ELSEVIER
SAUNDERS

Child Adolesc Psychiatric Clin N Am
16 (2007) 323–339

CHILD AND
ADOLESCENT
PSYCHIATRIC CLINICS
OF NORTH AMERICA

Genetically Informative Designs in the Study of Resilience in Developmental Psychopathology

Meike Bartels, PhD[a,*], James J. Hudziak, MD[a,b,c,d]

[a]*Department of Biological Psychology, Vrije Universiteit, van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands*
[b]*Department of Psychiatry, University of Vermont, College of Medicine, Given B229, Burlington, VT 05405, USA*
[c]*Department of Medicine, University of Vermont, College of Medicine, Given B229, Burlington, VT 05405, USA*
[d]*Department of Psychiatry, Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, NH 03756, USA*

Some children apparently suffer from emotional or behavioral problems, beginning with conception and continuing their entire life, whereas other children are affected at times and are well at other times. Epidemiologic studies show that the majority of the children are free of emotional/behavioral problems at any given time. Emerging evidence from longitudinal studies suggests that within this group of well children, many have always been well, whereas others may have been ill at one point but are relatively well at others. It is not clear what factors influence the shift from illness to wellness or why some children recover from illness and remain well. The study of resilience, defined here as the ability to recover from a prior illness or the capacity to remain well in the face of extraordinary genetic or environmental risk factors, is the focus of this article.

We believe that to study resilience in the domain of developmental psychopathology it is necessary to use genetically informative strategies. In this era of genomic medicine, it is important to accept that genetic and environmental factors place children at risk for developmental

This work was supported by the National Institute of Mental Health (NIMH, RO1, MH58799-03) and The Netherlands Organization for Scientific Research (NWO 575-25-006, NWO/SPI 56-464-14192, and NWO 463-06-001). Dr Bartels is financially supported by NWO (VENI: 451-04-034).

* Corresponding author.
E-mail address: m.bartels@psy.vu.nl (M. Bartels).

doi:10.1016/j.chc.2006.12.008

psychopathology. Thus, twin, family, adoption, and molecular genetic studies that measure environmental mediators and modifiers are needed to estimate genetic and environmental factors that put children at risk for or protect them from psychopathology. Extending this argument to the study of resilience (eg, why some kids recover?) is the focus of last part this article and our research strategies in the next decade.

Nature versus nurture

For several years, the nature-versus-nurture debate has endured. There is general agreement upon the importance of the influences and interaction of nature and nurture. Within and beyond the field of behavior genetics, many studies have been conducted on the relative importance of genetic and environmental factors in explaining individual differences in psychopathology. Recently, investigations have gone beyond the estimation of genetic and environmental factors to focus on more complex matters, such as cultural transmission, epigenetics, gene–environment correlations (rGE), and gene–environment (G×E) interactions (see, for example, the article by Kim-Cohen in this issue). This article provides an introduction and explanation to the terminology and methods of behavioral genetics research in developmental psychopathology, followed by recent findings in the study of resilience in the field of developmental psychopathology.

Individual differences

Almost all measured behavior in humans (eg, psychopathology in children) shows variation across the population. The aim of behavioral genetic studies is to disentangle the sources of this variation. Quantitative genetic theory states that an individual's phenotype (ie, measured traits and behavior) is influenced by genetic and environmental factors. It is argued that no behavior is entirely determined by genetic effects or environmental factors.

The proportion of the phenotypic variance attributable to genetic variance is known as the heritability (h^2). Because heritability is a proportion, its numerical value ranges from 0.0 (genes do not contribute at all to phenotypic individual differences) to 1.0 (genes are the only reason for individual differences). For human behavior, almost all estimates of heritability are in the moderate range of 0.30 to 0.60; however, for some phenotypes, estimates as high as 0.75 are found (eg, attention problems) [1,2]. The scatter plots in Fig. 1 [3] give some indication of the extent to which genetic individual differences contribute to individual differences in observed behavior. If the heritability is high (eg, 0.8; right part of Fig. 1), there is a strong relationship between genotypic values and phenotypic values. In other words, a large

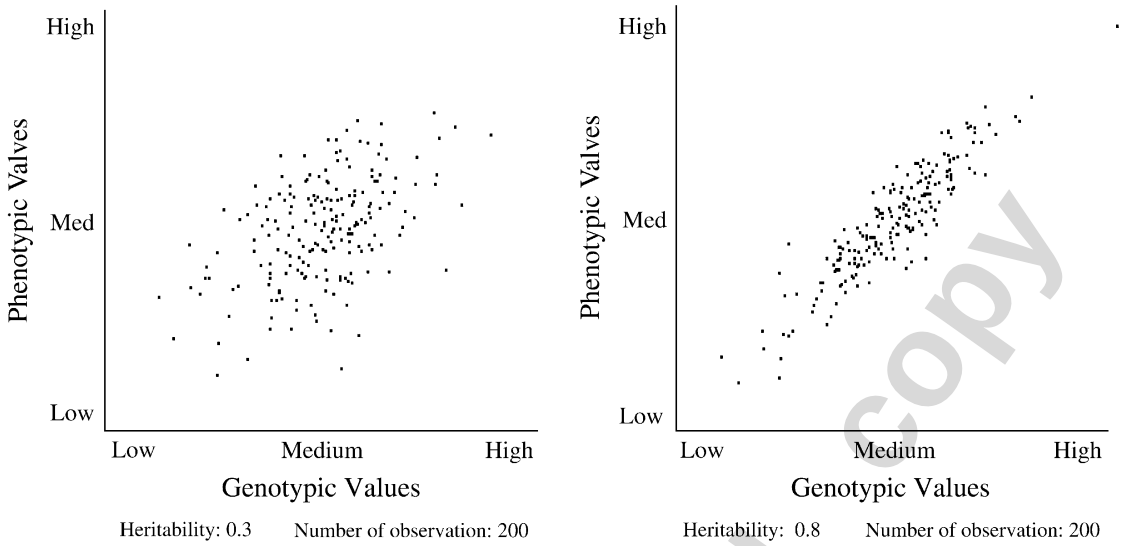

Fig. 1. Scatter plots demonstrating the relationship between genotypic values and phenotypic values for different heritabilities. (*From* Cary G. Human genetics for the social sciences. Thousand Oaks, CA: Sage Publications; 2002. Available at: http://psych.colorado.edu/hgss/.)

part of the phenotypic individual differences is accounted for by genotypic individual differences. If the heritability is low (eg, 0.3; left part of Fig. 1), the relationship between genotypic values and phenotypic values is low. In other words, environmental individual differences rather than genetic individual differences account for a large part of the phenotypic individual differences.

Genetic variation

Genetic information is present in nearly every cell of an organism and resides on long strands of DNA called chromosomes. Humans have two copies of a chromosome, one of maternal origin and one of paternal origin. Humans have 23 pairs of chromosomes. DNA sequences that encode for particular products (proteins and RNAs) are referred to as genes, and their chromosomal locations are called loci. Different variants of a gene are called alleles, and each individual has two copies (one maternal and one paternal). If the two alleles of an individual are identical, the individual is said to be homozygous. If the two alleles are not identical, the individual is said to be heterozygous.

Mendel [4] began the science of genetics with his landmark studies concerning the inheritance of the physical traits of the garden pea (*Pisum sativum*), in which he studied round versus wrinkled seeds. Mendel formulated two principles of heredity that have become know as ''Mendel's laws.'' Mendel's laws pertain to the behavior of genes and alleles during sexual reproduction. Mendel's first law, the Principle of Segregation, states that during the formation of gametes, the two alleles of a gene segregate separate from each other such that half of the gametes carry one allele and half carry the other allele. Mendel's second law, the Principle of Independent

Assortment, states that during formation of gametes, the segregation of alleles of one gene occurs independently of the segregation of alleles of other genes. A monogenetic model, though, cannot explain genetic influences on most kinds of behavior. Ficher [5] extended Mendel's single/two locus system to a multilocus system. He indicated that each gene in the polygenetic model (many genes influencing a trait) segregates according to Mendelian rules and that small effects of many genes can lead to a continuous range of measured traits by summing the genetic effects of each contributing locus and their interaction [5,6].

Most complex traits, like psychopathology or cognitive abilities, are not influenced by single loci. The genetic influences are assumed to be a result of the combination of the effects of multiple genes. Genotypic variance can be divided into additive genetic variance and nonadditive genetic variance. Additive genetic variance represents the sum of the effects of alleles of all genes that influence the trait. Nonadditive effects concern interactions between genes, which can occur in two ways. Dominant genetic effects stem from the summation of the interaction between two alleles at the same locus. Epistatic variance reflects the interaction between alleles at different loci (at the same or difference chromosomes). In human populations, the effects of epistasis are difficult to estimate in the absence of control over breeding or environmental condition.

To summarize, genetic influences on complex traits, such as psychopathology, are assumed to be a result of the combination of the effects of multiple genes. Genetic influences can be additive (summation of effects of different genes) or a result from interaction between genes.

Environmental variation

Environmental variance is all variation of nongenetic origin. Even in the absence of direct measures of environment, it is possible to make estimates of the influence of environment by using the biometrical genetical approach used in twin studies. Two sources of environmental variance are typically estimated: those environmental factors shared by members of a family and those not shared (ie, environmental factors that are unique to an individual). Any environmental factor that creates differences between families or makes family members relatively more similar can be considered as a shared environmental influence (eg, socioeconomic level, religion, or style of parenting). Nonshared environmental influences are experiences that contribute to differences between members of the same family, such as an illness, diseases, trauma, or unique relationships with peers. Measurement error is also captured in the nonshared environmental influences.

To summarize, every phenotype is influenced by environmental factors. The environmental influence can be shared by members of a family or unique to an individual. Genetically informative samples enable estimation of environmental influences, without a direct measure of environment.

Genotype–environment effects

Several factors defy the simple separation of genetic and environmental effects (eg, rGE and G×E interaction). (For an in-depth discussion of gene–environment effects in light of resilience, see the article by Kim-Cohen in this issue.) We present a short overview of terminology and a summary of results.

Passive, active, and evocative gene–environment correlation

rGE refers to genetic influences on individual differences relative to exposure to particular environmental circumstances. In other words, environmental effects can be influenced by genetic factors. Because of the fact that the magnitude of rGE is unknown, it is best regarded as part of the genetic variance. This is because the nonrandom aspects of the environment are a consequence of the genotypic value; therefore, an individual's environment can be thought of as part of its genotype [7]. rGE adds to the phenotypic variance for a trait, but it is difficult to detect the overall extent to which phenotypic variance is due to rGE [8]. Three forms of rGE can be distinguished: (1) Passive rGE occurs because parents transmit genes (genetic transmission) to their offspring and create their primary living environment (cultural transmission) [9]. (2) Active rGE arises when a person actively creates an environment suitable to his genetic make-up. (3) Reactive or evocative rGE refers to the case in which (genetically predisposed) behavior of an individual provokes certain reactions from his/her environment. For instance, in a parent–child relationship, such correlations occur when the (negative) behavior of the child gives rise to negative parenting and vice versa [10].

In the context of rGE, Jencks [11] spoke of the ''double advantage'' phenomenon for cognitive ability and education. Individuals who begin life with advantageous genes that increase their cognitive ability relative to the average may be born into homes that provide them with more enriched environments (eg, being more committed to learning and teaching). This double advantage model can be expanded to a triple advantage model because of the possibility that children who are born with genes that increase their cognitive ability and who live in an enriched environment are also more capable of profiting from this environment and will actively seek a more cognitive challenging environment.

To summarize, the genetic and environmental influences can be correlated. Many so-called environmental effects are influenced by genetic factors. rGE correlation can be active, passive or evocative.

Genotype–environment interaction

G×E interaction refers to sensitivity or susceptibility to differences in the environment that vary by genetic make-up. In other words, different genotypes respond differently to the same environment [7,12–14]. The

contribution of G×E to the overall population variance is typically smaller than the main effects of genotype and environment. An example of G×E is that of inherited disease resistance. Genetically susceptible individuals are free of disease as long as the environment does not contain the pathogen. Resistant individuals are free of the disease even in a pathogenic environment. One approach for detecting G×E interaction is to estimate components of phenotypic variance that are conditional on environmental exposure [15]. Because some genotypes may be more sensitive to environmental differences than others, to some extent the environmental variance is a property of the genotype, but the source of the variation is environmental and not genetic. The interaction between genetic effects and nonshared environment, G×E, contribute to the total variance but not to the resemblance of twin pairs. In other words, this interaction term is confounded with nonshared environmental effects [16]. If G×E is due to interaction between genes and shared environmental influences, assuming its absence results in an overestimation of the effect of genes on the phenotype and an overestimation of the influences of the shared environment on the phenotype. The separate detection of these two biased effects in the presence of genes by shared environmental interaction necessitates the inclusion of twins reared apart [16,17].

G×E is suggested to be the underlying mechanisms in explaining depression, the so-called "stress-diathesis hypothesis," which refers to the finding that the development of depression is a product of allele combination at the risk gene (in this case the serotonin transporter gene [5-HTT]) and the number of life events a person encounters [18–20].

Results from behavior genetic studies of psychopathology, the estimates of genetic and environmental variation, and their interaction can be extended to the study of resilience (Why do some children get better? Why are some children well and other presumably ill?). What follows is a description of methods used to test these outcomes.

Research methods

The classical twin design

A powerful tool to unravel the genetic and environmental architecture of individual differences in the development of behavioral problems, emotional problems, and resilience is to study genetically related individuals. Family studies give a first impression of familial aggregation, but they cannot distinguish between genetic and environmental effects. Similarities between family members may be created by genetic relatedness or by sharing the same family environment. A method that solves this problem is the classical twin design. Monozygotic (MZ) twins derive from a single zygote; therefore, two individuals of a MZ twin pair are genetically identical. Dizygotic (DZ) twins develop from two distinct zygotes and share on average 50% of their genes,

like ordinary brothers and sisters. Hence, the only way to explain the variation in problem behavior between two members of a MZ twin pair are environmental effects that are not shared by those two: the so-called nonshared "environmental influences." Conversely, the variation in problem behavior between two members of a DZ twin pair could result from different genes or nonshared environmental influences. The difference in relatedness between MZ and DZ twin pairs (mostly expressed as correlation coefficients) gives information about the strength of the genetic and environmental influences on the trait under investigation and allows the separation of environmental influences into those of the environment shared by members of a family and those that are unique to each individual.

In summary, the classical twin design enables disentangling of genetic and environmental influences by comparing behavioral overlap in MZ twins with behavioral overlap in DZ twins.

Extensions of the twin design

In recent years, the classical twin design has been expanded to more complex pedigrees [21]. In several studies, the nontwin siblings of twin pairs are added to the design. By adding nontwin siblings to the classical twin design, an increase in power is gained [22]. Adding nontwin siblings allows testing of more sophisticated measures of the contribution of shared environment testing for social interaction and special twin effects. Information on the parents of twins can be included to study cultural transmission and rGE. Parents of twins can be studied in a quasi-longitudinal design to determine genetic and environmental stability. Finally, assortative mating (nonrandom mating on the phenotype under study) can be studied if spouses of twins are included.

Individual differences in psychopathology: from genetic and environmental influences to candidate genes

By using the classical twin methods described previously, we are able to gain insight into the causes of individual differences of many phenotypes, including psychopathology. Over the years, many studies have used varying measures of childhood psychopathology to estimate genetic and environmental influences. In general, moderate to high estimates of heritability are found, whereas effects of shared environmental factors are small to moderate. Estimates vary depending on the measurement method, the rater/observer, the kind of psychopathology, gender, age, sample size, and statistical methodology. The highest estimates of genetic influences have repeatedly been reported for disorders related to attention problems. Heritability estimates of parent ratings on attention problems (AP) or hyperactivity usually vary between 50% and 80% [1,2,23–25].

Environmental influences unique to the individual take up the remaining part of the variance. No evidence for influences of shared environmental influences has been reported, but using a distinct rater changes these results. For example, by using teacher rating, estimates in the range of 40% to 70% have been found [1,26–30].

Psychopathology and development: the key to the study of resilience

Although information on the causes of individual differences in psychopathology at certain ages is of interest for clinical and research purposes, insight into stability and change of problem behavior throughout childhood into adolescence is essential to gain insight into resilience. Childhood problem behavior has been linked to psychiatric problems in adulthood [31,32]. Further, the longer an individual continues along a maladaptive pathway, the more difficult it is to reclaim a normal developmental trajectory [33]. Early recognition of problem behavior and causes of stability leads to early intervention in families and successful prevention programs [34].

Problem behavior during childhood shows considerable continuity. For example, Richman and colleagues [35] found that 61% of the problematic children at 3 years of age showed considerable difficulties on a clinical rating scale 5 years later. Graham and Rutter [36] showed that 75% of the 10- to 11-year-old children who received a diagnosis of conduct disorder and 46% of the children who received a diagnosis of emotional disorder remained deviant at 4-year followup. Caspi and colleagues [31] tested whether behavioral observations at 3 years of age were predictive of psychiatric disorders at 21 years of age. Undercontrolled and inhibited children were at risk of later psychiatric problems. The Christchurch study also reported strong continuities of behavioral problems [37]. Patterson [38] reported that three out of four antisocial adolescents grow up to be extremely maladjusted adults.

Stability is not confined to clinical groups and has been found in general population samples. Verhulst and Van der Ende [39] (the Zuid Holland study, the Netherlands) reported a correlation of 0.56 for problem behaviors across a 6-year period in a population sample of Dutch children originally aged 4 to 11 years. For this sample, it has been reported that high levels of childhood behavioral and emotional problems are related to DSM-IV diagnoses in adulthood [40]. Ghodsian and colleagues [41] studied a national sample of British children assessed at 7, 11, and 16 years of age. Correlations for parental ratings of problem behavior were 0.48 between 7 and 11 years of age, 0.38 between 7 and 16 years of age, and 0.46 between 11 and 16 years of age. Besides information on phenotypic stability of problem behavior, it has been found that there are different average developmental trajectories for boys and girls for four externalizing behaviors: aggression, opposition, property violations, and status violations. In their study, Bongers and

colleagues [42] demonstrated that the average development is different for these four types of externalizing behavior, with higher levels for boys than for girls. They found decreasing average developmental trajectories for aggression, opposition, and property violations and increasing trajectories for status violations.

A caveat of examining the etiology of developmental stability and underlying factors for resilience is that the mechanisms responsible could differ for genetic and environmental influences [43–45]. Bartels and colleagues [44] found that stability in internalizing behaviors (INT) and externalizing behaviors (EXT), based on parental ratings, was accounted for by genetic and shared environmental influences. The genetic contribution to stability (INT, 43%; EXT, 60%) resulted from the fact that a subset of genes expressed at an earlier age was active at the next time point (a so-called ''transmission'' or ''simplex'' model). Further, a common set of shared environmental factors operated at all ages (INT, 47%; EXT, 34%). The more general conclusion that genetic factors contribute primarily to stability, whereas nonshared environments contribute largely to change, has also been supported with findings for other phenotypes, such as attention problems [46] and aggression [47]. In a recent longitudinal twin/adoption study, a transmission pattern for genetic influences on stability of internalizing and externalizing behavior has also been found [43].

The finding of distinct developmental patterns for genetic and environmental influences is important for scientific and clinical purposes. The shared environmental influences, for instance, exert a continuous influence from their time of onset, so the children who continue to experience an adverse shared environment are at risk for later maladjustment. For additive genetic influences, parts of previous effects are transmitted to later ages. The genetic influence is less static because of new genetic influences that come into play at each age. Nonshared environmental influences seem to be important for age-specific behavior problems and have almost no developmental significance.

This implies that influences of nonshared environment are important but are mostly of a transient nature and specific to a moment in time. Multivariate behavior genetic analyses of patterns of problem behavior make it possible to divide disordered children into groups that have mainly a genetic, a shared environmental, or a nonshared environmental etiology to make the crucial differential diagnosis [48,49]. In combination with the knowledge about mechanisms that underlie stability and change and in combination with results of actual experimental intervention studies with random assignment and appropriate control groups, this division into groups can be useful. For instance, for internalizing and externalizing problem behavior, continuing genetic and shared environmental effects are important for stability. When these results are generalized, it implies that children who have high genetic liability or children who continue to experience an adverse shared environment are especially at risk for later maladjustment. Future

research could investigate whether, for these children, a wait-and-see policy would be inappropriate and an active intervention would be required.

Besides the importance for clinical prevention and intervention strategies, knowledge of the underlying developmental pattern for genetic influences is essential for gene hunting. The finding of a transmission/simplex pattern for genetic influences on problem behavior throughout development point out that one cannot merge all age groups together as new genetic influences come into play at certain ages. On the other hand, merging over age groups may increase the power to find the genes that play a role at all ages due to transmission from one age to another.

To summarize, genetic influences are the most important factor in explaining individual differences in psychopathology. For most phenotypes, estimates of the influences of genetic factors vary across development; however; the heritability estimate for AP remains approximately 75%. Changes in the size of genetic influences are inversely related to changes in the importance of shared environmental influences. Nonshared environmental influences remain more or less constant. Additive genetic influences are also important for stability of problem behavior, whereas nonshared environmental influences mainly account for change.

Gene–environment interaction: an overview of research results

Recently, several researchers have focused on the complex interplay of genes and environment for psychopathology (for a more extensive background and overview, see the article by Kim-Cohen in this issue). In the beginning, the complex interplay was investigated on a phenotypic level, without direct measurement of genes. Differences in heritability under distinct environmental circumstances indicate G×E interaction. For example, it has been found that the heritability for problem behavior was significantly lower in children having a very low birth weight in relation to gestational age than in those having normal birth weight [50]. Further, findings of G×E using quantitative genetic designs have been reported for anxiety/depression in the context of family discord and negativity and negative life events [51]. A point of critique in quantitative G×E studies has been the uncertainty over the extent to which the so-called ''environmental effects'' are genetically or environmentally mediated [52]. This argument can be overcome by parallel modeling of G×E and rGE [53]. Two studies using this approach found evidence for G×E in the context of anxious/depression and negative life events [54,55].

Developments in the field of molecular genetics pushed G×E studies in the direction of measured genotypes. A groundbreaking study came from Caspi and colleagues [56], in which G×E is reported for polymorphisms in the monoamine oxidase A (MAOA) gene, childhood maltreatment, and antisocial behavior. The positive relation between childhood maltreatment

and adolescent antisocial behavior was found to be moderated by the MAOA genotype. Severely maltreated individuals who have the low-MAOA-activity genotype showed significantly more antisocial behavior than equally maltreated children who had the high-MAOA-activity genotype. Several research groups attempted to replicate this finding, with mixed results. A positive replication was conducted by Foley and colleagues [57], with white male twins from the community-based, longitudinal Virginia Twin Study for Adolescent Behavioral Development. A recent study extended the finding to childhood by investigating a sample of 7-year-old boys [58] and a study with a randomized sample of 16- and 19-year old boys from the county of Västmanland, Sweden [59]. Two other studies, one [60] using data from the National Longitudinal Study of Adolescents Health and the other using male adolescent conduct and patients involved with substance abuse [61], do not support this finding. A meta-analysis showed that across studies from the published findings, the association between maltreatment and mental health problem is significantly stronger in the group of boys who have the genotype conferring low MAOA activity [58]. New evidence from a study with a more diverse population, including whites, nonwhites, and male and female subjects, found that genotypes associated with high levels of MAOA activity buffered abused and neglected whites from increased risk of becoming violent or antisocial. This protective effect was not found for nonwhite individuals [62]. Similar results for a variant of the COMT gene, cannabis use, and adult psychosis have been published [63].

A similar train of replication studies followed the finding of G×E for a functional polymorphism in the promoter region of 5-HTT, stressful life events, and depressive symptoms [18], again with mixed results. Partial to full replications of these patterns have been reported by [64–69]. A large-scale study of 1099 adults from the Australian volunteer twin register [70] and a large-scale study of 4175 adult English men and women [71] did not replicate the finding of a G×E interaction between the 5-HTTLPR genotype, social adversity, and depression.

G×E research offers many exciting features and findings. With the mainly positive replications, evidence for the existence of these mechanisms becomes strong, although most studies are conducted in adults and are based on rather extreme environmental factors, such as childhood abuse.

Recent work from the Netherlands Twin Register

With data from the large longitudinal database of the Netherlands Twin Register [72], we are investigating the role of familial factors on adolescent wellness and problem behavior. Large studies in our samples of twin children showed moderate to large genetic influences on aggressive behavior during childhood [47]. This classical twin study does not reveal information

on the possible interacting effects of genes and environment on aggressive behavior. In our new project, "A Twin-Sibling Study of Adolescent Wellness," we have tested the effects of familial conflict, measured with the 11-item conflict scale from the Family Environment Scale [73] on the etiology of Aggressive behavior from the Youth Self Report [74]. The Dutch Health and Behavior Questionnaire has been collected in adolescent twins (n = 1000 pairs) and their nontwin siblings (n = 500 individuals).

A main effect of familial conflict on adolescent aggressive behavior (AGG) has been found, with significantly higher levels of AGG in families that have high levels of familial conflict ($P = .00$). Preliminary analyses based on twin correlations indicate G×E interaction effects because a higher h^2 (0.70) for AGG is found for the adolescents who have low familial conflict in comparison to heritability estimates for the group with moderate familial conflict (h^2 for AGG, 0.53) and the group who reports high familial conflict (h^2 for AGG, 0.28). Sophisticated model fitting, which includes tests for gender effects and possible effects of G×E correlations, will be conducted to gain more insight into the role of familial conflict in adolescent aggressive behavior. Molecular genetic analyses will be conducted with genotypes of interest.

Following molecular genetic analyses, we aim to use developmental strategies (eg, longitudinal growth curve analyses) to examine the developmental trajectories of adolescents who have remained well throughout our study (which began at birth) versus those who were initially well and then became ill versus those who were ill at one point and became well later in life. In this way we can begin to estimate the measured genetic and environmental influences on resilience by determining factors that move children into wellness or illness or by identifying factors that seem to be protective against inferred genetic and environmental risk factors.

Clinical relevance and limitations

The study of resilience may yield insights into a wide variety of complex questions. Why, for instance, do some children benefit from exposure to sports participation and music, nutritional, and other widely implemented social programs? Why do these social programs, which common sense would indicate should benefit all children, often help only a small percentage? Why do prevention programs work for only some children and families? Why do pharmacotherapies and psychotherapies not work in all children with the same "diagnosis"? Although the answers are so complex that many approaches are needed to dissect the relative contribution of a wide variety of factors, it is suggested that the study of the genetic and environmental influences on resilience may lead to a more clear understanding of which children will respond to which interventions and may help us to design more effective prevention programs.

Such research may lead to strategies that will change the way we assess children who have emotional behavioral illness. By assessing a child's (and the family's) relative risk for psychopathology using family and molecular genetic approaches in concert with an assessment of the risk and protective environmental factors, we may be able to better design the complex interventions that are needed for the complex problems of developmental psychopathology.

Although molecular genetic testing is a long way from being implemented in clinical settings, it is not too early to learn from the research presented in this article. A more thorough and complete assessment of the child's developmental trajectory, family, unique environmental risk and protective factors, and the estimation of the contribution of relative risk genes may help in the design of more effective treatment and prevention strategies for at-risk children. The work of Kaufman and colleagues [65], in which children who had one relative risk genotype (SS allele of the SERT) were more likely to benefit from social support in the face of extreme environmental disadvantage, offers us the promise of potentially understanding which children will respond to supportive therapies. Such an advance could benefit patients, their families, and the clinical teams who serve them. One of the great sadnesses of the practice of clinical child psychiatry is the inability to help children achieve wellness despite using all of the methods available in our clinical formulary. It is our contention that the study of resilience, as long as it includes well and suffering children and assesses genetic and environmental factors, is likely to lead to improvement in the ability to design effective treatments for children and their families and thus is likely to improve the efficiency of our clinical efforts with the end result of healthier, happier families.

References

[1] Derks EM, Hudziak JJ, Beijsterveldt van CEM, et al. Genetic analyses of maternal and teacher ratings on attention problems in 7-year-old Dutch twins. Behav Genet 2006;36: 833–44.
[2] Rietveld MJ, Hudziak JJ, Bartels M, et al. Heritability of attention problems in children: I. cross-sectional results from a study of twins, age 3–12 years. American Journal of Medical Genetics B Neuropsychiatric Genetics 2003;117(1):102–13.
[3] Carey G. Human genetics for the social sciences. Thousand Oaks, London: Sage Publications; 2002. Available at: http://psych.colorado.edu/hgss/. Accessed September 20, 2006.
[4] Mendel G. Experiments in plant hybridization. 1865. Available at: www.Mendelweb.org. Accessed September 9, 2006.
[5] Ficher RA. The correlation between relatives on the supposition of Mendelian inheritance. Trans Royal Soc Edinburgh 1918;52:399–433.
[6] Philips PC. The language of gene interaction. Genetics 1998;149:1167–71.
[7] Falconer DS, Mackay TFC. Introduction to quantitative genetics. Essex (UK): Longman Scientific and Technical; 1996.
[8] Plomin R, DeFries JC, Loehlin JC. Genotype-environment interaction and correlation in the analysis of human behavior. Psychol Bull 1977;84:309–22.

[9] Reiss D, Neiderhiser JM, Hetherington E, et al. The relationship code: deciphering genetic and social influences on adolescent development. Cambridge (MA): Harvard University Press; 2000.
[10] O'Connor TG, Deater-Deckard K, Fulker D, et al. Genotype-environment correlations in late childhood and early adolescence: antisocial behavioral problems and coercive parenting. Dev Psychol 1998;34:970–81.
[11] Jencks C. IQ, heritability and inequality, Part 2. In: Block NJ, Dworkin G, editors. Philosophy and public affairs. Princeton, NJ: Princeton University Press; 1974.
[12] Eaves LJ. The resolution of genotype x environment interaction in segregation analysis of nuclear families. Genet Epidemiol 1984;1(3):215–28.
[13] Mather K, Jinks JL. Introduction to biometrical genetics. London: Chapman and Hall Ltd; 1977.
[14] Boomsma DI, Martin NG. Gene-environment interactions. In: D'haenen HD, den Boer JA, Willner P, editors. Biological psychiatry. John Wiley and Sons, Ltd; 2002.
[15] Eaves LJ. The utility of twins. In: Anderson VE, Hauser WA, Penry JK, Sing CF, editors. Genetic basis of the epilepsies. New York: Raven Press; 1982. p. 249–76.
[16] Eaves LJ, Last KA, Martin NG, et al. A pregressive approach to non-additivity and genotype-environmental covariance in the analysis of human differences. Br J Math Stat Psychol 1977;30:1–42.
[17] Heath AC, Todorov AA, Nelson EC, et al. Gene-environment interaction effects on behavioral variation and risk of complex disorders: the example of alcoholism and other psychiatric disorders. Twin Res 2002;5(1):30–7.
[18] Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301(5631):386–9.
[19] Kendler KS, Kuhn JW, Prescott CA. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol Med 2004;34(8):1475–82.
[20] Eaves LJ. Genotype x environment interaction in psychopathology: fact or artifact? Twin Res Hum Genet 2006;9(1):1–8.
[21] Boomsma D, Busjahn A, Peltonen L. Classical twin studies and beyond. Nat Rev Genet 2002;3(11):872–82.
[22] Posthuma D, Boomsma DI. A note on the statistical power in extended twin designs. Behav Genet 2000;30(2):147–58.
[23] Hudziak JJ, Derks EM, Althoff RR, et al. The genetic and environmental contributions to attention deficit hyperactivity disorder as measured by the Conners' Rating Scales-revised. Am J Psychiatry 2005;162:1614–20.
[24] Martin N, Scourfield J, McGuffin P. Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. Br J Psychiatry 2002;180:260–5.
[25] Hudziak JJ, Rudiger LP, Neale MC, et al. A twin study of inattentive, aggressive and anxious/depressed behaviors. J Am Acad Child Adolesc Psychiatry 2000;39(4):469–76.
[26] Vierikko E, Pulkkinen L, Kaprio J, et al. Genetic and environmental influences on the relationship between aggression and hyperactivity–impulsivity as rated by teachers and parents. Twin Res 2004;7:261–74.
[27] Kuntsi J, Rijsdijk F, Ronald A, et al. Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. Biol Psychiatry 2005;57:647–54.
[28] Thapar A, Harrington R, Ross K, et al. Does the definition of ADHD affect heritability? J Am Acad Child Adolesc Psychiatry 2000;39:1528–36.
[29] Eaves LJ, Silberg JL, Meyer JM, et al. Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of adolescent behavioral development. J Child Psychol Psychiatry 1997;38:965–80.
[30] Sherman DK, Iacono WG, McGue MK. Attention-deficit hyperactivity disorder dimensions: a twin study of inattention and impulsivity–hyperactivity. J Am Acad Child Adolesc Psychiatry 1997;36:745–53.

[31] Caspi A, Moffitt TE, Newman DL, et al. Behavioral observations at age 3 years predict adult psychiatric disorders: longitudinal evidence from a birth cohort. Arch Gen Psychiatry 1996; 53(11):1033–9.
[32] Hofstra MB, Van der Ende J, Verhulst FC. Pathways of self-reported problem behaviors from adolescence into adulthood. Am J Psychiatry 2002;159(3):401–7.
[33] Scroufe LA. Considering normal and abnormal together: the essence of developmental psychopathology. Dev Psychopathol 1990;2:335–47.
[34] Hermanns J, Leu HR. Familiy risk and family support: theory, research, and practice in Germany and in the Netherlands. Delft (the Netherlands): Eburon; 1998.
[35] Richman N, Stevenson J, Graham PJ. Preschool to school: a behavioral study. New York: Academic Press; 1982.
[36] Graham P, Rutter M. Psychiatric disorder in the young adolescent. Proc R Soc Med 1973;66: 1226–9.
[37] Fergusson DM, Horwood LJ, Lynskey MT. The stability of disruptive childhood behaviors. J Abnorm Child Psychol 1995;23:379–96.
[38] Patterson GR. Centre gets $4 million grant to study delinquency, by Jef Wright. The Register Guard. April 5, 1988.
[39] Verhulst FC, Van der Ende J. Six-year stability of parent reported problem behavior in an epidemiological sample. J Abnorm Child Psychol 1992;20:595–610.
[40] Hofstra MB, Van der Ende J, Verhulst FC. Continuity and change of psychopathology from childhood into adulthood: a 14-year follow-up study. J Am Acad Child Adolesc Psychiatry 2000;39:850–8.
[41] Ghodsian M, Fogelman K, Lambert L, et al. Changes in behavior ratings of a national sample of children. Br J Soc Clin Psychol 1980;19:247–56.
[42] Bongers IL, Koot HM, van der Ende J, et al. Developmental trajectories of externalizing behaviors in childhood and adolescence. Child Dev 2004;75(5):1523–37.
[43] Haberstick BC, Schmitz S, Young SE, et al. Contributions of genes and environments to stability and change in externalizing and internalizing problems during elementary and middle school. Behav Genet 2005;35(4):381–96.
[44] Bartels M, Van den Oord EJCG, Hudziak JJ, et al. Genetic and environmental mechanisms underlying stability and change in problem behaviors at ages 3, 7, 10, and 12. Dev Psychol 2004;40(5):852–67.
[45] Bishop EG, Cherny SS, Corley R, et al. Developmental genetic analysis of general cognitive ability from 1 to 12 years in a sample of adoptees, biological siblings, and twins. Intelligence 2003;31:31–49.
[46] Rietveld MJH, Hudziak JJ, Bartels M, et al. Heritability of attention problems in children: longitudinal results from a study of twins, age 3 to 12. J Child Psychol Psychiatry 2004;45(3): 577–88.
[47] Van Beijsterveldt CEM, Bartels M, Hudziak JJ, et al. Causes of stability in childhood aggression: longitudinal genetic analyses in Dutch twins. Behav Genet 2003;33(5): 591–605.
[48] Boomsma DI, Molenaar PCM, Orlebeke JF. Estimation of individual genetic and environmental factor scores. Genet Epidemiol 1990;7:83–91.
[49] Van den Oord EJCG, Simonoff E, Eaves LJ, et al. An Evaluation of different approaches for behavior genetic analyses with psychiatric symptom scores. Behav Genet 2000;30(1): 1–18.
[50] Wichers MC, Purcell S, Danckaerts M, et al. Prenatal life and post-natal psychopathology: evidence for negative gene-birth weight interaction. Psychol Med 2002;32(7): 1165–74.
[51] Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry 1999;156(6):837–41.
[52] Turkheimer E. Mobiles: a gloomy view of the future of research into complex traits. In: Parens E, Press N, Chapman A, editors. Wrestling with behavioral genetics: science, ethics,

and the prospect of public conversation. Baltimore (MD): Johns Hopkins University Press; 2006.
[53] Purcell S. Variance components models for gene-environment interaction in twin analysis. Twin Res 2002;5:554–71.
[54] Lau JY, Eley TC. Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. Br J Psychiatry 2006;189:422–7.
[55] Silberg JL, Rutter M, Eaves L. Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls. Biol Psychiatry 2001;49(12): 1040–9 [Erratum in: Biol Psychiatry 2001 Sep 1;50(5):393].
[56] Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. Science 2002;297:851–4.
[57] Foley DL, Eaves LJ, Wormley B, et al. Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. Arch Gen Psychiatry 2004;61:738–44.
[58] Kim-Cohen J, Caspi A, Taylor A, et al. MAOA, maltreatment, and gene–environment interaction predicting children's mental health: new evidence and a meta-analysis. Mol Psychiatry 2006;11(10):903–13.
[59] Nilsson K, Sjoberg R, Damberg M, et al. Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biol Psychiatry 2005;59:121–7.
[60] Haberstick B, Lessem J, Hopfer C, et al. Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. Am J Med Genet B Neuropsychiatr Genet 2005;135B:59–64.
[61] Young S, Smolen A, Hewitt J, et al. Interaction between MAO-A genotype and maltreatment in risk for conduct disorder: failure to confirm in adolescent patients. Am J Psychiatry 2006;163(6):1019–25.
[62] Widom CS, Brzustowicz LM. MAOA and the "cycle of violence:" childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. Biol Psychiatry 2006;60(7):684–9.
[63] Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol Psychiatry 2005; 57(10):1117–27.
[64] Eley TC, Sugden K, Corsico A, et al. Gene–environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 2004;9:908–15.
[65] Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci U S A 2004; 101(49):17316–21.
[66] Grabe HJ, Lange M, Wolff B, et al. Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. Mol Psychiatry 2005;10(2):220–4.
[67] Kendler KS, Kuhn JW, Vittum J, et al. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry 2005;62(5):529–35.
[68] Wilhelm K, Mitchell PB, Niven H, et al. Life events, first depression onset and the serotonin transporter gene. Br J Psychiatry 2006;188:210–5.
[69] Taylor SE, Way BM, Welch WT, et al. Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. Biol Psychiatry 2006;60(7):671–6.
[70] Gillespie NA, Whitfield JB, Williams B, et al. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol Med 2005; 35(1):101–11.
[71] Surtees PG, Wainwright NW, Willis-Owen SA, et al. Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. Biol Psychiatry 2006; 59(3):224–9.

[72] Boomsma DI, de Geus EJC, Vink JM, et al. Netherlands twin register: from twins to twin families. Twin Res Human Genet 2006;9(6):849–57.
[73] Moos RH, Moos BS. Manual for the Family Environment Scale. Palo Alto (CA): Consulting Psychologists Press; 1974.
[74] Achenbach TM, Rescorla LA. Manual for ASEBA school-age forms & profiles. Burlington (VT): University of Vermont Research Center for Children, Youth, Families; 2001.