8 Studying the development of children's problem behaviors using quantitative genetic techniques

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Problem behaviors in children: A general health problem worthy of investigation

The last three decades have shown problem behaviors in children to be quite prevalent. Of preschool children, Richman et al. (1975, 1982) using parental reports, identified 6-7% of 3-year-old children as moderately or severely disturbed. They found no significant differences between the sexes in overall scores, but the individual items showed boys to be significantly more likely to be overactive and girls to be more likely to be fearful. In middle childhood, Rutter et al. (1976) using parental interviews, diagnosed 12.7% boys versus 10.9% girls of 10-year-old children and 13.2% boys versus 12.5% girls of 14- and 15-year-old children to have a psychiatric disorder. Rutter concluded that although psychiatric conditions were probably a little commoner during adolescence than during middle childhood, the difference was not a large one. Verhulst and Koot (1992), in a review of 38 studies (using different techniques, sample sizes, age ranges, assessment methods, informants and case definitions) calculated the median prevalence rate for general psychiatric dysfunction to be 13%. The majority of studies were consistent in their reports of sex differences with regard to types of disorders. Girls tended to show more internalizing or emotional problems, whereas boys were more inclined to show externalizing or disruptive behavior problems. The studies showed conflicting results as far as overall level of deviance was concerned.

Longitudinal studies have shown problem behaviors to be persistent. The Dunedin study (Caspi et al., 1995, 1996) found that temperamental qualities observed by examiners at ages 3 and 5, predicted specific behavior problems rated by parents at ages 9, 11, 13 and 15 and even DSM-III-R diagnoses of adult psychiatric disorders at age 21. Undercontrolled 3-year-olds were more likely at 21 years of age to meet diagnostic criteria for antisocial personality disorder and to be involved in crime, while inhibited 3-year-olds were more likely at 21 years of age to meet diagnostic criteria for depression. The best predictor of good outcome was the absence of early behavior problems, indicating that high levels of problem behaviors at a young age were not just a normal developmental aspect. Hofstra et al. (in press) conducted a longitudinal follow-up of a Dutch general population sample. Of the 1615 4-16 year-olds initially classified deviant, 41% still classified themselves as deviant 14 years later and 29% were still classified deviant according to their parents. Koot (1995) concluded in his review of longitudinal studies of general population and community samples that, across

studies, one-third to one-half of children with initial deviant scores maintain deviant scores across 2- to 6-year intervals. Although most children showed fluctuations over time in their level of deviant behavior, extreme changes were rare.
Taken together, the demonstration that high levels of problem behaviors are not just a normal developmental aspect, the median prevalence rate for general psychiatric dysfunction of 13%, and the fact that children do not simply grow out of their behavior problems indicate that problem behaviors in children are a general health problem worthy of investigation.

Outline of this chapter

For purposes of prevention and treatment of problem behaviors in children, it is important to understand their etiology. During the last decade, quantitative genetic studies have begun to disentangle the genetic and environmental influences on the interindividual differences in problem behaviors during childhood, adolescence and young adulthood.
In this chapter, quantitative genetic techniques and studies exploring the development of children's problem behaviors will be presented. First, the continuous distribution that most problem behaviors are assumed to show is discussed. Second, three different designs for examining the role of genetic and environmental influences on problem behaviors, that is family, twin and adoption studies, and their underlying assumptions are introduced. Third, various effects that might be incorporated in the theoretical model, like sex limited gene expression, gene - environment interaction and correlation, longitudinal effects and multivariate modelling, are outlined. Fourth, three issues pertaining to the measurement of children's problem behaviors, namely developmental changes, rater bias and sibling interactions, are discussed. Fifth, studies exploring the genetic and environmental influences on children's problem behaviors are presented. Sixth, the need for longitudinal behavior genetic studies is addressed, followed by a description of the Dutch twin study of problem behaviors. This study examines the genetic and environmental influences on the development of problem behaviors in children, by conducting a longitudinal follow-up of a large sample of twins. Finally, several research questions that are still in need of exploration are discussed.

Multiple genetic and environmental influences on continuously distributed problem behaviors

Most problem behaviors of children, such as aggression or anxiety, generally do not fall into distinct categories of behaviors that are either present or absent, but involve quantitative variations of behaviors that most children display to some degree.
These continuous variations in problem behaviors are hypothesized to be caused by multiple genes and environmental influences. The polymorphic genes (each possibly with a small effect) are assumed to combine to produce, together with various environmental influences, the observable differences among individuals

in a population. In twin and other genetic epidemiologic studies, the influences of the genetic and environmental components are estimated in terms of the amount of variance they explain of this underlying continuous distribution.

Different quantitative genetic designs

Different genetically informative designs can be used to examine the contributions of genetic and environmental factors, the three basic designs being: family, twin and adoption studies. No design is ideal for every purpose. For each research question a certain genetically informative design is best suited to answer it.

Faraone and Santangelo (1992) summarized a sequence of questions which tend to follow in a logical progression when doing genetic epidemiologic research. The first reasonable question to be asked is whether a disorder is familial, in other words: "Does it run in families?". Family studies are best suited to answer this question and detect familial transmission. The next logical question is: "What is the relative magnitude of genetic and environmental contributions to disease etiology and expression?". Twin and adoption studies are quite appropriate for this kind of research. Twin studies give direct and powerful tests of genetic and environmental effects and adoption studies are excellent for the detection of cultural effects. The third question in the sequence is: "How is the disease transmitted from generation to generation?". Segregation analyses, employing family data (pedigrees) can be used to study this issue. The fourth question in the sequence is: "If genes mediate this transmission, where are they located?". To be able to search for disease genes on the human genome, chromosomal material (DNA) has to be collected from the subjects that are to be studied. Linkage analysis requires DNA from the members of a family, for instance from sib pairs, to be able to assess the co-inheritance of a disease with a marker. Association studies test whether a particular allele is associated with a disease and therefore do not require information on family members, obtaining sufficient data from, for example, samples of unrelated patients and controls (if issues of population stratification can be assumed to be not important). The last logical question when doing genetic epidemiologic research is: "What are the genetic and environmental mechanisms of disease?". In other words what kind of function does the gene have and are there any kinds of environmental influences that have some effect on the gene's (in)activation? To answer this question, the position of the gene on the chromosome has to be known so its biochemical activities can be studied, possibly in interaction with various environmental influences.

The three basic genetically informative designs: family, twin and adoption studies and their underlying assumptions will be explained next. Because the most often used design is the twin study, some assumptions (like assortative mating) are described under that subheading even though they are also of importance for the other designs.

Family studies

Family studies are useful to answer the first question to be asked: whether or not there is familial resemblance for the behaviors being investigated. The idea behind the family study is that if a behavior has a genetic etiology, then the relatives of probands (individuals displaying the behavior) should have greater risk for demonstrating the behavior than the relatives of controls (individuals not showing the behavior). Also, the chance that relatives of probands display the behavior should be correlated with the degree of relationship the relative has to the proband. The risk should be greater for first-degree relatives (parents, siblings, children), who share on average 50% of their genetic material with the proband, than for second-degree relatives (grandparents, half-siblings, nephews, etc.), who share on average 25% of their genes with the proband. Thus, a genetic hypothesis predicts that the risk for relatives of probands is higher than the risk for relatives of controls, and that the risk for relatives of probands increases as the amount of genes shared increases (Faraone and Tsuang, 1995). Familiality has been found for family studies of depression, attention deficit / hyperactivity disorder, antisocial behavior, alcohol and drug problems, schizophrenia and autism, among others (Rutter et al., 1999b). However, results of family studies can only provide initial hints that a behavior might have a genetic etiology. The conclusion that the familial resemblance is caused by genes can not be made, because problem behaviors can also 'run in families' for nongenetic reasons such as shared environmental adversity, viral transmission, and social learning (Faraone and Tsuang, 1995). Twin or adoption studies are necessary to examine the relative magnitude of genetic and environmental contributions to the etiology and expression of the problem behaviors.

Twin studies

The second question in the chain of genetic epidemiologic research: "What is the relative magnitude of genetic and environmental contributions to the etiology and expression of behavior problems?" can be studied using twin or adoption studies. In twin studies, monozygotic twins, who are genetically identical and thus share 100% of all their genes, are compared with dizygotic twins, who share on average 50% of their segregating genes. Because both types of twins usually grow up in the same family, they are assumed to share on average the same kind of familial environment. A certain behavior is influenced by genes if monozygotic twins resemble each other to a greater extent than dizygotic twins, because the only difference between the two groups is in genetic relatedness. By comparing the correlation of problem behaviors between monozygotic twins with the correlation of problem behaviors between dizygotic twins, the magnitude of genetic and environmental influences can be estimated. Two kinds of environmental influences can be distinguished: shared environmental influences and nonshared environmental influences. Shared environmental influences denote life experiences affecting twins growing up in the same family similarly, for instance socioeconomic level, religion, or style of parenting. Nonshared environmental influences denote the impact of all environmental factors influencing only one of the subjects being studied, such as an illness, disease, trauma, expe-

riences at school, relationships with peers or the way one perceives the world. For each problem behavior under investigation, the following situations can apply:

- Only nonshared environmental influences are of importance. In this case, the correlation of problem behaviors between monozygotic twin pairs and the correlation of problem behaviors between dizygotic twin pairs are both zero, because the twins neither share genetic nor environmental influences. (For sake of brevity, the correlation of problem behaviors between monozygotic (dizygotic) twin pairs is often called the correlation between monozygotic (dizygotic) twins).
- In addition to the nonshared environmental influences, genetic effects are also of importance. Monozygotic twins, who have a genetic relatedness of 100%, are now expected to show a correlation that is twice as large as the correlation between the dizygotic twins, who share on average 50% of their genetic inheritance.
- Shared environmental influences and nonshared environmental influences are of importance, but there are no genetic effects. In this case the correlation between monozygotic twins will be bigger than zero and equal to the correlation between the dizygotic twins. Because genetic effects are absent, the correlation between monozygotic twins is not expected to be larger than the correlation between dizygotic twins. Individuals only resemble each other because of environmental influences, which monozygotic and dizygotic twins share to the same extent.
- All three influences are of importance to explain the variances between individuals in a population. In this situation the correlation between monozygotic twins will be bigger than the correlation between dizygotic twins but less than twice its size, because in addition to genetic influences shared environmental influences also cause twins to resemble each other.
- Genetic effects do not sum up (additive genetic effects) but interact with each other at the same locus (genetic dominance) or at different loci (epistatic influences). In this case the correlation between monozygotic twins, who have an identical genetic make-up, will be much larger than twice the correlation between dizygotic twins, because dizygotic twins do not share identical genes at the same loci.

To estimate the magnitude of the genetic and environmental influences, a theoretical model incorporating these possible correlational effects is fitted to the observed data which are summarized in variance-covariance matrices. The model describes the observed data to a satisfactory extent if the theoretical model can not be statistically rejected. Of course, the collected sample size should be large enough to enable rejection. A small sample size may result in a model being accepted that actually has a poor fit to the observed data (Marsh et al., 1988). The magnitude of the genetic and environmental influences are estimated in this theoretical model, regardless of the modes of action or the number of genes or environmental factors involved. Confidence intervals of the estimated influences can be obtained as a guide to their significance and precision, and goodness-of-fit tests show if the model is indeed consistent with the observed data within the limits of precision imposed by the sampling variation (Eaves, 1982).

When twins are used to study the etiology of problem behaviors in children, at least three assumptions are made which must be fulfilled in order to obtain valid results.

First, as explained above, quantitative genetic techniques assume that monozygotic and dizygotic twins experience on average the same shared environmental influences, the so-called equal environments assumption. The fulfilment of this assumption is crucial because, if the equal environments assumption is incorrect, excess resemblance of monozygotic twins compared with dizygotic twins ascribed to genetic factors could be partly or entirely due to environmental effects. The equal environments assumption has lead to at least two different concerns. One concern has been that parents are more likely to treat monozygotic twin pairs more similarly than dizygotic twin pairs because of their knowledge that they are identical. Kendler (1993) summarized five different ways in which the equal environments assumption can be tested, among others the effects on reported twin resemblance when parents are either correctly informed or misinformed about their twins' true zygosity. He concludes that available empirical evidence suggests that the assumption is probably at least approximately correct for the psychiatric disorders he studied, which included major depression, generalized anxiety disorder, phobia, and alcoholism in adult females. Another concern has been that parents and others are more likely to treat monozygotic twins, who look alike, more similarly than dizygotic twins. Fitting a structural equation model to examine the impact of physical similarity on phenotypic resemblance, Hettema et al. (1995) concluded that for the disorders mentioned by Kendler (1993), the equal environments assumption is supported. People do not seem to treat children who look alike more similarly than children who show less physical similarity.

The second assumption made when studying twins is that the level of problem behaviors reported for twins are comparable to those of singletons. The validity of this assumption is necessary in order to generalize the results of twin studies to singleton populations. Studies comparing twin and general population samples found few differences between the two groups. Van den Oord et al. (1995) compared preschool twins and singletons and concluded that the general level of problem behaviors in twins was broadly comparable to that in singletons. Gjone and Növik (1995) examined the impact of pre- and perinatal factors on parental reports of behavior problems and found that birth weight and birth order did not contribute significantly to differences between twins and a general population sample. When differences between twins and singletons were found, twins tended to have somewhat higher levels of externalizing behaviors than children from the general population (Gau et al., 1992; Simonoff, 1992). A possible reason for this result is sibling effects (Carey, 1986). Twins, always from a sibship of size 2, might show sibling interactions (imitation or cooperation) that are absent in singleton populations if the subjects grow up without siblings. Sibling interactions may also have caused the increased variance found for twins' externalizing behaviors by Gjone and Növik (1995). Nevertheless, differences found between twin and singleton populations were usually small.

The third assumption in classical twin designs (as in other designs) is that there has been no assortative mating between the (twins') parents. Assortative mating

denotes the nonrandom selection of a mate on basis of either similarities or differences between the spouses. For instance, spouses can select each other on the ground of similar psychiatric disorders, or on the basis of cross-assortment between disorders: alcoholism in husbands with depression in wives. Effects of assortative mating may be confounded with shared environmental factors (Neale and Cardon, 1992) because both assortative mating and shared environmental influences act to increase the variance and covariance between monozygotic and dizygotic twins equally. Therefore, without adjustment for significant levels of assortment, estimates of genetic influences on the liability of a certain trait will be biased downwards. Still, if effects of assortative mating exist, they will probably not be large because when spousal correlations are found they are mostly small, in the region of 0.1 to 0.3 (Simonoff et al., 1994). Meas et al. (1998) tested directly whether a significant association could be found for psychiatric diagnoses (alcoholism, generalized anxiety disorder, major depressive disorder, panic disorder and phobias) between husbands and wives in two population-based samples. They found significant but moderate assortment for psychiatric disorders and concluded that the bias in twin studies that have ignored the small amount of assortment is negligible.

Adoption studies

The advantage of adoption studies is that genetic and shared environmental influences are separated. Adoption studies can correlate traits measured in subjects from within the family or outside the family. Within the family, adopted children can either be compared with their nonadopted siblings or with their adoptive parents. With both family relations they only share the same environmental influences, because the adoptees have no genes in common with their adoptive parents. Thus, if the adoptees' behavior is correlated with the behavior of either their adoptive parents or their nonadopted siblings, only the shared environmental influences can be responsible for the phenotypic resemblance. Outside the family, adopted children can be compared with their biological parents or their biological siblings, with whom they share on average 50% of their genetic make-up. Because the adopted children and their biological parents or biological siblings do not share the same environment, similarities between adoptees and their biological parents or biological siblings must be effected by genetic influences.

A number of factors might cause the genetic and environmental influences in adoption studies to be not completely dissociated, thereby distorting the results. First, selective placement can cause the biological and adoptive parents to be correlated for the studied behavior or for characteristics which may affect the studied behavior. Second, the more the adoptive parents know regarding the biological parents, the more they could be biased in their expectations of and behavior towards their adopted children. Adopted children might also differ from nonadopted, biological children. First, the 'status of being adopted' could be an adversity which predisposes to problem behaviors. Second, biological parents who give up their child for adoption might differ from the general population and adoptive parents may also form a non-random sample from the population.

In a special kind of adoption study, using siblings that are both adopted as subjects, one can correct for the possible distortion of results by differences between adopted and biological children because in this case all subjects are adopted. Also, possible correlations between genotype and environment, that might occur when studying parents and their biological children, can not distort the results. Prerequisite is that large enough samples of adopted siblings can be collected. Van den Oord et al. (1994) compared two groups of adopted siblings: a group of siblings who were biologically related and both adopted into the same home, with another group of siblings who were not biologically related but also adopted into the same family. Biologically related adoptees shared on average 50% of their segregating genes (assuming they were full siblings), while nonbiologically related adoptees had no genetic resemblance. The adoptees shared the same environmental influences because both groups grew up in the same adopted family. Therefore, the correlations between the biologically related siblings can be compared with the correlations between the nonbiologically related siblings, the same way as the correlations of monozygotic and dizygotic twins can be compared. If the biologically related adoptees resemble each other to the same degree as the nonbiologically related adoptees do, only environmental factors are of importance in explaining sibling resemblance. However, when the biologically related adoptees resemble each other more than the nonbiologically related adoptees do, genetic factors are of importance, since the only difference between the two groups is in their genetic relatedness. In contrast to twin studies, genetic dominance or epistasis cannot be detected, because biologically related adoptees do not share identical genes at the same loci as monozygotic twins do. Later in this chapter we will present some of the longitudinal results found using this adoption design (van der Valk et al., 1998a).

Various effects that might be incorporated in the theoretical model

Depending on the elaborateness of the collected data and the inspiration of the investigator all kinds of genetic models can be tested. For instance, the genetic model can be extended to test not only for genetic and environmental influences, but also for effects of sex differences, gene - environment correlation or interaction, longitudinal effects or incorporating multiple variables simultaneously.

Sex-limited gene expression

When data are available from opposite-sex twin pairs (boy-girl pairs), it is interesting to test whether different genes are expressed in males and females. Two basic types of sex-limited gene expression can be distinguished (Neale and Cardon, 1992). One is called scalar sex limitation and points to those situations when the same genes affect both males and females, but their effects differ by some constant multiple over all the genes involved. The other is called non-scalar sex-limitation and concerns those cases when the genetic effects are not just a constant multiple of their effects in the other sex. In this case, different genes control the expression in the two sexes, like for instance in chest-girth. Correlations of dizygotic opposite-sex twins (boy-girl pairs) in comparison with

correlations of same-sex twins (boy-boy or girl-girl pairs) indicate if similar genes are active in both sexes. For if one gender has different genetic influences than the other, correlations between opposite-sex dizygotic twin pairs are expected to be either higher or lower than the correlations between same-sex twin pairs. Several studies have found differences in observed behaviors for boys and girls (girls tend to show more internalizing or emotional problems, and boys display more externalizing or disruptive behavior problems) making the inclusion of sex-limited gene expression in the model sensible.

Genotype-environment interaction and correlation

Problem behaviors are thought to develop as a result of interactions between genetic vulnerability and environmental risk factors. Genes might increase the risk for certain problem behaviors by making individuals more sensitive to environmental risk factors (genotype-environment interaction), or by making individuals more likely to select high-risk environments (genotype-environment correlation). Genotype-environmental interaction refers to the sensitivity of genes to differences in the environment. It relates to the way genes and environment ultimately affect the phenotype (Neale and Cardon, 1992). As an example of genotype-environment interaction one can consider an environment which is changed by introducing a pathogen. This will have a different impact on susceptible individuals than on resistant ones. Resistant individuals will be free of the disease even in a pathogenic environment. Genetically susceptible individuals however will be free of disease only as long as the environment does not contain the pathogen but they will get sick when the pathogen is introduced. For gene-environmental interactions to be studied specific hypothesis must be proposed, discriminating measures of the environmental risk factors must be made, appropriate samples must be used and statistical techniques must be employed that are well adapted to detect and test the postulated variety of genetic sensitivity (Kendler and Eaves, 1986). Both twin and adoption studies can be used to study possible gene-environment interactions. Essential is that the genetic risk can be measured directly, so molecular genetic findings with strong effects will help tremendously (Plomin and Rutter, 1998). Genotype-environmental correlation reflects a non-random distribution of environments among different phenotypes (Neale and Cardon, 1992). It can either be passive (for instance, parents who pass on their genes to their children are the same parents who provide their rearing experiences) or active / evocative (for example, children actively select their environments based on their genetic make-up and other people (parents) evocatively react on the behavior shown by the child). As Rose (1995, p.648) has stated, "We inherit dispositions, not destinies. Life outcomes are consequences of lifetimes of behavior choices. The choices are guided by our dispositional tendencies, and the tendencies find expression within environmental opportunities that we actively create." Both twin and adoption studies provide ways of studying possible gene-environment correlations. To examine the effects of gene-environment correlations it is essential to differentiate parental effects on children from children's effects on parents. In order to do this, genes and environmental factors must be identified and their mutual behaving must be determined (Rutter et al., 1999a). Again, molecular genetic findings with strong effects

will probably be of tremendous help.

Longitudinal genetic models

When data have been collected on different assessment points, the genetic and environmental influences can be estimated at each time interval separately. However, using a longitudinal model one can also estimate how genes and environmental influences operate throughout development. For example, is an increase in heritability due to new, additional, genetic factors being expressed as children grow older, or is there an amplification of existing genetic influences? Such a longitudinal model can address the question to what extent the stability of showing a certain problem behavior is due to the same genes being expressed at different ages and to what extent the stability is due to the same environmental influences being of importance. Contrary to popular points of view, genetically determined characters need not be stable, nor are longitudinally stable characters always influenced by heredity (Molenaar et al., 1991).

Multivariate genetic models

Another important class of models are multivariate genetic models. Like ordinary factor analyses, multivariate models make a distinction between a (genetic or environmental) factor that influences only one, specific behavior problem, called a unique factor, and a (genetic or environmental) factor that influences all the different behavior problems, called a common factor (Martin and Eaves, 1977; Boomsma and Molenaar, 1986). The common genetic and environmental factors explain the covariances between the problem behaviors, while the unique genetic and environmental factors explain the remainder of the variance that is not shared by the different problem behaviors. In this way, multivariate models can construct a picture of the causes of the relationships between the several problem behaviors. The multivariate approach is more powerful than the univariate approach, but its unambiguous interpretation often requires that univariate results are already known.

Issues of concern when measuring problem behaviors during development

To study the etiology of problem behaviors during development, children have to be followed over time. In order to tap developmental changes in the level and type of children's problem behaviors, assessment instruments should be sensitive to these variations. The instruments should also allow different responders, like parents, parent surrogates or teachers, to report on the child's behavior, because young children are unable to reflect on their own behaviors.

The Child Behavior Checklist (CBCL)

The Child Behavior Checklist (CBCL) developed by Achenbach (1991a, 1992)

is a standardized questionnaire for parents to report on the frequency of problem behaviors shown by the child. Responders rate each behavior on a three-point scale: zero when the child never exhibits the behavior, one if the child sometimes shows the behavior and two when the behavior is frequently seen. Depending on the age of the child either the CBCL for 2- and 3-year-old children (CBCL2/3; Achenbach, 1992) or the CBCL for 4- to 18-year-old children (CBCL/4-18; Achenbach, 1991a) can be filled out. The 118 behaviors of the CBCL/4-18 have been summarized into eight empirically validated syndrome scales. The eight syndrome scales were named: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. The first three syndrome scales can be summed to form a broad-band grouping, called Internalizing. The last two syndrome scales can be summed to form a broad-band grouping called Externalizing. A Total Problem score is derived by summing all the individual item scores. The psychometric stability of the CBCL/4-18 is well established (Achenbach, 1991a) and replicated for a Dutch clinical sample (De Groot et al., 1994).
The CBCL/2-3 (Achenbach, 1992) was modelled after the CBCL/4-18 and measures similar syndrome scales. Several scales of the CBCL/2-3 are fairly comparable to scales of the CBCL/4-18. However, their precise content differs in accord with the age differences and findings on the covariation among items from the different instruments (Achenbach, 1992). The CBCL/2-3 scales that have the clearest counterparts on the CBCL/4-18 are: Anxious / Depressed, - Withdrawn, Somatic Problems, Aggressive Behavior, Internalizing, Externalizing, and Total Problem score. The American factor solution for the CBCL/2-3 is not replicated for Dutch samples, so for the CBCL/2-3 Dutch syndrome scales are developed (Koot et al., 1997). Koot showed that the Dutch syndrome scales are comparable to those developed by Achenbach. The broad-band grouping Internalizing is composed of the syndrome scales Anxious and Withdrawn / Depressed, while the broad-band grouping Externalizing consists of the syndrome scales Aggressive, Oppositional and Overactive.
Using the CBCL, the child's problem behaviors can be rated at different assessment points during development and can be compared with norm groups of similar age and sex. By comparing the child's score with the scores obtained from a norm sample, one can determine whether the child shows significantly more problems than children of a similar age.

Rater bias

Especially for children up to age 12, parents (or other kinds of informants) are needed to report on possible problem behaviors shown by the child. However, informants might have their own rater biases (see Van der Ende, this volume). For example, some might judge behaviors more severely than others and the child might show different problem behaviors depending on the kind of relationship it has with the informant. Disentangling the child's phenotype from that of the rater becomes and important methodological problem when relying on ratings of the child by an observer. Using a rater bias model, the variance in the parental ratings can be partitioned into their components due to reliable trait

variance, due to parental bias, and due to unreliability or error in the particular rating of a particular child. The reliable trait variance can then be decomposed into its components due to genetic influences, shared environmental influences, and nonshared environmental influences (Neale and Cardon, 1992). Rater bias models can only be fitted when data from more than one kind of informant, for instance from both parents, are available.

Sibling interactions

Sibling interactions are a special type of gene - environment correlation, referring to the fact that children might influence each other to either express or suppress certain behaviors. For example, aggressive behaviors in one twin might evoke the same kind of behaviors in the other twin. Especially when studying twins (who are of similar age) the effects of sibling interactions, when not taken along in the analyses, might bias the obtained genetic and environmental estimates (Eaves, 1976; Hewitt et al., 1992).
Sibling interactions might either involve cooperation (imitation) effects, when the behavior of one twin tends to evoke the same kind of behavior in the other twin, or the interactions may produce competition (contrast) effects, when a certain behavior of one twin causes the opposite behavior in the other twin. Effects of sibling interactions depend on the degree of biological relationship between the socially interacting siblings. Monozygotic twins are reared with a cotwin of identical genotype. If there are cooperation (imitation) effects, the total variance of monozygotic twins is expected to be greater than that of dizygotic twins (which in turn would exceed that of singletons) (Eaves, 1976). Apart from the effects in variances, both the correlations between monozygotic and between dizygotic twins will be inflated in case of cooperation effects, thereby mimicking the effects of shared environment. Competition (contrast) effects are expected to make the total variance of monozygotic twins smaller than that of dizygotic twins (which again would be smaller than that of singletons). In twin data competition effects can also reduce the correlation between the dizygotic twins to very low values, thereby inflating the estimates of (non-additive) genetic variance.
Of course, the process of having informants report on the behavior of the children might also implicitly lead to "sibling" effects, for informants may unconsciously compare one twin with the other in rating the children. In order to get less biased estimates, the effects of sibling interactions and of rater biases need to be incorporated in the theoretical model that is to be fitted to the observed data.

Studies exploring the etiology of children's problem behaviors using the CBCL

Twin studies

To obtain sufficient statistical power to fit a theoretical model to the observed data that incorporates not only genetic and environmental influences on variations in problem behaviors, but also the effects of rater biases and sibling interac-

Table 1 *Quantitative genetic studies of behavior problems during childhood, using the Child Behavior Checklist Internalizing and Externalizing problems (Achenbach, 1991, 1992)*

Twin Registry / Project	Author	Instrument	Responder	N (pairs)		Age (years)	Sex diff?	Genetic Influences		Shared Environmental Influences	
				MZ	DZ			Ext.	Int.	Ext.	Int.
Western Reserve Twin Project	Edelbrock, et al. (1995)	CBCL/4-18	mother (91.5)	99	82	7-15	--	51	50	28	25
Oregon Twin Project	Leve, et al. (1998)	CBCL/4-18 (among others)	mother	77	77	6-11	--	44	56	41	--
Colorado Twin Registry	Schmitz, et al. (1995)	CBCL/2-3 CBCL/4-18 longitudinal	mother	77 66 30	183 137 65	2.8 7.6	-- --	34 57 early childhood mostly shared environment, middle childhood mostly genetic influences.	17 37	32 22	45 26
	Zahn-Waxler, et al. (1996)	CBCL/4-18 (among others)	mother father (teacher and observations)	184 139		5	No (with CBR: yes)	57 48	56 --	30 35	-- 57
Norway Twin Registry	Gjone, et al. (1996)	CBCL/4-18	pooled together: mother (77.3) father (6.6) joint (16.1)	526	389	5-15	No	52 logtransformed variables showed no changes in heritability with increasing level of severity of problem behaviors.	33	38	41

Twin Registry / Project	Author	Instrument	Responder	N (pairs)		Age (years)	Sex diff?	Genetic Influences		Shared Environmental Influences	
				MZ	DZ			Ext.	Int.	Ext.	Int.
Norway Twin Registry	Gjone, et al. (1997)	CBCL/4-18	pooled together: mother (77.3) father (6.6) joint (16.1)	526	389	5- 9 12-15	No	genetic factors were most influential for separate Externalizing and Internalizing, shared environmental factors explained most of the variance for comorbid conditions.			
Virginia Twin Registry	Silberg, et al. (1994)	CBCL/4-18	mother	515	749	8-11 boys 8-11 girls 12-16	Yes (only for: External. young group)	38 13 24	23	46 62 57	36
	Eaves, et al. (1997) Hewitt, et al. (1997)	questionnaires and interviews	mother father	689	666	8-16	No	all measures of Internalizing and Externalizing problems showed moderate genetic effects.			
Netherlands Twin Registry	van den Oord, et al. (1996)	CBCL/2-3	average rating of mother father	446	912	3	No	60	77	20	--
	van der Valk, et al. (1998)	CBCL/2-3	mother	1328	2292	3 boys 3 girls	Yes (only for: External)	50 74	68	22 --	--

Note. MZ = monozygotic twins, DZ = dizygotic twins, differ.? = differences, Shared envi. = shared environmental influences, Exter = Externalizing problems, Inter = Internalizing problems. Nonshared environmental influences= 1 - genetic influences - shared environmental influences.

tions, large samples of related individuals are needed. For this reason, twin registries in various countries have, during the last two decades, started to enlist large samples of twins and their parents for participation in their studies.
With the help of these registries a large number of twin and adoption studies of behavioral disorders have been conducted. In this chapter, for sake of comparability, we only consider behavioral genetic studies of children and adolescents using the CBCL (see Table 1: Internalizing and Externalizing problems). Zahn-Waxler et al. (1996) collected mother, father and teacher ratings on 5-year-old twin pairs from Colorado. Their largest sample of informants (although still relatively small) were mothers who rated the twins (184 pairs) on the CBCL. For these ratings they found significant genetic influences, explaining more than half of the variance for Internalizing, Externalizing and Attention/Activity problems. An effect of shared environmental influences was found only for Externalizing problems. Edelbrock et al. (1995) collected mostly mother ratings on the CBCL for a (also relatively small) sample of 181 pairs of same-sex twins, aged 7-15 years, of the Western Reserve Twin Project. They found significant genetic influences for all areas of problem behaviors. Shared environmental influence was detected for Anxiety/Depression and Delinquent behavior, but was negligible for most other areas of problem behaviors. Leve et al. (1998) collected mother ratings on the CBCL (and observational data) on 154 twin pairs, aged 6-11 years. Their results indicated that genetic variation accounted for the majority of the variance in child reported maladaptive behaviors (average = 62%). Silberg et al. (1994) collected mother ratings on the CBCL on 1264 twin pairs, aged 8-16 years, residing in the state of Virginia. They found that genetic, shared, and nonshared environmental factors all played a significant role in explaining individual differences in maternal ratings of Externalizing and Internalizing behaviors in boys and girls. The shared environmental factor had the largest influence, accounting for 36% of the variance of the Internalizing scale and around 57% of the variance of the Externalizing scale. Externalizing behaviors showed a sex difference for 8- to 11-year-olds, but not for 12- to 16-year-olds. The data for boys showed larger genetic influences, while the data for girls showed larger environmental influences. For Internalizing behaviors neither a sex difference nor an age effect was found.
Van den Oord et al. (1996) collected mother and father ratings on the CBCL on 1358 3-year-old twin pairs from the Netherlands Twin Registry (NTR). They found that genetic influences accounted on average for about 64% of the variance of various problem behaviors. Shared environmental influences were smaller than nonshared environmental influences, accounting for 9% and 27% of the variance, respectively. Genetic influences for Internalizing problems were somewhat larger than for Externalizing problems. For most problem behaviors no sex differences were found at this young age. Van der Valk et al. (1998b) used the same 1358 twin pairs, enlarged with an additional sample from the NTR of 2658 twin pairs, giving a total same of 4016 3-year-old twin pairs. For 3620 twin pairs complete CBCL's were filled out by the mothers. Using this larger sample of twin pairs, which provided a higher statistical power to detect influences of small size, evidence for sex differences and for sibling interactions was found. These effects were only detected for Externalizing problems and not for Internalizing problems. One twin's behavior stimulated the expression of the same behavior in the other twin. Since only maternal ratings were analysed,

these cooperation (imitation) effects might also have been caused by informants unconsciously comparing one twin's behavior with the behavior of the other twin. For boys, genetic factors explained 50% of the variance of Externalizing problems, while shared environmental factors explained 22% of the variance. For girls, genetic factors explained 74% of the variance and no shared environmental influences were found. The correlations of same-sex (boy-boy or girl-girl pairs) and the correlations of opposite-sex dizygotic twin pairs (boy-girl pairs) were quite similar, indicating that the same genes seemed to be responsible for the genetic influence in both sexes. In the same sample, no sex differences or sibling interactions were found for Internalizing problems. Genetic and nonshared environmental factors accounted for all of the variance, genetic factors explaining 68%. For both Internalizing and Externalizing problems, nonshared environmental factors explained 25 to 32% of the variance.

The Virginia Twin Study (Hewitt et al., 1997; Eaves et al., 1997) did not employ the CBCL but used various other instruments and interviews to assess behavioral development and psychopathology. We still mention this study because it collected a population-based, unselected sample of 1412 twin pairs. Most twin studies use twins who are part of a twin registry, but this study ascertained twins trough Virginia schools. Using a sequential cohort design, twins from 8 through 16 years of age and their parents, were followed longitudinally. The first wave of data showed that across informants, questionnaire scales provided as good a prediction of symptoms as clinical interviews did. All the measures of Internalizing and Externalizing behavior showed moderate genetic effects. No sex differences in genetic or environmental factors were seen, which (as noted by the authors) could have been caused by their relatively low power to detect sex-limited gene expression for moderately heritable traits. Attention Deficit Hyperactivity Disorder showed, apart from genetic influences, also contrast effects. However, having only parents and the twins themselves to rate the behaviors, it was not possible to determine whether these effects reflected social interaction between the twins themselves or whether they were artifacts of asking parents to rate their children. Simonoff et al. (1998), using ratings from mothers and teachers for 1644 twin pairs in the Virginia Twin Study, concluded that the contrast effects found for maternal hyperactivity ratings were a form of rater bias and did not reflect social interaction between the twins themselves.

Gjone et al. (1996) conducted a cross-sectional twin study in Norway, using five birth cohorts (aged 5-6, 8-9, 12-13, 13-14, and 14-15 years) giving a total of 915 twin pairs. For most twins, the mother's ratings on the CBCL were collected. Results indicated significant heritability for Internalizing and Externalizing problems. Logtransformed variables showed no changes in heritability with increasing level of severity of problem behaviors. Using the same sample, Gjone and Stevenson (1997a) found that genetic factors were most influential for separate Internalizing and Externalizing behaviors, while shared environmental factors were more influential for comorbid conditions, meaning for disorders which co-occur. Silberg et al. (1996) studied the genetic and environmental influences on the covariation between hyperactivity and conduct disturbance, rated with the Rutter Parent 'A' scale (Rutter et al., 1970). Using the same sample of twin pairs from Virginia, they found that for the 557 younger twin pairs (8-11 years) the covariation could be attributed to a common set of genetic influences, whereas for the 640 older twin pairs (12-16 years) a different set of

genes contributed to the two behaviors independently. O'Connor et al. (1998a) used a national sample of 720 same-sex adolescent siblings between 10 and 18 years of age, consisting of monozygotic and dizygotic twins, and full, half and unrelated siblings. They employed different observational measures and adolescent and parent reports, one of them being the Behavior Problem Index (Zill, 1985), a 32 item questionnaire adopted from the CBCL and another the Child Depression Inventory (Kovacs, 1981). Using composite scores, results showed that 45% of the observed correlation between depressive and antisocial symptoms could be explained by a common genetic liability. In their conclusions, the authors make a plea for research using longitudinal methods to examine genetic influences on change and stability of depressive and antisocial symptoms. Longitudinal studies may possibly provide evidence for genetic risks for co-occurring dimensions of psychopathology.

We know of only three twin studies which have examined the etiology of problem behaviors longitudinally. O'Conner et al. (1998b) approached the same adolescent siblings again three years later and collected longitudinal data on 405 families. The central findings were that genetic influences explained 54% of the stability of antisocial symptoms and 64% of the stability of depressive symptoms. Half of the phenotypic correlation between wave 1 antisocial symptoms and wave 2 depressive symptoms were mediated by genetic influences. The second longitudinal twin study is a two year follow-up of 759 Norwegian same-sex twin pairs, aged 7 through 17 (Gjone and Stevenson, 1997b). CBCL ratings were collected from one of the parents, preferably the mother. Results showed temperament, particularly negative emotionality, to be an important factor in the development of behavior problems. The third is a study of Schmitz et al. (1995). For a small longitudinal sample of 95 twin pairs from Colorado, measured at the age of 2 years and 10 months and followed-up at the age of 7 years and 7 - months, they collected (mostly) mother ratings on the CBCL. Results suggested that shared environmental influences were more important in early childhood than in middle childhood, while the reverse held for genetic influences. However, as also pointed out by the authors themselves, these results need to be replicated by larger samples of genetically informative data.

The Dutch twin study of problem behaviors (described later in this chapter) is currently collecting longitudinal CBCL data on a large sample of young twins (4016 3-year-old twin pairs and 1926 7-year-old twin pairs). The contributions of genetic and environmental factors to the covariation of behavior across time will be examined using this sample.

A longitudinal adoption study

In a sample of adolescents who were all adopted before their second birthday, we collected longitudinal data (van der Valk et al., 1998a). These siblings were either biologically related and adopted into the same family (111 pairs) or nonbiologically related but also adopted into the same family (221 pairs).

The adoptees were first assessed at 10 to 15 years of age (95.9% of the sample was between 11-14 years) (van den Oord et al., 1994) and followed up three years later. At the second assessment, usable CBCL/4-18 questionnaires were obtained from 75 biologically related and 154 nonbiologically related pairs. The

longitudinal correlations, which were mostly around .60, pointed to a considerable stability of the problem behaviors during the three-year interval. At both assessments, most of the variance for Externalizing Problems and Aggressive Behavior was explained by genetic factors, while nonshared environmental factors were most important for Internalizing Problems, Thought Problems and Delinquent Behavior. Structural equation models showed that the stability of Externalizing Problems over time was caused mostly by genetic factors. The stability of Internalizing Problems was caused mostly by nonshared environmental factors, suggesting that idiosyncratic experiences were largely responsible for the stability of Internalizing problems over a three-year interval.
Unfortunately, rater biases could not be studied in this sample of adoptees because only one of the parents had been asked to complete a CBCL. Also sex differences were not examined because the obtained longitudinal sample size was too small to be divided into boys and girls.

The need for longitudinal studies

As shown by the twin study of O'Conner et al. (1998b) and the results of the adoption study, longitudinal data enable the researcher to examine the contributions of genetic and environmental factors to the covariation of behavior across time. In this way, one can determine if the relative importance of genetic versus environmental factors change over time. When a child shows the same behavior at various points in time, this phenotypic stability might be caused by the same genes or the same environmental influences operating throughout development. Also, longitudinal studies can reveal if the same or different genetic and environmental factors exert their influence during development. For example, is an increase in heritability due to new, additional, genetic factors being expressed as children grow older, or is there an amplification of existing genetic influences? As already mentioned, genetically determined characters need not be stable, nor are longitudinally stable characters always influenced by heredity (Molenaar et al., 1991). Longitudinal studies (using appropriate longitudinal models) are essential to understand the etiology of children's problem behaviors.

Conducting a sound prospective longitudinal study

During this last decade, behavior genetic studies (see also Table 1) have examined the genetic and environmental influences on children's problem behaviors. To our awareness, only three twin studies have examined the etiology of problem behaviors longitudinally. However, both the study of O'Connor et al. and the study of Gjone et al. used twins of a very wide age range (13-21 years and 7-17 years, respectively) who were all of same-sex, and both the study of - O'Connor et al. and the study of Schmitz et al. used relatively small longitudinal samples (405 families and 95 twin pairs, respectively). To conduct a sound longitudinal study on the etiology of problem behaviors in children, the study should:

- collect samples of (twin) pairs that are large enough to match most of the demands of statistical power required for the genetic analysis of kinship data

(Martin et al., 1978),

- use samples of children measured at more or less similar developmental stages, like for instance: preschool, middle childhood, and adolescence,
- use assessment instruments that are sensitive to developmental changes,
- collect data of same-sex and opposite-sex (twin) pairs to be able to study possible sex differences in the etiology of problem behaviors,
- use multiple informants:
  - ask both mothers and fathers to fill out a questionnaire (for example the CBCL/2-3 or CBCL/4-18 (Achenbach 1991a, 1992)). This will also enable the analyses to correct for possible rater biases,
  - if the children are going to school, ask their teachers to fill out a questionnaire, for instance the Teacher's Report Form (TRF) (Achenbach, 1991b). This extra source of information can be compared with the information collected on the CBCL by using the cross-informant syndrome constructs (Achenbach, 1991d),
  - if subjects in the sample are 11 years or older, ask them to either fill out a questionnaire about themselves, for instance the Youth Self-Report (YSR) questionnaire (Achenbach, 1991c) (which also has cross-informant syndrome constructs with the CBCL and the TRF), or ask them to rate each others behaviors or the relationship they have with their sibling(s). At this age, they might also be able to fill out a life-events questionnaire, providing information about their nonshared environmental influences,
- use statistical techniques that can deal with missing data.

The Dutch twin study of problem behaviors

In an effort to conduct a sound prospective longitudinal study examining the etiology of problem behaviors during development, we have collected CBCL/2-3 questionnaires on 3-year-old twin pairs and four years later CBCL/4-18 questionnaires when the children reached their 7th birthday. The twins are members of the Netherlands Twin Registry (NTR), which registers 40-50% of all multiple births in the Netherlands. Data from all twin pairs from the NTR and born between 1987 and 1991 have been used to investigate the genetic and environmental influences on problem behaviors. At this moment, questionnaires on 4016 3-year-old twin pairs and 1926 7-year-old twin pairs are available, giving a group of preschool children and a group of school-aged children (middle childhood) that are both large enough to fulfill most demands of statistical power.
We have chosen to start collecting longitudinal data on preschool and subsequently on school-age children because, with the exception of the relatively small sample of the Colorado Twin Registry, no other behavior genetic study has been conducted using preschool children. Analysing these longitudinal data, we will not only get a better understanding of the genetic and environmental influences on various problem behaviors during these young ages, but also of age-related changes in the contribution of genes and environment over time. At these young years, children experience many developmental transitions that might cause the etiology of problem behaviors to change during this period. Preschool children spend most of their time at home with their parents or care-takers. They are largely passive recipients of their social worlds. Shared environmental influ-

ences will probably be largest during this period. School-age children are away from home for at least half the day and therefore have more freedom to choose their own network of friends and activities. Genetic influences might be more expressed in these school-age children, because they are better able to follow their own genetically induced interests and potentials (Kendler, 1995).
We have collected data on twin pairs of similar sexes and of opposite sexes, to enable the exploration of sex differences in genetic and environmental influences on various problem behaviors. Both mothers and fathers have been asked to fill out a CBCL at both assessment points, enabling us to estimate the effects of rater biases in the theoretical model. Also the effects of sibling interactions can be incorporated in the model because questionnaires have been filled out by each parent for each child.

Future intentions and possible research questions

The longitudinal results of the twin sample (all children) will be complemented with the longitudinal results of the adoption sample (all adolescents). Hopefully the results will give a clearer picture of the etiology of problem behaviors during childhood.
Future studies (if funds can be found) will follow-up the same twins again during adolescence and young adulthood. Currently, the oldest of the twins are being assessed again at the age of 12. By following the twins during their development, the operation of genes and environmental influences throughout development can be estimated. Also the genetic and environmental effects on comorbidity, the tendency of some problem behaviors to co-occur, can be explored. Over time, some distinct problem behaviors might be the different expressions of the same underlying genetic or environmental influence. Knowing the underlying etiology of the behaviors that tend to co-occur might help in developing distinct diagnoses and effective treatments.
Once it is known what the relative contributions of genes and environmental influences for the different problem behaviors at specific ages are, and how these influences change during development, the last three questions in the sequence of genetic epidemiologic research can be addressed: "What is the mode of transmission, where are the gene(s) located on the chromosome, and what are the genetic and environmental mechanisms of disease?". Although we are a long way of answering these questions, some techniques enabling this kind of research have been developed.
The mechanism of transmission from parent to child (Is a single gene responsible, multiple genes or are environmental factors implicated? Is the gene dominant or recessive?) can be studied using segregation analysis. This technique allows one to detect the contribution of individual genes of large effect against the background of other genetic and environmental effects. Using a theoretical model of familial transmission, assumptions about the genetic and environmental causes are translated into mathematical equations. These equations are then used to predict the distribution of a disorder in pedigrees. The theoretical model is accepted when the pattern of a disorder predicted by the model is close to what is observed (when the model cannot be statistically rejected) (Faraone and Tsuang, 1995). When studying the mode of transmission of children's problem

behaviors, family studies have the difficulty of collecting accurate information not only from the child but also from adult family members about their behavior problems when they were children (Simonoff et al., 1994).

To answer the fourth question in the chain: "Where is (are) the gene(s) located?" sib-pair strategies have been developed (Haseman and Elston, 1972). Complex traits are multifactorial in nature, involving a number of genes, each with relatively small effect (Cardon, 1995). These multiple genetic loci that are thought to influence continuous traits are known as 'quantitative trait loci' or QTL's (Gelderman, 1975). In sib-pair strategies, trait and marker data are obtained from siblings and (optimally) their parents in a number of different families. The methods do not involve any assumptions concerning the mode of transmission and are robust with respect to genetic heterogeneity (meaning the same phenotype resulting from the expression of different genes or gene combinations) (Cardon, 1995). The idea behind the Haseman and Elston approach for continuous traits is that under linkage between a trait and a QTL, differences between siblings in their phenotypes will decrease in accordance with greater similarity at the marker locus. Haseman and Elston employ the proportion of alleles that siblings share identical-by-descent (IBD) as their measure of QTL resemblance. Extensions of this approach have been developed to take multiple markers or multiple traits simultaneously into account, which strengthens the statistical power of the method (Fulker et al., 1991, Fulker and Cardon, 1994; Cardon and Fulker, 1994, Boomsma, 1996, Boomsma and Dolan, 1998, Dolan et al., 1999). The sib-pair design for QTL linkage analysis corresponds well to the classical twin study. Except for the collected data on different phenotypes, all that is needed are DNA samples drawn from blood samples or buccal swaps, because dizygotic twins are full siblings.

When a gene is localised its function must be explored. For instance, what proteins does the gene code for and are there any environmental effects that influence the workings of this gene? This of course is the last question in the chain of genetic epidemiologic research: "What are the genetic and environmental mechanisms of the behavior?" but to answer this question genes and environmental influences must be identified first.

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