally linked. For example, genetic factors affecting A/D at age 3 years influence genetic factors affecting A/D at age 5 years (see Figure 8–1). The model also allows for genetic and environmental innovations (Neale and Cardon 1992) that introduce new variation at a time point. Because at the first time point the first latent factor cannot be explained by previous factors, these factors are handled as an innovation. Both developmental mechanisms predict different patterns of age-to-age correlations. A factor model predicts a correlational pattern across measures at different ages in which the size of the correlations does not depend on the time interval between measures. The simplex model predicts correlations that decrease with increasing time (Boomsma and Molenaar 1987). To test the fit of the two developmental models, we used the unconstrained Cholesky decomposition as a reference model.

The Rater Model

After the best longitudinal model is found, we combine this model with a multiple rater model. The psychometric model (Hewitt et al. 1992) estimates the influence of a genetic (A), a shared environmental (C), and a nonshared environmental (E) factor common to the phenotypes of the twins as rated by both parents. In addition, three rater specific factors—genetic ($A_{m/f}$), shared environmental ($C_{m/f}$), and nonshared environmental ($E_{m/f}$)—are estimated for the ratings of mother/father. Disagreement between parents in this model can be caused by rater specific behavioral views, leading to different but valid information from each rater. These rater-specific behavioral views can have their own unique influences, estimated in the rater-specific A, C, and E factors. Disagreements can also be caused by rater bias, which will confound the rater-specific shared environmental effects, or by unreliability, which will confound the rater-specific nonshared environmental effects. The three common factors loading on the twins' phenotypes contain only reliable variance, causing the common nonshared environmental factor to contain only pure independent environmental effects

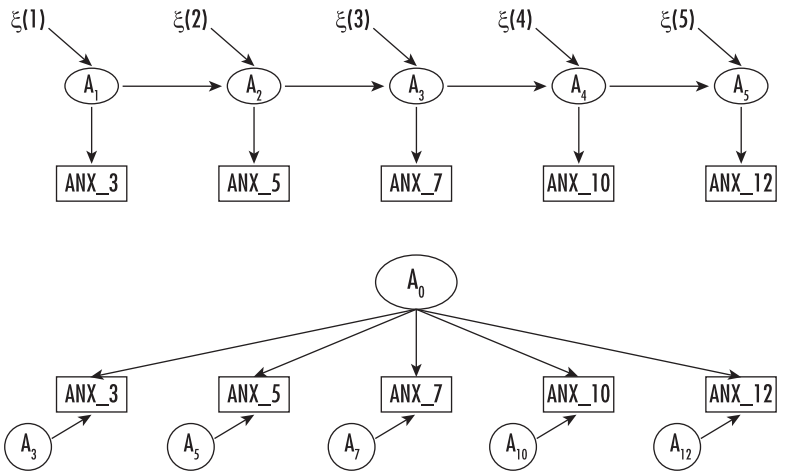

FIGURE 8–1. Path diagrams of the two different models used to investigate the underlying developmental mechanism in the latent factors across five time points (Anx_3, Anx_5, Anx_7, Anx_10, and Anx_12).

The upper figure represents a simplex model, and the lower figure represents a common factor model with age-specific effects. The two models are given for additive genetic (A) factors. The same models were applied to common environmental (C) and nonshared environmental (E) factors.

(McArdle and Goldsmith 1990) and the common shared environmental factor to contain only pure shared environmental effects.

Model-Fitting Procedures

Using raw data, Mx provides the possibility of handling missing data and allowed us to retain twin pairs who have missing data at one or more assessments. In this procedure the likelihood is calculated separately for each pedigree and the product of these likelihoods (i.e., the sum of the log likelihood) is maximized. This procedure assumes that the data are at least missing at random (Wothke 2000), meaning that the probability of missing depends on the observed data but not on the unobserved data, given the observed data (Little and Rubin 1987). From previous studies that used the same data set as the present one, it is tenable that the pattern of missing data in our study is at least missing at random (Rietveld et al. 2004; van Beijsterveldt et al. 2003).

The use of maximum likelihood estimation requires that the data be approximately normally distributed. The A/D scales of the CBCL and DCB showed a positively skewed distribution. Therefore, prior to the genetic anal-

yses the normalizing procedure of PRELIS (Jöreskog and Sörbom 1993) was applied to the data to approximate a normal distribution.

Goodness of fit was assessed by likelihood-ratio χ^2 tests. These tests compare the differences between –2-log likelihood of a full model with that of a restricted nested model. This difference is distributed as a χ^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 a restricted model. A large χ^2 value in comparison to the number of degrees of freedom suggest that the simpler model does not fit to the data as well as the more complex models. To select the best model, we used Akaike's information criterion (AIC). The AIC is the χ^2 minus twice the degrees of freedom (Akaike 1987). The model with the lowest AIC value is considered as the most parsimonious model.

RESULTS

Phenotypic Stability

Table 8–3 displays the phenotypic stability coefficients for the different time intervals. The stability coefficients did not differ between girls and boys ($\Delta\chi^2 = 16.33$, $df = 10$, $P = 0.091$). It can be seen that the degree of stability depends on age of the child and length of time interval. The stability is lower at younger ages and lower for longer time intervals. Moderate stability coefficients were found for age 7 years and older. From ages 3 and 5 years the continuity of A/D is low, but after age 7 years A/D becomes more stable. At first sight, the pattern of coefficients does not provide a clear insight in the nature of the underlying developmental processes. The correlation pattern did not point to a common factor model, which predicts a stable pattern of correlations, or to a simplex model, which predicts a decreasing correlation with increasing time intervals. This unclear picture could be a result of a mixture of developmental processes for the genetic and environmental factors.

Genetic Analyses

The lower part of Table 8–3 presents the twin correlations (at the diagonal) and twin cross-correlations for A/D. At each age, the MZ correlations were larger than the DZ correlations, suggesting additive genetic influences. The cross-correlations provide insight into the involvement of genes and environment in the observed stability of A/D across age. At first sight, it seems that at younger ages MZ cross-correlations were only slightly higher than the DZ cross-correlations and suggested that both genetic and environmental influences contributed to the stability. From age 7 years, the differences

TABLE 8–3. Phenotypic (within-person) correlations across age for Anxious/Depression (average rater score), cross-sectional twin correlations (on diagonal), and across-age twin correlations in males (below diagonal) and females (above diagonal) for monozygotic and dizygotic male and female same-sex twin pairs and dizygotic opposite-sex twin pairs

	Age 3 years	Age 5 years	Age 7 years	Age 10 years	Age 12 years
All twins					
Age 3 years	–	–	–	–	–
Age 5 years	0.30	–	–	–	–
Age 7 years	0.30	0.39	–	–	–
Age 10 years	0.30	0.36	0.59	–	–
Age 12 years	0.27	0.33	0.53	0.67	–
Monozygotic males and females					
Age 3 years	0.69/0.73	0.29	0.27	0.23	0.21
Age 5 years	0.26	0.74/0.74	0.31	0.3	0.24
Age 7 years	0.22	0.34	0.64/0.65	0.44	0.42
Age 10 years	0.24	0.31	0.47	0.61/0.69	0.49
Age 12 years	0.22	0.29	0.4	0.45	0.61/0.63
Dizygotic males and females					
Age 3 years	0.34/0.36	0.24	0.25	0.24	0.2
Age 5 years	0.22	0.44/0.46	0.21	0.26	0.23
Age 7 years	0.22	0.27	0.39/0.40	0.33	0.27
Age 10 years	0.18	0.31	0.28	0.40/0.47	0.35
Age 12 years	0.2	0.27	0.28	0.35	0.39/0.41

TABLE 8–3. Phenotypic (within-person) correlations across age for Anxious/Depression (average rater score), cross-sectional twin correlations (on diagonal), and across-age twin correlations in males (below diagonal) and females (above diagonal) for monozygotic and dizygotic male and female same-sex twin pairs and dizygotic opposite-sex twin pairs *(continued)*

	Age 3 years	Age 5 years	Age 7 years	Age 10 years	Age 12 years
Dizygotic opposite-sex twin pairs					
Age 3 years	0.38/0.31	0.19	0.17	0.22	0.25
Age 5 years	0.21	0.52/0.49	0.21	0.24	0.24
Age 7 years	0.22	0.26	0.41/0.41	0.31	0.27
Age 10 years	0.25	0.25	0.28	0.37/0.48	0.4
Age 12 years	0.26	0.28	0.28	0.3	0.43/0.51

between MZ and DZ cross-correlations seemed to be larger, suggesting that genetic factors became more important. However, the DZ correlations were still larger than expected on the basis of genetic influences alone, and it is expected that environmental factors play a role in the stability of anxiety in the older ages.

Next, a series of model-fitting analyses were conducted to test which developmental model best described the data. Each variance component (A, C, and E) was tested to see which developmental model best explains the data. The analyses started with a general developmental model, a Cholesky decomposition, which served also as the reference for evaluating of the fit of the other models. In all models the estimates of the parameters were allowed to differ across sex. Table 8–4 presents the fitting results of the various models. For the genetic component, neither the common factor model nor the simplex model provided a better fit than the Cholesky decomposition. Thus, it seems that a common factor or a simplex model alone is not a sufficient model to explain the developmental processes. For the shared environmental influences, a common factor model provided a better fit. This model contains one common factor loading on all five age groups and age-specific influences at each age. For the nonshared environmental influences neither the simplex nor the common factor model provided an adequate fit. Thus, a model with a common factor for shared environmental influences and a Cholesky decomposition for genetic and nonshared environmental influences provided the best description of the data. As a last step, we tested whether the parameter estimates in the best model differed between males and females. In contrast to the model with sex differences, the fit did not deteriorate after constraining the parameters to be equal across sex.

On the diagonal of Table 8–5, the proportion of explained variance by genetic and environmental factors is given for A/D at each age. Genetic factors explained 63% of the variance of anxiety at age 3 years and declined slowly to 41% at age 12 years. The contribution of shared environment at a specific age consisted of age-specific shared environment and environmental influences shared with all ages. The role of age-specific shared environment was low at all ages (ranging from 0 to 5). The total variance explained by shared environment factors was 8% at age 3 years and increased to 23% at age 12 years. The contribution of nonshared environmental factors remained quite stable and ranged from 26% to 36%.

Because our focus was on developmental processes, of special interest are the contributions of genetic and environmental factors on the stability of anxiety as reported on the off-diagonal in Table 8–5 and the genetic and environmental correlations in the lower part. At younger ages (3 and 5 years), the genetic and environmental factors contributed to stability to the same degree. Genetic factors accounted for, on average, 48%, and shared

TABLE 8–4. Model fitting results for longitudinal developmental models of anxious/depression (average rater scores)

	–2 LL	*df*	Compared with model	χ^2	*df*	*P*	AIC	Critical value χ^2
1. Triangular decomposition for A, C, E	301164.9	65655						
2. A simplex	301250.4	65667	1	85.501	12	0.000	61.501	21.026
3. A common factor	301201.2	65665	1	36.276	10	0.000	16.276	18.307
4. C simplex	301174.7	65667	1	9.777	12	0.636	–14.223	21.026
5. C common factor	301166.4	65665	1	1.478	10	0.999	–18.522	18.307
6. E simplex	301221.8	65667	1	56.928	12	0.000	32.928	21.026
7. E common factor	301198.8	65665	1	33.905	10	0.000	13.905	18.307
8. Model 5 without sex differences	301216.4	65705	5	50.051	40	0.133	–29.949	55.758

Note. AIC=Akaike's information criterion (c^2; df=2); LL=log likelihood; χ^2=–2 (difference in log likelihood) between models; *df*=degrees of freedom; *P*=probability value associated with χ^2.

TABLE 8–5. Upper part: relative contribution of genetic and environmental factors to the total variance (i.e., heritability on diagonal of first matrix) and covariances of Anxious/Depression (based on the across-rater score). Lower part: correlations between genetic and environmental factors for Anxious/Depression (based on the across-rater score)

	Additive genetic					Common environment					Unshared environment				
Age	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years
3 years	0.63					0.00/ 0.08[a]					0.29				
5 years	0.50	0.52				0.43	0.00/ 0.22[a]				0.08	0.26			
7 years	0.67	0.51	0.51			0.27	0.35	0.05/ 0.09[a]			0.06	0.13	0.35		
10 years	0.56	0.34	0.58	0.49		0.43	0.54	0.21	0.01/ 0.17[a]		0.01	0.11	0.21	0.33	
12 years	0.47	0.27	0.55	0.47	0.41	0.46	0.60	0.24	0.27	0.04/ 0.19[a]	0.07	0.13	0.21	0.26	0.36
Age	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years
3 years	1.00					1.00					1.00				
5 years	0.26	1.00				1.00	1.00				0.08	1.00			
7 years	0.35	0.39	1.00			0.79	0.79	1.00			0.06	0.17	1.00		
10 years	0.27	0.24	0.69	1.00		0.99	0.99	0.78	1.00		0.01	0.14	0.37	1.00	
12 years	0.24	0.20	0.63	0.70	1.00	0.91	0.91	0.72	0.90	1.00	0.05	0.14	0.32	0.50	1.00

[a]Effect of shared or common environment effects (C) is partitioned into age-specific C (first number) and to C common to all ages (second number).

environmental factors accounted for 44%, of the phenotypic stability across ages. From age 7 years the contribution of genetic influences to the stability was comparable (53%), but the contribution of shared environmental influences was reduced (24%). The contribution of nonshared environmental factors to stability was small in the younger ages (8%) and became more important after age 7 years (on average 23%).

The lower part of Table 8–5 presents the correlations among the genetic and environmental factors, which represent the extent to which the same genes or same environmental factors contribute to the phenotypic stability. A high correlation suggests that the same factors play a role, whereas a low correlation points to processes of change. The genetic correlations between the younger ages and older ages were low, suggesting that different genes operate at these ages. The genetic correlations were substantially higher at ages 7–12 years but still were suggestive for change processes. The correlations among the shared environmental correlations were high and indicated that the same shared environmental factors were important during childhood. The correlations among the unique nonshared environmental correlations were very low at the younger ages but were higher between the factors at the higher ages. Thus it seems that nonshared environmental influences were mainly age specific at younger ages, but after age 7 years some influence of the nonshared factors persisted over time.

Longitudinal Rater Models

Finally, we combined the best-fitting longitudinal model with a psychometric rater model. In the previous models, the assumption was that both parents rate the same underlying phenotype. From previous results it is known that the parents indeed assess the same behavior in their twins but that there is also a component specific to each rater (Boomsma et al. 2005). This rater-specific part contains rater-specific views but also rater bias and may lead to biased estimates of the genetic and environmental components. To get insight into the contribution of rater-specific factors to the total variance of anxiety, a model was applied that takes into account the effects of the specific rater part. The model decomposes the variance into a part that is similarly assessed by both raters and into a part that is specific for each rater. Table 8–6 and Figure 8–2 show the age-specific parameter estimates of A, C, and E accounted by the common parental part and by the specific rater part. Genetic factors accounted for 61% (43% [common]+18% [specific]) at age 3 years to 35% (22%+13%) at age 12 years of the total variance of anxiety as rated by the mother. For anxiety rated by the father, genetic factors explained 56% (47%+9%) of the variance at age 3 years and 42% (31%+11%) at age 12 years. The largest part of the genetic variance was accounted

TABLE 8–6. Proportion of variance and covariance explained by genetic factors common to raters (father and mother), by environmental factors common to raters, and by rater-specific genetic and environmental factors

		Mother rating					Father rating				
	Age	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years
A common	3 years	0.43					0.47				
	5 years	0.42	0.32				0.51	0.34			
	7 years	0.50	0.42	0.28			0.65	0.58	0.41		
	10 years	0.45	0.32	0.37	0.25		0.60	0.45	0.57	0.37	
	12 years	0.36	0.24	0.38	0.31	0.22	0.54	0.33	0.55	0.48	0.31
C common	3 years	0.04					0.05				
	5 years	0.24	0.11				0.29	0.11			
	7 years	0.15	0.18	0.04			0.19	0.25	0.06		
	10 years	0.25	0.29	0.10	0.09		0.33	0.40	0.16	0.13	
	12 years	0.28	0.34	0.14	0.16	0.11	0.42	0.48	0.19	0.24	0.16
E common	3 years	0.16					0.18				
	5 years	0.07	0.14				0.08	0.14			
	7 years	0.03	0.10	0.16			0.04	0.13	0.24		
	10 years	0.00	0.08	0.16	0.16		0.00	0.11	0.24	0.23	
	12 years	0.04	0.10	0.14	0.16	0.17	0.05	0.14	0.20	0.26	0.24

TABLE 8–6. Proportion of variance and covariance explained by genetic factors common to raters (father and mother), by environmental factors common to raters, and by rater-specific genetic and environmental factors *(continued)*

		Mother rating					Father rating				
	Age	3 years	5 years	7 years	10 years	12 years	3 years	5 years	7 years	10 years	12 years
A rater-specific	3 years	0.18					0.09				
	5 years	0.13	0.19				–0.02	0.11			
	7 years	0.10	0.08	0.19			–0.05	–0.08	0.07		
	10 years	0.06	0.05	0.15	0.17		–0.02	–0.06	0.00	0.09	
	12 years	0.15	0.14	0.13	0.14	0.13	–0.28	–0.15	–0.07	0.00	0.11
C rater-specific	3 years	0.04					0.09				
	5 years	0.16	0.11				0.15	0.16			
	7 years	0.20	0.19	0.12			0.15	0.12	0.10		
	10 years	0.24	0.22	0.17	0.13		0.13	0.10	0.06	0.08	
	12 years	0.16	0.17	0.13	0.11	0.15	0.25	0.18	0.11	0.07	0.07
E rater-specific	3 years	0.15					0.13				
	5 years	–0.01	0.14				–0.01	0.13			
	7 years	0.02	0.03	0.21			0.03	0.01	0.13		
	10 years	0.01	0.05	0.06	0.21		–0.03	0.01	–0.03	0.11	
	12 years	0.01	–0.01	0.07	0.12	0.21	0.01	0.02	0.01	–0.04	0.12

Note. A=additive genetic effects; C= shared or common environment effects; E= nonshared environment effects.

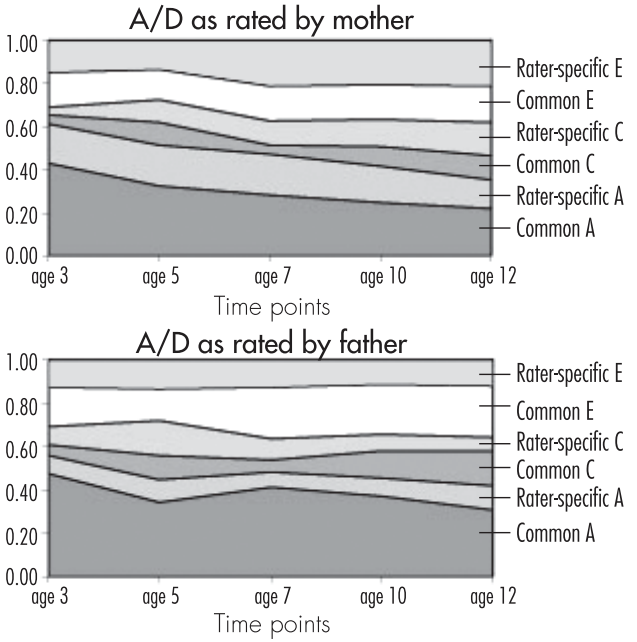

FIGURE 8–2. Relative influence of additive genetic effects (A) and environmental effects, common (C) and nonshared (E), across ages 3–12 years, separately for father and mother ratings of Anxious/Depression (A/D).

by the common parental view. Averaged over 5 ages, 66% (80% for fathers) of the genetic variance could be explained by a common parental view. The rater-specific genetic part of the mother accounted for 13%–19% of the total variance and was somewhat lower for the father (7%–11%). The total variance explained by shared environmental factors ranged between 8% (4%+4%) at age 3 years and 26% (11%+15%) at age 12 years, and the largest part of the shared environmental variance was accounted by rater-specific factors. The variance accounted by nonshared environmental factors was around 30%, and about the half of this variance was accounted for by rater-specific factors. The same picture emerged for the estimates of stability. The largest part of the covariance between ages was explained by the factors representing the common view of both parents. The rater-specific factors contributed only to a small part of the total variance.

DISCUSSION

We analyzed longitudinal data on A/D in a large sample of young twins ages 3–12 years who had been rated by both their parents. The purpose of the study was to determine the relative stability and change of genetic and environmental influences on common child A/D. Such research can be seen as providing a view on possible windows of development when environmental factors may be of greater importance than at other ages. Similar ideas about genetic influences can also be considered. By employing a longitudinal design it was possible to investigate how genes and environmental factors contribute to the processes of stability and change across development. Because our study included five time points we could also test the structure of the developmental process. By applying the longitudinal model to both mother and father ratings, we were able to disentangle the rater-specific views from that part of the phenotype upon which both parents agree.

As suggested by the results of the cross-sectional study of A/D in the same sample of twins, the influence of genetic factors declined with increasing age (Boomsma et al. 2005). The heritability was around 60% at age 3 years and declined to about 40% at age 12 years. The decrease in heritability when children grew older was accompanied by an increase in the influence of the shared environment (8% at age 3 years and 23% at age 12 years). Although not directly addressed in the analyses, findings such as these argue for shared environmental factors as playing a major role in protecting children from or putting them at risk for the expression of A/D. The contribution of nonshared environmental factors ranged from 26% to 36%. These data indicate that nonshared environment—or environmental influences that contribute to differences between siblings—plays a substantial role across development when considering the expression of A/D.

The results showed that the stability of A/D was relatively low between age 3 years and later ages (correlations around 0.30) but became higher after age 7 years (up to 0.67 between ages 10 and 12 years). Both genetic and shared environmental factors accounted for the phenotypic stability of A/D. Across all ages, genetic factors accounted for about 50% of the phenotypic stability. The genetic correlations between A/D assessed at 3 years and other ages were modest, suggesting a small overlap of genes that influence A/D in preschool children and in middle childhood (genetic correlations between 0.24 and 0.35 for A/D at age 3 years with other ages). These results raise the possibility of different genetic influences of genes across development, either by variable expression patterns, variable response to environmental mediators and modifiers, or simply evidence of developmental genetic processes. After age 7 years, the genetic correlations were larger (0.63–0.70), indicating that the extent to which the same genes operate across ages 7–12 years was increased.

The influence of common environmental factors shared by twins from the same family on the stability of A/D was highest in early childhood (around 50% for the preschool children) and was reduced after age 7 years. Across ages, the same common environmental factors were suggested, because a single C factor could explain the covariance pattern across age. Family variables such as parental conflict, negative familial environments, and separation are likely candidates for these shared environmental influences. Future genetic research should include such environmental variables (e.g., parental divorce) to specify the role of these environmental factors.

Nonshared environmental factors operate mainly in a time-specific manner. At younger ages, the role of nonshared environmental factors in stability of A/D is nearly nil but is somewhat increased (up to 26%) between ages 10 and 12 years. When children grow up they have a greater chance to experience life events outside the family. These individual outside experiences could promote A/D in one twin and not in the other.

It should be mentioned that a part of the shared environmental factors reflects parental bias. Because the same rater was used at two or more points, the prediction of A/D could reflect some shared rater bias. If this is the case, the observed stability is not only a reflection of stability of children's problem behavior but also a reflection of the stability of the mother's or father's perception. However, when the longitudinal model is applied to both father and mother ratings, it is possible to disentangle the effects caused by "real" environment and the effect caused by rater bias. As indicated by the results, there is still evidence for shared environmental influences on the stability of A/D when data from father and mother are analyzed simultaneously. However, results indicate also that the rater-specific shared environment contributes to stability of A/D. This could point to possible rater bias that is persistent and affects the stability of A/D.

In general the stability of A/D was lower than reported for the externalizing behaviors in the same sample of twins across all ages (Bartels et al. 2004; Rietveld et al. 2004; van Beijsterveldt et al. 2003). For example, the stability coefficient of aggression was 0.48 between ages 3 and 7 years and 0.42 between ages 3 and 12 years. The stability coefficients of aggression ranged from 0.67 to 0.77 for the shorter time intervals (between ages 7 and 10 years). The stability coefficients of attention problems were in between the coefficients of aggression and A/D. One possible explanation for the lower stability of A/D, compared with externalizing behaviors, is that preschool children have a limited ability to express feelings of anxiety and that parents have more difficulties recognizing A/D problems. In accordance with the externalizing problem behaviors, the stability of A/D became a more stable characteristic as children age. However, we cannot exclude that the lower stability of preschool A/D is due to the use of different assessment

instruments. Anxiety is measured with the CBCL/2–3 at age 3 years, with the DCB at age 5 years, and with the CBCL/4–18 at age 7 years. Although the items of the CBCL/2–3 and the CBCL/4–18 have some overlap, they may not measure the same underlying construct.

The developmental pattern of changing genetic and environmental influences of A/D during childhood also differed from externalizing problem behaviors as measured in the same sample of twins (Bartels et al. 2004; Rietveld et al. 2004; van Beijsterveldt et al. 2003). For aggression we found that the heritability increased from ages 3 to 12 years and that the relative influence of shared environmental influences decreased. For attention problems the heritability remained constant over the years, and shared environmental influences were of no importance at all.

This departure from the findings for aggressive behavior and ADHD is of tremendous importance from both a clinical and a research point of view. From our cross-sectional and longitudinal work on A/D, it appears that early in life the expression of an anxious phenotype is influenced significantly by genetic factors. These data are consistent with a wide literature on infant anxiety, behavioral inhibition, and temperament. From research in humans (Kagan and Snidman 1999) and animals (Suomi 2005), it is clear that life experience can affect both positively and negatively the childhood, adolescent, and adult outcomes of anxious children. Perhaps most importantly, with the evidence that the influence of shared environment increases with age comes the possibility that children at risk for anxiety can be influenced away from the expression of severe expression of A/D or, sadly, influenced toward the expression of the same phenotype. Recent, remarkable findings from association studies of the serotonin transporter gene and tryptophan hydroxylase gene provide evidence that children with different genotypes have variable responses to different environmental stimuli and are at highly variant risk for negative outcomes. For a review of this work, see Chapter 7, "Genetic and Environmental Modifiers of Risk and Resiliency in Maltreated Children," in this book.

Further support that childhood A/D has a different developmental profile than disruptive or externalizing disorders is provided by the study of childhood obsessive-compulsive behavior. The developmental pattern was comparable with that of anxiety: from ages 10 to 12 years a threefold increase in the shared environmental influences was reported (van Grootheest et al. 2007). These various developmental patterns of genetic and environmental influences have implications for parenting, clinical medicine, and ultimately research. For parents, it is important to know that having a child with early anxiety does not necessarily indicate a lifelong problem with this phenotype or outcome. Clinically, a commitment to behavioral (e.g., shared environmental mediation) therapies such as those embodied by cognitive-behavioral

therapy may yield robust, stable wellness outcomes. Indeed, research by Kendall and Panichelli-Mindel (1995; Kendall et al. 2004) reported that 90% of children who received cognitive-behavioral therapy at an index visit for child anxiety disorders no longer suffered from that disorder at 3.5 and 7 years posttreatment (and without any ongoing treatment other than the original course of cognitive-behavioral therapy). Other forms of therapy, such as exposure response prevention, for childhood anxiety disorders have consistently resulted in robust improvement in children who suffer from these disorders. A commitment to these treatments is at the very least supported by our findings.

Taking these results to the research community via translational research is already under way. Alleles of common candidate genes have been shown to place individuals at differential risk for the development of anxiety and depressive disorders on the basis of the genetic makeup of the individual and whether he or she has been exposed to stressful life events. As research identifies more candidate genes for anxiety and depressive disorders, it may well be that we will reconceptualize these genes as reactivity genes rather than as genes of illness. Such a perception could directly lead to a frameshift in how wellness medicine could be practiced. Children with certain genotypes may well benefit from different types of (therapeutically designed) environments.

CONCLUSIONS

With the evidence from family studies that affective and anxiety disorders are familial, combined with the evidence that parental psychopathology increases the risk of offspring psychopathology (perhaps by creating a more toxic shared environment), we may need to consider more robustly assessing for and treating parental psychopathology as a direct clinical intervention for children with A/D. This perception is supported at least in part by the recent study of Weissman et al. (2005, 2006), which demonstrates that with the successful treatment of maternal depression, children in that family will have a reduction in their internalizing psychopathology syndrome scores of a full standard deviation. To put it succinctly, by treating mothers, children's A/D scores improved without directly treating the children.

As we move into the generation of genomic and wellness medicine, combining consideration of the etiopathologic contributions to A/D throughout development invites us to consider how we can use traditional therapies (e.g., Kendall and Panichelli-Mindel 1995; Kendall et al. 2004) with greater confidence in at-risk populations. In addition, generalizing these lessons to educational programs for the better public health of all children could well

lead to a reduction in the morbidity and mortality associated with anxiety and affective disorders.

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