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Epigenetic approaches to developmental psychopathology

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Abstract
We evaluate the usefulness of 11 key epigenetic concepts from the behavior genetic research paradigm for advancing the field of developmental psychopathology. Key assumptions, empirical examples, and caveats in interpreting results are presented. We emphasize the usefulness of incorporating both dimensional (e.g., temperament trait) and categorical (e.g., diagnosis) variables, environmental measures, direct behavioral assessments, and multiple, theoretically relevant occasions of study into classic twin and family studies. We highlight contemporary techniques for identifying specific chromosomal regions associated with behavioral patterns, and the importance of considering nonmendelizing genetic influences when discerning the panorama of genetic influences on behavior.

Introduction

The behavior–genetic research paradigm is often exposed to readers only in fragments —for example, the results of a single comparison of identical and fraternal twins or the report of a gene linked to some form of psychopathology. Before we can place the behavior–genetic research paradigm in some perspective, examine its assumptions, and evaluate its potential for advancing the field of developmental psychopathology, it is useful to lay out the paradigm more completely. At its most generic level, an ideal long-term research program for studying genetic influences on the development of psychopathology would likely encompass the following elements:

1. Definition of a behavioral pattern reflective of psychopathology.
2. Observation that the behavioral pattern "runs in families."
3. Demonstration of heritable influence on the behavioral pattern, usually initially in twin studies.
4. Confirmation of initial [twin study] results in adoption studies or other family designs.
5. Possible decomposition of the behavioral pattern to highlight heritable or nonheritable features.
6. Study of genetic influences on continuity and change of the behavioral pattern.
7. Examination of environmental influences on the behavioral pattern within a behavior–genetic context (possibly including study of gene–environment correlation and interaction).
8. Search for associated phenotypes (endophenotypes), for example, cognitive or psychophysiological substrates of the behavioral pattern.
9. Analysis of whether the behavioral pattern and its associated endophenotypes share genetic sources of variation.

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10. If element 8 is successful, possible further redefinition of the behavioral pattern.
11. Given the availability of genetic probes, search for specific chromosomal regions associated with the behavioral pattern (association and linkage studies).
12. Development of animal models of the behavioral pattern or endophenotypes in the gene to behavior pathway (causal chain), which, if successful, would initiate a new sequence of investigations. These animal models have recently become much more feasible with the development of "knockout genetics" (Capecchi, 1994), techniques that allow for the inactivation, or knockout, of specific genes. For example, separate mouse lines can be prepared that are deficient in each of the dopamine receptors, and the phenotypic effects of each deficiency can then be studied.

It is hard to point to any research problem where the paradigm outlined above has been fully implemented. Historically, many programs of research have stopped at steps 3 or 4. However, behavioral genetics is a rapidly evolving field, and research activity is occurring for each of the 12 issues. The nature of explicit and implicit assumptions of behavioral genetics, the treatment of which is a central charge in writing this paper, is quite different as we progress through the different stages of the research paradigm. Some of the assumptions that pertain to earlier or simpler stages in the paradigm (e.g., linear genetic effects on the phenotype) do not pertain to latter stages.

We note at the outset that the current genetic literature in developmental psychopathology is dominated by twin and family studies. Some illustrations of how the twin method can be employed to understand childhood and adolescent psychiatric disorders are provided by LaBuda, Gottesman, and Pauls (1993) and Rutter, MacDonald, LeCouteur, Harrington, Bolton, and Bailey (1990). It is reasonably well documented that the modest similarity of siblings (as well as of parents and offspring) is mostly accounted for by shared genes rather than shared environmental factors for many aspects of personality and intellectual skills, especially when assessment is via paper and pencil. Although conclusions would be premature, emerging results from studies using objective behavioral assessment have validated this notion. However, there is nothing in the application of behavior–genetic methods that guarantees a positive result for genetic effects, and we shall mention instances where research has documented salient environmental effects.

In the 11 parts of the next section, we deemphasize strictly methodological considerations in favor of a focus on 11 ways in which the behavior–genetic paradigm can and has informed the field. We do not attempt equally comprehensive treatment of all 11 approaches because the extent of the relevant literature varies greatly. Some approaches are included for their future promise rather than realized findings. For each approach that has generated a substantial literature, we mention key assumptions and offer some caveats in interpreting results.

Behavior–Genetic Approaches to Developmental Psychopathology

Understanding the effects of heritable and environmental variance

Behavioral geneticists infer the relative strengths of various classes of genetic and environmental factors from patterns of covariation among family members with varying degrees of genetic and environmental similarity. The heritability statistic estimates the association between degree of genetic overlap and similarity on behavioral traits in relatives. More formally, behavioral geneticists gather data to solve a biometric equation decomposing phenotypic (observed) variance into genetic and environmental components. The genetic component is subdivided into additive and nonadditive effects and the environmental component is also subdivided into effects shared versus nonshared by relatives. This basic biometric model can be expanded for longitudinal, multivariate analyses. Simply describing how twin data can be statistically

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analyzed fills a recent 500-page text (Neale & Cardon, 1992).

Assumptions and caveats. The concept of heritability is circumscribed in several ways. Heritability applies only to differences among persons within populations, not to the development of single individuals nor to differences between populations. Heritability may also change at different points in the life span, due to the dynamic nature of gene action, changes in the presence or absence of the effects of environmental factors, changes in the nature of the trait being measured, or other constellations of factors (Carey, 1988). Because heritability is a ratio involving both genetic and environmental effects, variable environmental conditions (across a population) will obviously reduce heritability whereas uniform nongenetic conditions increase it (Falconer, 1989). Another caveat is that similar heritability estimates for two traits, even conceptually related traits, do not imply common genetic underpinnings. In fact, the great majority of heritability estimates for behavioral traits (estimated in large samples) lies in a range of 30–70%.

Several limits attend any developmental implications of simple heritability estimates. Failures to appreciate distinctions between individual differences and the development of an individual are common in popular renderings of behavior–genetic research. Such failures also occur among scientists who sometimes fail to appreciate that classic behavior–genetic inferences are confined to genetic and environmental *effects on phenotypic variance,* not genes and environments per se. Genes exert their effects on behavior via complex pathways that involve feedback loops, rate-limiting processes, etc. Environments likewise probably exert many of their effects in inherently nonlinear ways. However, there is no contradiction in analyzing individual differences by linear regression of outcome on sources of variation, even when the individual differences result from highly contingent, interactive developmental processes operating in the lives of individuals.

The other side of the heritability issue is, of course, the analysis of environmental effects. From the behavior–genetic perspective, environmental effects can be shared or nonshared by a particular set of family members. A common misunderstanding is that environmental effects are "what is left over" after genetic effects are estimated. Typical behavior–genetic methods treat genetic and *shared* environmental effects in an even handed manner, *given the assumptions about how these effects can be partitioned.* The more cogent criticism is that the genetic partitioning is based on sound theories of Mendelian inheritance whereas the environmental partitioning is based on familial units that might not be the most important markers of environmental influence.

Despite extensive explication of the issue (Plomin & Daniels, 1987), the meaning of "shared" and "nonshared" environments continues to create confusion. Behavioral geneticists have unwittingly contributed to this confusion by sometimes referring to the "shared" environment as the "between family," or simply the "familial" environment. However, all experience that is shared by a pair of relatives (say, cotwins) does not occur in the family context, and experiences within the family often affect family members differently. Furthermore, the variance component referred to as "shared environment" differs from one kinship design to the next. Thus, the environment shared by cotwins has a somewhat different quality from the environment shared by ordinary siblings or adopted siblings. Of course, these differences in the quality of the shared environment might well be irrelevant to the behavior under study. Fortunately, this "armchair" criticism can be subjected to empirical test, and such tests are common in the more technical behavior–genetic literature (see Loehlin, 1992, for an accessible illustration in the personality domain).

In addition to the shared versus nonshared distinction, the concept of "vertical environmental transmission variance" is relevant to the nature of environmental effects. The term "vertical" refers, of course, to factors transmitted from one generation to the next (in distinction from peer and sibling influences, for example). Conceptually, all factors—mechanisms operating inside or outside the family—

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that contribute to parent–offspring similarity are included in vertical environmental transmission. Bodmer and Cavalli–Sforza (1976) emphasized a useful distinction between two types of vertical transmission, direct phenotypic transmission and sociocultural transmission. Direct phenotypic transmission refers to processes involving the parent and child only, such as modeling of parental behavior. Sociocultural transmission refers to parent–offspring similarity that is due to extrafamilial factors that similarly affect the development of both phenotypes in both generations, such as cultural traditions. Together and along with genetic factors, these two types of vertical environmental transmission account for parent–offspring similarity.

The processes underlying vertical environmental transmission variance and shared environmental variance of siblings could be similar (e.g., social class) or very different. Moreover, the estimate of vertical environmental transmission variance might well be zero at the same time that parents exert strong effects on the offspring behavior in question. For example, hypothetically, aggressive fathers might induce inhibited behavior in children of a certain age. Such a hypothetical effect would not emerge in a univariate analysis of parent–offspring data of either aggressiveness or inhibition. Of course, part of the solution is the sort of multivariate analysis that has emerged with statistical and computing advances (e.g., McArdle & Goldsmith, 1990; Neale & Cardon, 1992). Still largely remaining is the task of integrating theories of how the environment works into these multivariate designs.

In summary, the distinctions between shared and nonshared environmental effects and transmitted environmental effects in behavior–genetic designs do not map well onto some issues concerning the nature and effects of interaction among family members (Hoffman, 1991). However, the empirical findings highlighting the importance of nonshared over shared effects need to be accommodated by researchers studying family processes.

Illustrating the classic twin study analysis. We briefly review the recent twin study literature on one of the most versatile and highly regarded instruments in developmental psychopathology, the Child Behavior Checklist (CBCL). This literature illustrates only the simplest principles discussed above. The CBCL has two age-graded forms for parents or teachers, the CBCL/4–16 and the CBCL/2–3, both developed by Achenbach and colleagues (Achenbach & Edelbrock, 1983, 1986; Achenbach, Edelbrock, & Howell, 1987). Subscales on the CBCL form an internalizing factor (composite of withdrawn, somatic complaints, and anxious/depressed subscales) and an externalizing factor (composite of the delinquent and aggressive behavior subscales). Reliability estimates for the CBCL are satisfactory, and validity evidence is accumulating (Achenbach, 1991; Achenbach, Howell, Quay, & Conners, 1991).

Intraclass correlations from twin studies using the CBCL are summarized in Table 1. From these intraclass correlations, we can obtain estimates of heritability, and shared and nonshared environmental influences on the CBCL scales.

As this literature is recent, we provide some commentary, beginning with the Externalizing factor for 2–3-year-olds. Van Den Oord, Verhulst, Boomsma, and Orlebeke (1993), with a sample of over 1000 Dutch twin pairs, found differential heritability for the CBCL subscales, with the Oppositional subscale yielding a heritability estimate of 34% and a large shared environment effect of 49%. The Aggressive and Overactive subscales, on the other hand, yielded an average heritability of 65%, with no effect of the shared environment. With a sample of over 200 pairs, Schmitz, Cherny, Fulker, and Mrazek (1994) estimated heritability at 40% and the shared environmental influence at 23% for the Externalizing factor. Turning to the Externalizing factor with 7–16-year-olds, studies by Silberg, Erickson, Meyer, Eaves, Rutter, and Hewitt (1994), Edelbrock, Rende, Plomin, and Thompson (1995), and Leve, Winebarger, Fagot, Reid, and Goldsmith (1996) yielded heritability estimates from 30 to 52% and shared environmental estimates from 27 to 51%. Thus, the externalizing factor appears to be influenced by both a genetic and a shared

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Table 1. *Intraclass correlations from twin studies using CBCL*

Study	No. Pairs	Age (Years)	Males MZ	Males DZ	Females MZ	Females DZ	OSDZ	Pooled MZ	Pooled DZ
Externalizing									
1. Van Den Oord et al. (1993)									
Oppositional	1281	2–3						.83	.66
Aggressive	1281	2–3						.67	.40
Overactive	1281	2–3						.65	.27
Sleep problems	1281	2–3						.47	.08
2. Schmitz et al. (1994)	229	2–3	.55	.46	.71	.39	.45		
3. Silberg et al. (1994)									
	652	8–11	.86	.60	.76	.66	.68		
	612	12–16	.83	.69	.80	.63	.72		
4. Edelbrock et al. (1995)	181	7–15						.79	.53
5. Leve et al. (submitted)	154	6–11						.86	.63
6. Ghodsian–Carpey & Baker (1987)									
Aggression	38	4–7						.78	.31
Internalizing									
1. Van Den Oord et al. (1993)									
Withdrawn/Depressed	1281	2–3						.75	.42
Anxious	1281	2–3						.78	.47
Somatic problems	1281	2–3						.68	.41
2. Schmitz et al. (1994)	229	2–3	.73	.60	.72	.49	.51		
3. Silberg et al. (1994)									
	652	8–11	.82	.54	.77	.65	.55		
	612	12–16	.74	.58	.78	.55	.59		
4. Edelbrock et al. (1995)	181	7–15						.75	.50
5. Leve et al. (submitted)	154	6–11						.80	.51

1. Van Den Oord, Verhulst, Boomsma, & Orlebeke (1993). Averaged mother and father ratings. n = 407 MZ (218 female), 874 same sex DZ (233 female), and 389 opposite sex DZ pairs.
2. Schmitz, Cherny, Fulker, & Mrazek (1994). Mother report. n = 69 MZ, 71 same sex DZ, and 89 opposite sex DZ pairs.
3. Silberg, Erickson, Meyer, Eaves, Rutter, & Hewitt (1994). Mother report. Formed their own internalizing and externalizing factors (used items that loaded in both age groups and genders). n = 514 MZ (272 female), 478 same sex DZ (223 female), 271 opposite sex DZ pairs, both age groups combined.
4. Edelbrock, Rende, Plomin, & Thompson (1995). 91.5% mother report, 5.9% father report, and 2.6% other report. n = 99 MZ (47% female) and 82 same sex DZ pairs (46% female). Correlations were adjusted for age and gender differences using regression.
5. Leve, Winebarger, Fagot, Reid, & Goldsmith (submitted). Mother report. n = 77 MZ (35 female), 42 same sex DZ (21 female), and 35 opposite sex DZ pairs.
6. Ghodsian–Carpey & Baker (1987). Mother report. n = 21 MZ (12 female), 14 same sex DZ (7 female), and 3 opposite sex DZ pairs.

environment component for both age groups, a notable finding because replicated shared environmental effects are rare in the personality literature.

For the Internalizing factor with 2–3-year-olds, Van Den Oord et al. (1993) reported an average heritability of 62%, and a shared environmental effect of 12% for the subscales of Withdrawn/Depressed, Anxious, and Somatic Problems. For the Internalizing factor, data from Schmitz et al. (1994) yielded a heritability of 40%, and a shared environmental effect of 33%. Thus, heritability seems to account for about one-half of the variance for Internalizing in 2–3-year-olds, with a smaller, yet significant, effect of the shared environment. Estimates for 7–16-year-olds with the Internalizing factor were very similar to the estimates found with 2–3-year-olds. Studies by Silberg et al. (1994), Edelbrock et al. (1995), and Leve et al. (1996) yielded heritability estimates from 40 to 58% and shared environmental estimates from 22 to 38% for the Internalizing factor.

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In summary, these CBCL results suggest that individual differences in the externalizing and internalizing tendencies are clearly genetically influenced. Given that these two tendencies are probably the broadest liability factors in the child psychopathology literature, the implication is that widespread genetic influences are expectable for childhood disorders. However, we must bear in mind the caveat that few clinical cases of externalizing or internalizing disorders actually contributed to the samples upon which the CBCL results above were based.

Multivariate extensions. Historically, the field has progressed from univariate to multivariate studies, and heritability analyses become increasingly informative when extended to the multivariate case. Even if several correlated phenotypes are heritable, we cannot assume that the phenotypic correlation is mediated genetically unless we use multivariate analyses. Also, the genetic correlation between two phenotypes can be high in the face of low heritability of each of the individual phenotypes. The multivariate analysis of two phenotypically correlated traits in twins or other informative relatives can tell us whether the basis of the observed correlation is common genetic effects, common environmental effects, or both. For example, in both population-based and clinical samples, major depression and generalized anxiety disorder cooccur at higher rates than would be expected by chance. Kendler, Neale, Kessler, Heath, and Eaves (1992) explored the etiology of these two disorders using bivariate genetic analysis with a population-based sample of over 1000 female same-sex twin pairs. Their results indicated that shared environment played no role in the etiology of either disorder. However, genetic factors were important for both disorders, and could be modeled as completely shared between them. Thus, the notion is that adult female liabilities to major depression and generalized anxiety disorder are influenced by the same genes, suggesting that it is the environment that determines whether a vulnerable woman develops major depression or generalized anxiety disorder.

Another bivariate case is the single variable measured on two occasions. Given some continuity of the trait or disorder, it is of interest to determine whether the basis of the continuity is genetic or environmental effects. For developmental psychopathologists, the bases of continuity for traits thought to be precursors or risk factors for disorders is of particular interest.

For multivariate analyses that extend to more than two occasions, computations become more complex but results more convincing. The Cholesky decomposition, or triangular model, parses the multivariate variance systematically and in a statistically tractable fashion; thus, it is a convenient starting point for longitudinal analysis. In the Cholesky decomposition, the genetic factor at time 1 influences the phenotype at time 1 and all subsequent occasions. The genetic factor at time 2 influences time 2 and all subsequent occasions (but not at time 1), and so on for as many genetic factors as there are occasions. The same triangular pattern of paths holds for environmental factors. In a sense, the Cholesky decomposition is equivalent to a principal components analysis. It is typically used as an initial approach to identifying how many underlying factors exist. Then, paths are dropped as indicated by the initial fit. See Neale and Cardon (1992) for the matrix representation of the Cholesky decomposition as well as other treatment of this popular approach.

Reaction surface as a framework for conceptualizing genetic and environmental influences on behavior

Currently, we have entered a period when specific genes are being linked to complex behaviors (Lander & Schork, 1994), but we are probably not very close to a time when the processes intervening between those genes and behaviors will be fully elucidated. There is still need for some broad metaphors to help understand the relationship of genes and behavior and to emphasize the developmental aspects of genetic effects. As long as we avoid interpreting them too literally, some such metaphors can hint at the complexities of development while we await explication

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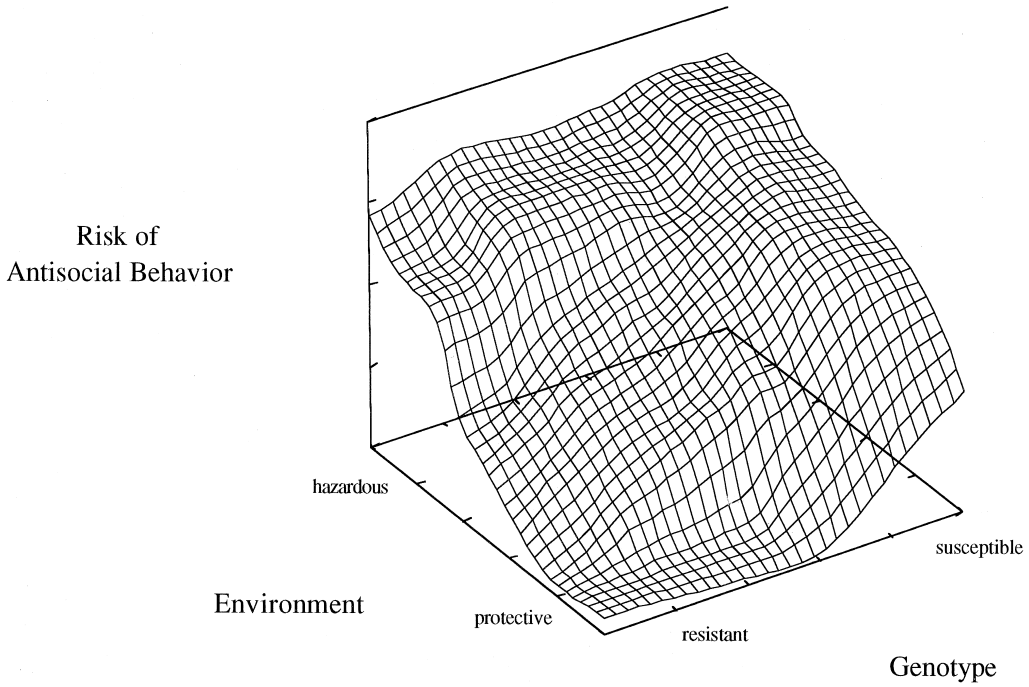


Figure 1. Hypothetical reaction surface for antisocial behavior.

from the molecular to the social level. One such metaphor is the "reaction surface" of behavior, which derives from Dobzhansky's (1955) "norm of reaction" (see Gottesman, 1963, for the application to human as a "reaction range"). Although there exists no methods to directly elucidate the reaction surface empirically, it is possible to give some quantitative meaning to the reaction range idea. For instance, the largest differences observed between identical cotwins with varying experiences would be a lower bound estimate of the reaction range for a given genotype. Figure 1 depicts a hypothetical "reaction surface" of a behavior, as previously discussed by us (see Turkheimer & Gottesman, 1991; Goldsmith & Gottesman, 1996; and especially Turkheimer, Goldsmith, & Gottesman, 1995, for detailed discussion of this concept).

The hypothetical reaction surface in Figure 1 shows risk for antisocial behavior on the vertical axis (any other heritable trait could have been chosen). The other two axes are the relevant genotype and environment. The diagram does not embody assumptions about the frequency distributions of either genotypes or environments. The shape of the surface suggests nonlinear and interactive effects. The left side of the environmental axis ("hazardous") would represent experiences that enhance the development of antisocial behavior. The right side of the environmental axis is labeled "protective." The shape of the surface implies that extremely protective environments will depress the phenotype, regardless of genotype. We have called the observed range of outcomes associated with a particular genotype a "reaction range" (Gottesman, 1963) and the observed range of outcomes associated with a particular environment an "affordance range" (Goldsmith & Gottesman, 1996). Investigation of reaction and affordance ranges can be an empirical matter. For instance, identical twin intrapair differences in IQ up to 2 standard deviations have been reported. Obviously, sampling more extremely restrictive and facilitative environments would lead to higher estimates of the reaction range for any particular genotype. Analogous issues apply to affordance ranges. Gottesman and Goldsmith (1994) and Goldsmith and Gottesman (1996) elaborate the reaction surface concept as it applies to the development of antisocial behavior.

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Genetic interpretations of the concept of liability to psychopathology

Building on the concept of a reaction surface above and in Figure 1, we can introduce the essential construct of *liability*. In its ordinary language sense, liability equates to the ideas of predisposition or potential. The term also has a technical, statistical meaning which dates back to Falconer's (1965, 1967) seminal explication. Falconer provided methods for estimating the inheritance of a continuous dimension of liability to such complex human diseases as diabetes and certain congenital malformations from the incidence of such patently discontinuous conditions in their relatives. Consistent with our discussion so far, psychological/behavioral traits or disorders are considered to be complex because their presence and levels of expression as phenotypes require some combination of genetic and experiential/environmental contributors, differing dynamically over time as well as by trait (Morton & Frith, 1995). Falconer's work, growing out of plant and animal breeding, was recognized as important for bridging the gap between concepts for studying Mendelizing traits and continuous or quasicontinuous ones where a threshold effect could be inferred (Gottesman & Shields, 1967; Gottesman, 1974). The concept itself has evolved over time and found service both in advancing our understanding of somatic phenotypes such as coronary artery disease (Sing, Zerba, & Reilly, 1994) and psychiatric ones (Moldin, 1994; Pogue–Geile, 1991).

The *X* and the *Y* axes of Figure 1 combined define the contributors to liability but not their covariation or interaction (see below). Furthermore, a large number of such reaction surfaces for each trait of interest are required to do justice to epigenesis. Some psychopathologies may show marked peaks or valleys in the complete series of surfaces defining their epigenesis and these peaks or valleys may thus be clues to critical or sensitive periods.

The contributors to the genotype axis can be differentiated hypothetically as specific genetic liability, general genetic liability, and genetic assets, with the combination of the three providing an entry point on the axis. Similarly for the experience/environment axis, the contributors can be differentiated into specific environmental liability (although none may yet have been discovered for a particular trait), general environmental liability, and environmental assets. Both classes of contributors and their components can be weighted differentially as a function of empirical research.

Although developmental psychopathologists are already familiar with such important concepts as nonlinear interactions, they must be combined with ideas about evolving hierarchical systems (Salthe, 1985), as well as the concepts introduced here, in order to make full use of the basic construct of liability.

Genetic heterogeneity

The notion of genetic heterogeneity refers to subsets of a patently single clinical disorder having different genetic roots. At least in the early stages of understanding a disorder, genetic heterogeneity is probably the norm rather than the exception. Some genetic approaches initially assume that all cases of a disorder have a common cause, but empirical results often reveal unsuspected heterogeneity.

Perhaps the salient example of genetic heterogeneity in the current literature is Alzheimer's disease. It is a slowly developing disorder with severe behavioral symptoms. Some 4 million Americans suffer from Alzheimer's, although about 15% of those diagnosed with it actually suffer from another condition that produces similar symptoms. Alzheimer's symptoms include a gradual loss of memory and eventual failure of other body functions that are directed by the brain, resulting in death. The disease is recognized histologically in brain tissue by characteristic neurofibrillary plaques and tangles, which are not normal concomitants of brain aging. Subtle signs of the disease may occur many years before the frank onset of the disease.

Both Norwegian (Bergem, 1993, 1994) and Finnish (Raiha, Koskenvuo, Kaprio, Rajala, & Sourande, 1994) twin data suggest genetic etiologies of Alzheimer's. However, only a minority of Alzheimer's cases are familial, with the remainder of cases not "running in families." Over the past few years,

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linkage studies have identified alleles associated with susceptibility to familial Alzheimer's. Well over half—and perhaps three-quarters—of familial cases carry the apolipoprotein E4 (APOE4) allele. This association is strong enough that APOE4 has been called the Alzheimer's "susceptibility gene." However, mutations in amyloid precursor protein (APP) and presenilin 1 (PS1) and 2 (PS2) genes account for much smaller proportions of familial cases, in particular, those with early onset. Additional genes associated with small proportions of, particularly, late-onset cases seem likely to be identified in the near future. One can easily understand how heterogeneity such as that seen in familial Alzheimer's leads to lack of replicability in early linkage studies.

A current hypothesis is that cerebrocortical amyloid deposition is an essential early element in the pathogenesis of all forms of Alzheimer's disease. If this proves true, the amyloid deposition would qualify as an endophenotype, as described in step 8 in the idealized research program outlined at the beginning of the article. Redefinition of Alzheimer's disease to make cerebrocortical amyloid deposition the criterial feature might soon be justified, but of course this depends on whether such deposits occur in other disorders as well. The complications that we are beginning to understand about Alzheimer's disease might prove prototypic for investigation of some forms of child psychopathology, such as autism. Attention deficit/hyperactivity disorder (ADHD) seems another good candidate for genetic heterogeneity. For ADHD, half-sibling, twin, adoption, and segregation analysis studies all point to partial genetic mediation of familial aggregation (Faraone & Biederman, 1994).

Using genetics to elucidate comorbidity

The concept of comorbidity. Epidemiological studies indicate that comorbidity for many aspects of child psychopathology exceeds that expected by chance (Caron & Rutter, 1991). There are several explanations of observed comorbidity that need to be empirically tested. Some of the explanations represent artifacts of diagnostic and research practices. Comorbidity could be due to nosological confusion; thus, one disorder could be a component or stage of another disorder or an early manifestation of that other disorder. An obvious example is the relationship among oppositional defiant disorder (ODD), conduct disorder (CD), and antisocial personality disorder (APD). Young children are diagnosed with ODD, and this diagnosis may be changed to CD as the child grows older and manifests more symptoms; then, in adulthood, the same person may be diagnosed with APD. Also, comorbidity could be a function of the categorical nature of our classification system. If forms of psychopathology such as personality disorders are better represented by dimensional personality extremes, then comorbidity could simply be the result of an individual scoring high on two or more of these dimensions. In addition, personality dimensions probably operate as risk factors for later-appearing disorders. As another obvious example, a high standing on the dimension of anxiety proneness could be a risk factor for all of the anxiety disorders, whereas low standing appears to be one of the risk factors for APD. Comorbidity could also be due to overlapping diagnostic criteria, a particular problem due to the many nonspecific symptoms in child psychiatry (e.g., poor concentration).

Additionally, "true" comorbidity of two disorders can stem from three possibilities: from shared or correlated risk factors; from one disorder putting an individual at risk for a second disorder; and because the comorbid condition actually represents a separate, third, syndrome (Caron & Rutter, 1991; Rutter, 1995). In all three cases of true comorbidity, genetic analyses can be informative. A comprehensive research program should attempt to rule out the artifactual explanations before interpreting behavior–genetic analyses of comorbidity.

An extended example. Behavior genetic designs allow us to determine whether or not multiple phenotypes stem from the same or different genotypes. The relationship between the childhood behavioral disorders and adult antisocial behavior serves as an example. Genetic analyses of behavioral disorders are difficult because the DSM classification system

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does not necessarily yield homogeneous phenotypes. For example, within attention deficit/hyperactivity disorder (ADHD), the symptoms of impulsivity, motoric activity, and inattention can differ from one sample to another, and these symptoms have different correlates. In addition, ADHD and CD or ODD are frequently comorbid, and there are different diagnostic criteria for APD for older persons. Given these limitations, there are several good studies of the family aggregation of externalizing symptoms.

Twin, family, adoption, biochemical, and molecular biochemical studies indicate that ADHD has a genetic basis. Goodman and Stevenson (1989) examined twin concordance for hyperactivity in an English sample of 39 identical and 54 same-sex fraternal probands (using a broad, but clinically relevant, definition of hyperactivity). The identical concordance rate was 51% and the fraternal rate was 33%, yielding a heritability estimate of 64%. This estimate may be slightly inflated by rating biases. Adverse family factors in this sample were only weakly related to hyperactivity.

In the United States, any childhood disorder can be concurrently diagnosed with ADHD. In fact, children with ADHD in the United States show a broad spectrum of symptoms. Most samples of individuals with ADHD yield concomitant CD rates of 20–50%; this range of comorbidity creates problems for interpretation. Lilienfeld and Waldman (1990) reviewed the literature on childhood ADHD and adult APD and concluded that this association might simply reflect the persistence of antisocial behavior from childhood to adulthood, a link reflected in diagnostic criteria that view CD during childhood as a prerequisite for the diagnosis of adult APD.

Additionally, Faraone, Biederman, Keenan, and Tsuang (1991) found that APD and childhood ODD were observed in excess only among the parents and siblings of ADHD probands with comorbid antisocial patterns. The risk for antisocial disorder among relatives of probands fell upon a continuum of severity, with relatives of ADHD + CD probands at the highest risk (34%), then ADHD + ODD relatives (24%), and 4% for control and 7% for other psychiatric probands. In families in which a child had ADHD uncomplicated with antisocial tendencies and the parents also did not have APD, ADHD was more common in the parents, as compared to parents of normal controls. ADHD + CD also appears to be a distinct subtype, because the degree of comorbidity in relatives was found to be greater than that expected by chance. See Goldsmith and Gottesman (1996) for a review of additional studies of the family aggregation of externalizing symptoms.

Work in this area could benefit from considering the genetic association of comorbid disorders, using the multivariate genetic model fitting described above. For example, are the genetic factors that influence ADHD the same as those that influence CD and APD? Probably not, based on the studies cited above, but convincing answers to questions such as this should lead to advances in nosology.

Current reviews of behavior genetic studies of childhood antisocial behaviors indicate that genetic influences are low to modest, whereas the shared environmental influence is moderate to high (Cloninger & Gottesman, 1987; DiLalla & Gottesman, 1989; Rutter et al., 1990). However, the studies reviewed typically consider delinquency or externalizing behaviors, rather than diagnosed CD.

In contrast to these findings, Slutske, Heath, Dinwiddie, Madden, Bucholz, Dunne, Statham, and Martin (in press) considered the etiology of conduct disorder retrospectively in a community-based Australian sample of over 2500 male, female, and opposite-sex twin pairs. They found that the genetic influence on risk for CD accounted for 71% of the variance (95% confidence interval = 32–79%). The shared environmental influence on risk for CD was modest at best (95% confidence interval = 0–32%), and not statistically significant in the best-fitting model of CD. Their models also suggested that CD might be an extreme of the normal variation in conduct-disordered behavior found in the general population. Thus, the genetic analysis of CD is not a closed issue, with sample ascertainment differences, age differences, and differences in sources of information complicating comparison of studies.

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Considering the similarities and differences between CD and APD, Lyons et al. (1995), with over 3,000 adult male Vietnam era veteran twin pairs, estimated the heritability for juvenile traits of CD at 7%, whereas for adult APD it was 43%. In addition, the shared environmental effect was 31% for CD and 5% for APD. Interestingly, the CD genetic influences completely overlapped with the APD genetic influences, and the APD shared environmental influences completely overlapped with the CD shared environmental influences.

In summary, issues of comorbidity and genetic influence on covariation are closely intertwined. The behavior–genetic literature relating hyperactivity and antisocial tendencies has advanced understanding of both disorders, and entirely different understandings may emerge from consideration of other forms of comorbidity.

The genetics of experience

Multiple perspectives on the nature of the environment. A behavior–genetic approach to psychopathology includes multiple perspectives on the environment. One perspective—the distinction between shared and nonshared environments—was already treated above. This concept of the environment is an abstract one. However, there are no barriers other than lack of theoretical guidance and measurement difficulties to incorporating concrete measures of environments into behavior–genetic research designs. In fact, behavior–genetic models published in the mid-1970s allowed direct measures of the environment (e.g., Morton, 1974).

A second perspective has achieved the status of a truism: gene expression is always environmentally mediated. Clearly, behavior is the result of both genes and the environment—neither genes nor the environment can produce behavior alone.

A third broad perspective has certainly *not* become a truism among psychologists. Behavioral geneticists suggest that the role of experience in creating individual differences may differ depending on the genotype of the person undergoing the experience (Plomin & Bergeman, 1991) and that genetic relationships between family members may moderate the effects of their joint experience. However, enough evidence has accumulated to suggest the plausibility of these two ideas. Several recent studies of the "genetics of experience" suggests that genes are relevant to life stresses (Plomin, Lichtenstein, Pedersen, McClearn, & Nesselroade, 1990), divorce (McGue & Lykken, 1992; Trumbetta, Gottesman, & Turkheimer, 1995), and social support (Bergeman, Plomin, Pedersen, McClearn, & Nesselroade, 1990).

The genetics of parenting. Can parenting and childrearing practices, like other experiences, be viewed from a genetic perspective? If so, some plausible mechanism through which genes might exert their influence on parenting should be suggested. The most obvious such mechanism is parental personality (Chipuer, Plomin, Pedersen, McClearn, & Nesselroade, 1993). Studies from outside the behavioral genetics realm indicate that parental maturity, ego strength, and other indicators of healthy personality integration predict maternal responsiveness and other parenting behaviors (Brunnquell, Crichton, & Egeland, 1981; Feldman & Nash, 1986; Heinicke, Diskin, Ramsey–Klee, & Given, 1983). Evidence that differences in most facets of adult personality are moderately influenced by genetic differences is widespread. For instance, the heritable influences on the "Big Five" factors of adult personality are suggested by diverse data (Bouchard, 1994; Loehlin, 1992; Goldsmith, Losoya, Bradshaw, & Campos, 1994). If personality is heritable and childrearing practices are—at least in part—manifestations of parental personality, measures of childrearing might also be influenced by variation in the genes that impact personality. (However, recent evidence implies that personality as reflected in simple self-report measures cannot be the sole source of genetic mediation on childrearing; see Plomin, 1994.)

A brief literature review. A handful of studies from a limited group of researchers have examined the home environment as a phenotype for genetic analysis. The first studies focused

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on the child's perceptions of parental behavior, and two recent studies have centered on the perspective of the parent. In two twin studies, Rowe (1981, 1983) examined adolescent twins' ratings of their parenting and found that monozygotic (MZ) twins were significantly more alike than dizygotic (DZ) twins in how they perceived parental warmth, indicating genetic influence. In contrast, for perceptions of parental control, MZ and DZ twins were equally similar, suggesting no genetic influence. This finding was supported by a study of older twins in Sweden who were asked about their family environment a half century earlier (Plomin, Pedersen, McClearn, Nesselroade, & Bergeman, 1988). Although in this case the twins were adults and the reporting was retrospective, Plomin et al. (1988) found evidence for genetic influences on a "warmth" factor, as well as on other aspects of family environment.

Investigating the issue from another perspective, Daniels and Plomin (1985) reported that different perceptions of experiences of siblings within the family, including parental treatment, were primarily environmentally rather than genetically influenced. To test the hypothesis that genetic differences between siblings within the family could lead them to experience the environment differently, Daniels and Plomin constructed a questionnaire to tap children's perceptions of their environments while growing up, as contrasted to perceptions of what their siblings' environments were like. Genetic influences would be indicated by nonadoptive sibling difference scores smaller than adoptive sibling difference scores. The subjects (adolescents and young adults) responded retrospectively about the family in which they were reared. Adoptive sibling differences were not significantly greater than the nonadoptive sibling differences in their ratings of maternal and paternal affection or control.

The first behavior–genetic investigation of the family environment that targeted parents rather than children was a Swedish study that included twin pairs raised together as well as apart (Plomin, McClearn, Pedersen, Nesselroade, & Bergeman, 1989). The results demonstrated genetic influences on the adult ratings of their current family environment. The average MZ-reared-apart correlation was about .25, which is a direct estimate of heritability. However, the Control scale showed as much genetic influence as others on the Family Environment Scale, in contrast to the lack of heritable influence in previous studies of children's perception of parental control. Losoya, Callor, Rowe, and Goldsmith (1996), studying both twins and adoptees who were themselves parents of young children, provided evidence that differences in parents' reports of childrearing practices and attitudes as well as the emotional atmosphere of the home were associated with genetic differences and that childrearing variables are significantly related to the major factors of parental personality.

Reiss, Hetherington, and Plomin studied same-sex siblings (MZ and DZ twins, full sibs, full sibs in step families, half sibs in step families, and genetically unrelated sibs in step families) in the Nonshared Environment and Adolescent Development (NEAD) project. They found moderate genetic effects on both child and parent report of parenting that involved conflict and negativity, that is, interaction characterized by conflicts between parent and child, use of severe punishment and verbal violence, and the degree to which parents yielded to the child's coercive behavior (Reiss, 1995). In addition, they inferred genetic influences on parenting for directly observed parent–adolescent interactions. Ten-minute video segments were coded and heritabilities were computed for mother–child interactions for three domains: warmth/support (.18), conflict/negativity (.38), and monitoring/control (nonsignificant). The corresponding heritabilities for father–child interactions were .18, .24, and .24, respectively. In this study, genetic factors also contributed to measures of psychopathology (e.g., depressive symptoms and antisocial behavior).

Pike, McGuire, Hetherington, Reiss, and Plomin (1996) conducted genetic model fitting analyses to analyze the phenotypic correlation between mothers' conflict negativity and children's antisocial behavior ($r = .60$) and depressive symptoms ($r = .33$). For children's antisocial behavior and mother's conflict negativity, the common genetic, shared

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environmental, and nonshared environmental components accounted for, respectively, 67, 25, and 8% of the covariance. For each of the children's depressive symptoms and the mothers' conflict negativity, the genetic component of the covariance was 72% and the shared and nonshared environmental components each accounted for 14% of the variance. Thus, NEAD results revealed that measures of parenting reflected genetic differences among adolescents and that parenting measures and child outcome measures shared genetic variance.

Brown, Ye, Bronson, Dikkes, and Greenberg (1996) recently added a molecular dimension to the study of mammalian parenting by noting that absence of the *fosB* gene, which is normally expressed in the brain early in life, is associated with grossly defective care of newborn mouse pups. Mouse mothers who carry the defective gene fail to nurture their young, even after having multiple litters or sharing care with competent mothers. Although the *fosB* gene exists in humans, there is no evidence yet of its relevance to human parenting.

Limitations of the literature and relevance to developmental psychopathology research. The human literature on the "genetics of experience" is presently far too dependent on respondents' reports of their experience, rather than direct observational measures of, say, parenting behavior, which is assessed in only a few studies (Leve, Winebarger, Fagot, Reid, & Goldsmith, 1996). There are artifactual reasons that experience assessed by questionnaire might reflect characteristic modes of responding to paper-and-pencil measures. Such response modes could be heritable and common to other questionnaires, such as self-report of personality. Such a scenario could mimic a "genetic effect on parenting." Fortunately, the literature has begun to respond to this potential artifact (Reiss, 1995). However, simply observing parenting (or some other experience) on a single occasion is not a fully sufficient solution to the problem because the genetic issue concerns effects on the *pattern* of experience; a single *instance* of experience would likely be largely under the proximal influence of environmental contingencies.

Although the literature on the genetics of experience uses nonclinical samples, the relevance to understanding environmental sources of psychopathology should be clear. In particular, without the advantage of a genetically informative design, inferring that some feature of the environment affects the development of the disorder independently of genotype would be hazardous.

Gene–environment (GE) covariance and interaction

Upon first exposure to behavioral genetics, scientists often question how mutual or interactive processes are treated. The concepts of GE covariance and interaction provide a partial answer. These two concepts figure into almost every "textbook" presentation of the behavior–genetic paradigm. However in empirical research, both concepts are difficult to operationalize and often simply uninvestigated.

Multiple concepts of GE covariance. Individuals can be differentially exposed to environments that contribute to further development of heritable traits. This gene-conditioned, differential exposure is often viewed as reflecting three types of GE correlation: passive, reactive, and active (Goldsmith, 1988; Plomin, DeFries, & Loehlin, 1977). If a child's genotype is correlated with the environment provided by parents and siblings and such provision is associated with heritable traits of the parents or siblings, then "passive" GE correlation results. "Reactive" or evocative GE correlation refers to others' reacting to a particular child on the basis of some of the child's inherited characteristics. For example, children who are inattentive in school may be taught less material in a less effective manner. Thus, the environment becomes correlated with genotypic differences. Lastly, an active GE correlation refers to the situation in which a child seeks an environment conducive to further developing some of his or her heritable tendencies. Thus, aggressive youths may actively choose to become friends with peers who are also easily frustrated and prone to attribute hostile intent to benign actions of oth-

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ers, and these friendships would contribute to further development of the phenotype. Buss (1993) partitions the broad category of active GE correlation into two causal processes: selection and manipulation. Selection describes the situation in which an individual chooses some environments over others, and manipulation refers to an individual altering or influencing an environment after it has been selected. Obviously, many situations are ambiguous or combinations of all three types of correlation. Scarr and McCartney (1983) postulate a shift from passive to reactive and then to active GE correlation during childhood, as children begin to select more of their own experiences and environments.

Versions of the idea of GE correlation have captured the attention of many developmental psychologists, as illustrated by the frequent citation of Scarr and McCartney's (1983) article. However, some behavioral geneticists argue that active GE correlation cannot be meaningfully distinguished from "direct" genetic effects. That is, even direct genetic effects are always instances of genes correlated with environments although the environments might occasionally be entirely nonpsychological in nature. In the case of social environments, suppose that genotypic differences are correlated with, say, antisocial behavioral tendencies. As described above, these tendencies might be manifest, in part, by seeking peers who are experienced in antisocial behaviors themselves. The association with peers might be the most proximal influence on antisocial acts. This scenario would usually be characterized as active GE correlation, of the type in which the individual selects an environment on the basis of genetically influenced behavioral predispositions, that is, "birds of a feather flock together." But do not all genetic effects on behavior involve selection of relevant environments, in the sense that genes and their proximal and distal products must be expressed in a facilitative context, where the "context" may range from the physiological to the social? Perhaps so, but it may still be useful to retain the concept of active GE correlation for scenarios in which the environment is a measurable experience.

Although the idea is intuitively appealing, the importance of GE correlations for psychopathology largely remain to be demonstrated. GE correlations may be negative correlations, such that caregivers and others provide emotionally labile children with especially stable and predictable environments. On the other hand, GE correlations may be positive, such that emotionally labile children experience unsettled and unpredictable environments.

Empirical implications of GE covariance. GE correlations, or covariance, will obviously increase phenotypic variance but in many cases may not bias heritability estimates greatly. If GE covariance is present but not accounted for in the data analytic model, it will bias the estimates of genetic and environmental variance. Assuming that the direction of GE covariance is positive, it will inflate similarity of both fraternals and identicals, and thus the shared environmental variance will be overestimated. Given their greater genetic similarity, identical twins' similarity will likely be more affected by GE covariance than fraternal similarity, thus inflating the genetic variance estimate as well. Depending on the size of the GE covariance and its association with linear (vs. nonadditive) genetic effects, heritability estimates may not be much affected. Of course, if the direction of the GE covariance is negative, both the genetic and environmental variance components will be underestimated (Plomin, DeFries, & Loehlin, 1977).

The adoption study is unaffected by most GE correlations and is a convenient design for estimating their importance (Plomin, DeFries, & Loehlin, 1977).

The concept of GE interaction. GE interaction refers to the differential effects on the phenotype of an environmental factor for persons with different genotypes. In this sense, GE interaction is a statistical rather than a process-oriented interaction. For example, having poor sibling, peer, or adult models for the development of empathy might affect the development of aggressive tendencies primarily for those children with genes associated with, say, low frustration tolerance (assuming that lack of empathy and frustration tolerance are

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both precursors of aggressive behavior). The few attempts to isolate these interactions in human data have been largely unsuccessful (Plomin & Daniels, 1984).

Empirical investigation of GE interaction. In principle, analyzing GE interaction effects need not be complicated. Plomin, DeFries, and Loehlin (1977) introduced a 2×2 ANOVA method adapted from animal studies for human adoption studies. In brief, for a heritable trait, the parent's (or midparent's) phenotype may be taken as an estimate of the child's genotype. Of course, the parent's phenotype is an indirect and possibly poor estimate of the child's genotype, depending on the heritability and the association between the childhood and mature forms of the phenotype in question. The environmental measure can be, for example, a characteristic of the adoptive parents. In the simplest case, a 2×2 table is set up with one variable being genotype and the other environment, and with the dependent variable being some behavioral pattern of the child (e.g., psychopathology). Each main effect indicates an independent effect of genotype or environment, and the interaction of the two yields, of course, the GE interaction. Likewise, multiple regression with family data can be used to analyze continuous data, and logistic regression can be used when only the outcome is discontinuous. The analysis of GE interaction in designs such as those described above requires large sample sizes.

The strongest promise of identifying GE interactions is on the horizon when genes associated with traits of interest can be assayed directly, as with quantitative trait loci (QTLs, see below). A simple first approach, now used in studying maize and tomato genetics, would be to ask whether QTLs identified as affecting a trait in one environment also affect it in contrasting environments (Tanksley, 1993).

Genetics as a nosological tool

Yielding taxonomies based on genetic relationship rather than simply on observed covariation is another goal of genetic approaches. As described above, behavior–genetic analysis can help determine, for example, whether the comorbidity of childhood conduct disorder and attention deficit/hyperactivity disorder is due to common genetic effects—present evidence suggests that it is not. In the psychiatric nosology literature, this is referred to as trying to "carve nature at its joints." The analysis can involve more than two disorders. For example, childhood attention deficit disorder (with and without hyperactivity), conduct disorder, and adult antisocial personality disorder (ASP) constitute a complex package for genetic analysis oriented toward nosology. Such efforts are complicated by definitional overlap, or in the case of ASP, presence of early CD as a "gateway diagnosis" to the adult form.

A related issue is whether dimensional or categorical approaches are more appropriate for a particular form of psychopathology. One can ask whether the dimensional or the categorical approach yields higher heritability estimates in the same data set. Behavioral inhibition has been treated from this perspective. DiLalla, Kagan, and Reznick (1994), using data collected from over 100 same-sex 24-month twin pairs from the MacArthur Longitudinal Twin Study, examined the heritability of inhibition using both a dimensional and a categorical approach. Under the dimensional approach, they found that heritability for inhibited behavior for the entire sample was significant, yielding intraclass correlations of .82 for MZ twins, and .47 for DZ twins. Under the categorical approach, they identified probands whose scores on inhibition were in the top 20% of the distribution. To test the etiology of these extreme scores, they used DF multiple regression analysis to predict the Cotwin's inhibition score from the proband's score and the degree of genetic relationship (see DeFries & Fulker, 1988, for an explanation of this methodology). In this sample, the heritability estimate obtained for the extreme group was not significantly different from the estimate obtained from the total sample with 64 probands, although it was higher. In addition, when different thresholds were used to define more extreme groups, heritability estimates increased. Thus, this study tentatively supports the hypothesis that extreme inhibi-

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tion is more influenced by heredity than mid-range inhibition. It also encourages similar efforts to examine oppositional behavior, impulsivity, internalizing tendencies, and other behavioral dimensions that are components of categorical diagnoses.

Genetics of "developmental phenotypes" associated with adult disorders

As Cicchetti (1993) explains, the field of developmental psychopathology is not confined to disorders of childhood. Indeed, the developmental (time-related) features of disorders with typical onset during any life phase can be subjected to genetic analysis. Thus, we can analyze the genetics of the age of onset and of the clinical course of, say, schizophrenia, as Gottesman and Shields (1972) showed. Questions about whether the genetic liability to the disorder itself overlaps with the liability to age of onset can then be addressed. These questions can be framed for polygenic or single-gene effects.

Initial molecular genetic approaches: Linkage and association studies

Identifying individual genes that contribute to the etiology of behavioral disorders is currently feasible though unrealized for any complexly inherited childhood disorder. This task of identifying genes will inevitably follow from the results of the Human Genome Project. In this paper, we can only outline the methods that some researchers already use in the field and others will soon need to understand. Our premise is that the disorders of interest are not single gene disorders but are of "complex inheritance," a term that can encompass single genes of discernible effect operating in a background of both polygenic and environmental effects. The idea of complex inheritance also encompasses some of the complications mentioned earlier (e.g., genetic heterogeneity, phenocopies).

The methods that are applicable to complex inheritance are varieties of linkage analysis and association studies. These methods are reviewed at length and in technical detail by Ott (1991) and in many other texts (e.g., McGuffin, Owen, O'Donovan, Thapar, & Gottesman, 1994). For humans, linkage methods include classic pedigree analysis in which statistical transmission models are tested in large families with many affected members.

A class of nonparametric analyses called "allele-sharing methods" (Lander & Schork, 1994) involve studying affected relatives to determine whether a gene (or a region of genetic material) is shared, through inheritance from a common ancestor, by these affected relatives more frequently than expected on a random basis. The most common implementation of allele-sharing methodology is the analysis of affected sib pairs. For instance, this technique was used in the highly publicized studies implicating a region of the X chromosome in the etiology of male homosexuality (Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993). Positive evidence for the importance of a single gene can accrue without any indication that the gene is inherited in a dominant or recessive manner.

Allelic association studies compare the frequency of a marker (e.g., a blood group) in two samples (e.g., an affected versus a control group). A classic association is between the blood group O and duodenal ulcer. Unless the marker locus and the actual gene responsible for the disorder are very tightly linked, results from properly conducted association studies will be negative. Of course, association studies can be used to test candidate genes that might themselves be responsible for the disorder. Recently and of most relevance to psychopathology, most association studies have been conducted with genetic probes that systematically cover large expanses of the genome, thus allowing a search for association with so-called QTLs. QTLs are genetic regions responsible for small but discernible quantitative effects on a polygenically based phenotype. The smallest QTL effect that can be detected by association with a marker depends on distance from marker to QTL, the size of population, and the heritability of the trait or disorder. In plant genetics, QTLs accounting for as little as 0.3% of the phenotypic variance have been reported, as reviewed by Tanksley (1993); for humans, the current lower limit might be closer to 3%.

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At first blush, it would seem straightforward to compare extreme groups (e.g., highly inhibited versus uninhibited children) for different frequencies of a candidate gene or QTL. However, high levels of behavioral inhibition in one subset of individuals might have different roots than similarly high levels in another subset. This trait heterogeneity problem haunts current attempts to link behavior with specific genes. There are other practical difficulties in this genre of research. For instance, individuals at the extreme of the distribution might possess several alleles (at different loci) promoting higher trait values. The effect of any one allele may be more difficult to discern against this "high value" genetic background than in more typical genetic backgrounds.

In conceptualizing genes that have only small effects on the phenotype, it is important to realize that they might be related to major genes of large effect. That is, if a major gene leading to qualitative dysfunction is identified, other alleles at the same locus as the major gene could affect more subtle quantitative variation. The allele that leads to qualitative dysfunction could code for an inactive protein whereas a different allelic variant of the same gene might lead to an active but physiologically nonoptimal protein.

The best current example of an allelic association with a psychopathology-relevant trait in humans is a report that a polymorphism in a promoter of the serotonin transporter gene on chromosome 17q accounts for 3–4% of the variance in self-reported anxiety proneness. This finding held in two samples totaling 505 individuals, and the allele in question also differentiated affected from unaffected siblings (Lesch et al., 1996). Although enthusiasm for initial reports such as this one must be tempered for the reasons we have already discussed, some credence must be accorded this finding because of its consonance with known mechanisms of action of antianxiety drugs. Serotonin is, of course, involved in neurotransmission in regions of the limbic system and cortex associated with anxious behavior, and some antidepressant and antianxiety drugs inhibit uptake of serotonin. The serotonin transporter is a protein that helps "fine-tune" this neurotransmission. The allele of the serotonin transporter promoter that leads to decreased transporter activity—at least in lymphoblast cell lines—occurred at a high frequency, 43%, in the samples studied (Lesch et al., 1996). Persons with this allele would be expected to show increased serotonergic transmission, and they report higher Neuroticism scores (but are not different on the other factors of the Big Five personality traits). Lesch et al. (1996) caution that their results, from a normal sample, may not generalize as a cause of clinically significant levels of anxiety in patients.

The field can expect a series of such reports over the next few years. One challenge for behavioral scientists is to take a role in such studies so that the assessment of the phenotype—the pattern of psychopathology—incorporates developmental concerns and any available endophenotypic indicators. In other words, the behavioral side of the investigation should be at least as sophisticated as the genetic side.

Non-Mendelizing genetic influences

Even when combined with linkage and association studies, traditional behavior–genetic analysis of genetic variability using family, twin, and adoption studies is not the whole story of genes and behavior. An obvious and important aspect of genetic influence that is not encompassed by these designs comes from nonpolymorphic genes (genes that have only one allelic form in the population). Nonpolymorphic genes presumably specify the fundamental blueprint for the species. They do not contribute to individual variability, but they are transmitted via Mendelian principles. However, there are genetic sources of variability that are not transmitted via Mendelian principles and thus not captured by behavior–genetic designs. One list of such mechanisms includes mitochondrial inheritance, gonadal mosaicism, imprinting (wherein a gene's expression is modulated based on whether it is transmitted from the father or the mother), and progressive amplication (Morton, 1992, 1993).

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The mechanism of progressive amplication has received tremendous attention over the past 5 years. Fragile X disorder, a leading cause of mental retardation, exemplifies the pattern of progressive amplication through pedigrees. A CGG trinucleotide in an untranslated segment of the FMR-1 gene on the X chromosome is normally repeated less than 50 times. When the gene mutates, these unstable CGG repeats are amplified, resulting in hundreds or even thousands of copies. The premutations are expanded to full mutations (termed "triplet repeats") only when transmitted by the mother. Fathers with the premutation have normal daughters who may be at risk to pass on the disorder.

The implications of triplet repeat mutations for psychopathology may be substantial. Huntington's disease follows the same pattern of inheritance (Huntington's Disease Collaborative Research Group, 1993). The extent of the amplified region (a CAG repeat) is associated with age of onset, with earlier onset cases having longer repeated regions. Early onset cases are more likely to be those with the "at-risk" allele transmitted from father, an apparent example of genomic imprinting. These associations of molecular processes with age of onset illustrate the need to incorporate developmental aspects of psychopathology into behavioral genetics.

As mentioned above, genomic imprinting confers functional differences on genes derived from paternal versus maternal genomes during development. The phenomenon of genomic imprinting has been well established in mice, and is hypothesized to be important in mammalian (and primate) forebrain evolution (Keverne, Martel, & Nevison, 1996). Experimental evidence from mice shows that maternally derived genes are expressed preferentially in cortex, striatum, and hippocampus, and paternally derived genes are expressed preferentially in certain hypothalamic regions (Keverne, Fundele, Narasimha, Barton, & Surani, 1996). Given the different roles of these regions in behavior, such differential expression could obviously affect the behavioral resemblance of relatives if the genes involved are polymorphic. The question of whether imprinting is actually a significant and widespread factor in normal human development awaits further study, but studies of human mutations suggest that imprinted genes do affect brain development and behavior in some syndromes (Christian et al., 1995; Nicholls, 1993).

Recent empirical results and theorizing suggest the plausibility of variability in degree of homozygosity as a source of genetic variability for psychopathology. A key construct in this line of theorizing and research is "developmental instability" (e.g., see Yeo & Gangestad, 1993, for illustrations with human data). Indicators of developmental instability include some types of minor physical anomalies and fluctuating asymmetries (deviations from symmetry in bilateral physical characteristics). Among others, Markow and Gottesman (1989, 1993) and Yeo and Gangestad (1993) have documented associations between developmental instability—likely during the prenatal period—and psychopathology, including childhood disorders. These authors explain that genetic heterozygosity leads to multiple forms of proteins, and these multiple forms may confer upon the organism better ability to adapt to changing metabolic demands resulting from changing environmental demands. Conversely, genetic homozygosity would reduce the organism's metabolic buffering and thus render it susceptible to insult from environmental perturbations.

The degree of genetic homozygosity is, of course, a function of the state of paired alleles, manifest only when the zygote is formed. Thus, homozygosity is not transmitted from parent to offspring and is not detectable as a genetic effect in traditional twin, family, or adoption studies. Effects of genetic homozygosity would be misidentified as environmental variance in parent–offspring analyses and as nonadditive genetic variance in twin studies.

These brief considerations of non-Mendelizing genetic effects caution us not to become paradigm bound—even to useful paradigms such as the twin design—if we wish to discern the entire panorama of genetic influences on behavior.

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Pathways Toward Progress

Behavior–genetic research on developmental aspects of psychopathology is hardly at an impasse. Indeed, even the initial elements of the behavior–genetic research paradigm, up to and including twin studies, have not yet been fully implemented. Particularly lacking are traditional quantitative genetic studies of internalizing disorders during childhood, twin studies of clinical samples as opposed to "clinically relevant" behavior in normal samples of children, and of behavioral assessment by methods other than self-report and parental report. Some of these gaps in the literature will only be filled as nosology of childhood disorders improves.

Perhaps the most general recipe for progress in the field is interdisciplinary research. It should be clear that behavior–genetic methodology does not *fully* elucidate psychopathology. As in most areas of science, fuller understanding requires the joint perspectives of several methodologies, including epidemiology, neuroscience, and various approaches to investigating the effects of experience.

We have reviewed several specific routes to progress in understanding the genetics of psychopathology from a developmental perspective. Classic twin and family studies need to become highly multivariate, incorporating both dimensional (e.g., temperament trait) and categorical (e.g., diagnosis) variables, environmental measures, direct behavioral assessments, and multiple, theoretically relevant occasions of study. Such studies would ideally be conceptualized in terms of genetic and environmental components of liability and incorporate investigation of plasticity using concepts such as the reaction surface and modern systems theory. Such studies should feedback to our current diagnostic systems to elucidate the comorbidity issue and show us where dimensional concepts of psychopathology might replace categorical ones.

Approaches to studying the environment, which behavior–genetic studies have already shown to be a major source of variation in all complexly inherited disorders, will benefit from incorporating quasicontrol on genetic similarity in environmentally oriented research programs. On the social side of the environment, measures of specific interactional processes need to be refined and incorporated into studies. And environmental assessment needs to extend into the realm of biological measures as well.

The Human Genome Project seems likely to produce a "bottom-up" research agenda, wherein numerous alleles are identified that increase the risk of particular psychopathologies. We can project that some of the findings will prove ephemeral as sampling or diagnostic flaws in the studies become apparent. Overly broad conclusions will be retracted as genetic heterogeneity and environmentally caused variants arise. Some of these findings of single gene effects will occur in well-worked domains such as schizophrenia, where they can rather quickly be tied to neurologic and pharmacologic research. In other cases, these molecular genetic findings will await explanation of developmental process until neuroscience approaches yield results. As we emphasized above, geneticists will also need to be cognizant of the various non-Mendelizing genetic effects, which, in the aggregate and if significant, are likely to distort genetic and environmental parameter estimates from classic designs but to reveal unsuspected sources of genetic influence.

Regardless of the technical progress possible in elucidating genetic influences on psychopathology, there is a sociopolitical context that affects progress. Almost any treatment of genetics and behavior can be (mis)interpreted —especially out of context—as an argument for reductionism, for determinism, and against plasticity. We wish to explicitly offer qualifications to counteract such interpretations. As Rose (1995) reminds us, "We inherit dispositions, not destinies. Life outcomes are consequences of lifetimes of behavior choices." Unfortunately, behavioral geneticists sometimes speak in a "short-hand" manner and refer to, say "genes for antisocial behavior" or "genes for depression." More properly, rather than speaking of genes for psychopathology, we realize that there may be *partially* genetically influenced *predispositions* for basic be-

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havioral tendencies, that under certain experiential contexts, make the *probability* of developing psychopathology higher for individuals who possess greater rather than lesser degrees of such behavioral tendencies. Researchers should keep in mind this awkward set of qualifications, especially when discussion assumes policy implications. In dissecting our awkward statement, a key question is how common the relevant experiential context is. If it is part of the everyday experience of most individuals, then the probability of developing a disorder given predisposing genes can be high, as in Huntington's disease. In other disorders, the relevant experiential context is rarer and the probability of developing a disorder will be much lower, and such disorders can be recognized by low identical twin concordance rates.

We also caution against tendencies to equate genetics or biology with "constraint" and experience with "possibility." At best, these equations are oversimplifications. However, in science as well as public discourse, such an equation is commonplace. It should also be clear that contemporary researchers recognize that *different* explanatory factors are not always *competing* explanatory factors. Genes as distal influences on psychopathology do not compete with situations as proximal factors in a developmental sense although the effects of genes and situations can be quantified in the common metric of phenotypic variance, as explained near the outset of this paper. The effect sizes in the prediction of childhood psychopathology are typically modest, and thus there is ample room for multiple predictors from different domains.

Developmentalists have long been sensitive to the roles of distal (e.g., prenatal) and proximal (e.g., trauma/stress) contributors as partial causes of the psychopathologies. By more fully integrating the concepts and tools of behavioral genetics, the field will be better prepared to maintain viable research programs, easily integrated into the neurosciences, at the dawn of the 21st century.

References

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4–18 and 1991 Profile.* Burlington: University of Vermont, Department of Psychiatry.

Achenbach, T. M., & Edelbrock, C. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile.* Burlington: University of Vermont, Department of Psychiatry.

Achenbach, T. M., & Edelbrock, C. (1986). *Manual for the teacher's report form and teacher version of the Child Behavior Profile.* Burlington: University of Vermont, Department of Psychiatry.

Achenbach, T. M., Edelbrock, C., & Howell, C. T. (1987). Empirically based assessment of the behavioral/emotional problems of 2- and 3-year-old children. *Journal of Abnormal Child Psychology, 15,* 629–650.

Achenbach, T. M., Howell, C. T., Quay, H. C., & Conners, C. K. (1991). National survey of problems and competencies among four- to sixteen-year-olds: Parents' reports for normative and clinical samples. *Monographs of the Society for Research in Child Development, 56* (3, Serial No. 225).

Bergem, A. (1993). Estimation of concordance rate in demented twin pairs as a function of age of onset and age of sample. *Psychiatric Genetics, 3,* 139 (Abstract).

Bergem, A. L. M. (1994). Heredity in dementia of the Alzheimer type. *Clinical Genetics, 46,* 144–149.

Bergeman, C. S., Plomin, R., Pedersen, N. L., McClearn, G. E., & Nesselroade, J. R. (1990). Genetic and environmental influences on social support: The Swedish Adoption/Twin Study of Aging (SATSA). *Journal of Gerontology, 45,* 101–106.

Bodmer, W. F., & Cavalli–Sforza, L. L. (1976). *Genetics, evolution, and man.* San Francisco: Freeman & Company.

Bouchard, T. J., Jr. (1994). Genes, environment, and personality. *Science, 264,* 1700–1701.

Brown, J. R., Ye, H., Bronson, R. T., Dikkes, P., & Greenberg, M. E. (1996). A defect in nurturing in mice lacking the immediate early gene *fosB. Cell, 86,* 297–309.

Brunnquell, D., Crichton, L., & Egeland, B. (1981). Maternal personality and attitude in disturbances of childrearing. *American Journal of Orthopsychiatry, 51,* 680–691.

Buss, D. M. (1993). Strategic individual differences: The evolutionary psychology of selection, evocation, and manipulation. In T. J. Bouchard, Jr. & P. Propping (Eds.), *Twins as a tool of behavior genetics* (pp. 121–138). Chichester, UK: Wiley.

Carey, G. (1988). Inference about genetic correlations. *Behavior Genetics, 18,* 329–338.

Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry, 32,* 1063–1080.

Capecchi, M. R. (1994). Targeted gene replacement. *Scientific American, 270,* 52–59.

Chipuer, H. M., Plomin, R., Pedersen, N. L., McClearn,

https://doi.org/10.1017/S0954579497002095 Published online by Cambridge University Press

G. E., & Nesselroade, J. R. (1993). Genetic influence on family environment: The role of personality. *Developmental Psychology, 29,* 110–118.

Christian, S. L., Robinson, W. P., Huang, B., et al. (1995). Molecular characterisation of two proximal deletion breakpoint regions in both Prader Willi and Angelman syndrome patients. *American Journal of Human Genetics, 46,* 857–873.

Cicchetti, D. (1993). Developmental psychopathology: Reactions, reflections, projections. *Developmental Review, 13,* 471–502.

Cloninger, C. R., & Gottesman, I. I. (1987). Genetic and environmental factors in antisocial behavior disorders. In S. A. Mednick, T. E. Moffitt, & S. A. Stack (Eds.), *The causes of crime: New biological approaches* (pp. 92–109). Cambridge: Cambridge University Press.

Daniels, D., & Plomin, R. (1985). Differential experience of siblings in the same family. *Developmental Psychology, 21,* 747–760.

DeFries, J. C., & Fulker, D. W. (1988). Multiple regression analysis of twin data: Etiology of deviant scores versus individual differences. *Acta Geneticae Medicae et Gemellologiae, 37,* 205–216.

DiLalla, L. F., & Gottesman, I. I. (1989). Heterogeneity of causes for delinquency and criminality: Lifespan perspectives. *Development and Psychopathology, 1,* 339–349.

DiLalla, L. F., Kagan, J., & Reznick, J. S. (1994). Genetic etiology of behavioral inhibition among 2-year-old children. *Infant Behavior and Development, 17,* 405–412.

Dobzhansky, T. (1955). A review of some fundamental concepts and problems of population genetics. *Cold Spring Harbor Symposium on Quantitative Biology, 20,* 1–15.

Edelbrock, C., Rende, R., Plomin, R., & Thompson, L. A. (1995). A twin study of competence and problem behavior in childhood and early adolescence. *Journal of Child Psychology and Psychiatry, 36,* 775–785.

Falconer, D. S. (1965). The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Annals of Human Genetics, 29,* 51–76.

Falconer, D. S. (1967). The inheritance of liability to diseases with variable age of onset with particular reference to diabetes mellitus. *Annals of Human Genetics, 31,* 1–20.

Falconer, D. S. (1989). *Introduction to quantitative genetics* (3rd ed.). New York: Longman.

Faraone, S., & Biederman, J. (1994). Genetics of attention–deficit hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America, 3,* 285–302.

Faraone, S. V., Biederman, J., Keenan, K., & Tsuang, M. T. (1991). Separation of DSM-III attention deficit disorder and conduct disorder: Evidence from a family–genetic study of American child psychiatric patients. *Psychological Medicine, 21,* 109–121.

Feldman, S. S., & Nash, S. C. (1986). Antecedents of early parenting. In A. Fogel & G. F. Melson (Eds.), *Origins of nurturance: Developmental, biological, and cultural perspectives on caregiving* (pp. 209–232). Hillsdale, NJ: Erlbaum.

Ghodsian–Carpey, J., & Baker, L. A. (1987). Genetic and environmental influences on aggression in 4- to 7-year-old twins. *Aggressive Behavior, 13,* 173–186.

Goldsmith, H. H. (1988). Human developmental behavioral genetics: Mapping the effects of genes and environments. *Annals of Child Development, 5,* 187–227.

Goldsmith, H. H., & Gottesman, I. I. (1996). Heritable variability and variable heritability in developmental psychopathology. In M. F. Lenzenweger & J. Haugaard (Eds.), *Frontiers in psychopathology.* New York: Oxford University Press.

Goldsmith, H. H., Losoya, S. H., Bradshaw, D. L., & Campos, J. J. (1994). Genetics of personality: A twin study of the five factor model and parental–offspring analyses. In C. Halverson, R. Martin, & G. Kohnstamm (Eds.), *The developing structure of temperament and personality from infancy to adulthood* (pp. 241–265). Hillsdale, NJ: Erlbaum.

Goodman, R., & Stevenson, J. (1989). A twin study of hyperactivity—II. The aetiological role of genes, family relationships and perinatal adversity. *Journal of Child Psychology and Psychiatry, 30,* 691–709.

Gottesman, I. I. (1963). Heritability of personality: A demonstration. *Psychological Monographs, 77,* 1–21.

Gottesman, I. I. (1974). Developmental genetics and ontogenetic psychology: Overdue détente and propositions from a matchmaker. In A. D. Pick (Ed.), *Minnesota symposia on child psychology* (Vol. 8, pp. 55–80). Minneapolis: University of Minnesota Press.

Gottesman, I. I., & Goldsmith, H. H. (1994). Developmental psychopathology of antisocial behavior: Inserting genes into its ontogenesis and epigenesis. In C. Nelson (Ed.), *Minnesota symposium on child development:* Vol. 27. *Threats to optimal development: Integrating biological, social, and psychological risk factors* (pp. 69–104). Hillsdale, NJ: Erlbaum.

Gottesman, I. I., & Shields, J. (1967). A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences, Washington, 58,* 199–205.

Gottesman, I. I., & Shields, J. (1972). *Schizophrenia and genetics: A twin study vantage point.* New York: Academic Press.

Hamer, D. H., Hu, S., Magnuson, V. L., Hu, N., & Pattatucci, A. M. L. (1993). A linkage between DNA markers on the X chromosome and male sexual orientation. *Science, 261,* 321–327.

Heinicke, C., Diskin, S. D., Ramsey–Klee, D. M., & Given, K. (1983). Pre-birth parent characteristics and family development in the first year of life. *Child Development, 54,* 194–208.

Hoffman, L. W. (1991). The influence of the family environment on personality: Accounting for sibling differences. *Psychological Bulletin, 110,* 187–203.

Huntington's Disease Collaborative Research Group. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's Disease chromosomes. *Cell, 72,* 971–983.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). Major depression and generalized anxiety disorder. *Archives of General Psychiatry, 49,* 716–722.

Keverne, E. B., Fundele, R., Narasimha, M., Barton, S. C., & Surani, M. A. (1996). Genomic imprinting and the differential roles of parental genomes in brain development. *Developmental Brain Research, 92,* 91–100.

Keverne, E. B., Martel, F. L., & Nevison, C. M. (1996). Primate brain evolution: Genetic and functional considerations. *Proceedings of the Royal Society London B, 262,* 689–696.

LaBuda, M. C., Gottesman, I. I., & Pauls, D. L. (1993). Usefulness of twin studies for exploring the etiology of childhood and adolescent psychiatric disorders. *American Journal of Medical Genetics, 48,* 47–59.

Lander, E. S., & Schork, N. J. (1994). Genetic dissection of complex traits. *Science, 265,* 2037–2048.

https://doi.org/10.1017/S0954579497002095 Published online by Cambridge University Press

Leve, L. D., Winebarger, A. A., Fagot, B. I., Reid, J. B., & Goldsmith, H. H. (1996). *Environmental and genetic variance in observed and reported maladaptive behavior.* Manuscript submitted for publication.

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Muller, C. R., Hamer, D. H., & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527–1531.

Lilienfeld, S. O., & Waldman, I. D. (1990). The relation between childhood attention-deficit hyperactivity disorder and adult antisocial behavior reexamined: The problem of heterogeneity. *Clinical Psychology, 10,* 699–725.

Loehlin, J. C. (1992). *Genes and environment in personality development.* Newbury Park, CA: Sage.

Losoya, S. H., Callor, S., Rowe, D. C., & Goldsmith, H. H. (1996). *The origins of family similarity in parenting: A study of twins and adoptive siblings.* Manuscript submitted for publication.

Lyons, M. J., True, W. R., Eisen, S. A., Goldberg, J., Meyer, J. M., Faraone, S. V., Eaves, L. J., & Tsuang, M. T. (1995). Differential heritability of adult and juvenile antisocial traits. *Archives of General Psychiatry, 52,* 906–915.

Markow, T. A., & Gottesman, I. I. (1989). Dematoglyphic fluctuating asymmetry in psychotic twins. *Psychiatric Research, 29,* 37–43.

Markow, T. A., & Gottesman, I. I. (1993). Behavioral phenodeviance: A Lerneresque conjecture. *Genetica, 89,* 297–305.

McArdle, J. J., & Goldsmith, H. H. (1990). Alternative common factor models for multivariate biometric analyses. *Behavior Genetics, 20,* 569–608.

McGue, M., & Lykken, D. T. (1992). Genetic influence on risk of divorce. *Psychological Science, 3,* 368–373.

McGuffin, P., Owen, M. J., O'Donovan, M. C., Thapar, A., & Gottesman, I. I. (1994). *Seminars in psychiatric genetics.* London: Royal College of Psychiatrists.

Moldin, S. O. (1994). Indicators of liability to schizophrenia: Perspectives from genetic epidemiology. *Schizophrenia Bulletin, 20,* 169–184.

Morton, N. E. (1974). Analysis of family resemblance: I. Introduction. *American Journal of Human Genetics, 26,* 318–330.

Morton, N. E. (1992). The future of genetic epidemiology. *Annals of Medicine, 24,* 557–562.

Morton, N. E. (1993). Genetic epidemiology. *Annual Review of Genetics, 27,* 523–538.

Morton, J., & Frith, U. (1995). Causal modeling: A structural approach to developmental psychopathology. In D. Cicchetti & J. J. Cohen (Eds.), *Developmental Psychopathology* (Vol. 1). New York: Wiley.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families.* Dordrecht, The Netherlands: Kluwer.

Nicholls, R. D. (1993). Genomic imprinting and candidate syndromes. *Current Opinion in Genetics and Development, 3,* 445–456.

Ott, J. (1991). *Analysis of human genetic linkage.* Baltimore, MD: Johns Hopkins University Press.

Pike, A., McGuire, S., Hetherington, E. M., Reiss, D., & Plomin, R. (1996). Family environment and adolescent depressive symptoms and antisocial behavior: A multivariate genetic analysis. *Developmental Psychology, 32,* 590–603.

Plomin, R. (1994). *Genetics and experience: The interplay between nature and nurture.* Thousand Oaks, CA: Sage.

Plomin, R., & Bergeman, C. S. (1991). The nature of nurture: Genetic influence on "environmental" measures. *Behavioral and Brain Sciences, 14,* 373–427.

Plomin, R., & Daniels, D. (1984). The interaction between temperament and environment: Methodological considerations. *Merrill–Palmer Quarterly, 30,* 149–162.

Plomin, R., & Daniels, D. (1987). Why are children in the same family so different from each other? *Behavioral and Brain Sciences, 10,* 1–16.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype–environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin, 84,* 309–322.

Plomin, R., Lichtenstein, P., Pedersen, N. L., McClearn, G. E., & Nesselroade, J. R. (1990). Genetic influences on life events during the last half of the life span. *Psychology and Aging, 5,* 25–30.

Plomin, R., McClearn, G. E., Pedersen, N. L., Nesselroade, J. R., & Bergeman, C. S. (1989). Genetic influences on adults' ratings of their current family environment. *Journal of Marriage and the Family, 51,* 791–803.

Plomin, R., Pedersen, N. L., McClearn, G. E., Nesselroade, J. R., & Bergeman, C. S. (1988). Genetic influence on childhood family environment perceived retrospectively from the last half of the life span. *Developmental Psychology, 24,* 738–745.

Pogue–Geile, M. F. (1991). The development of liability to schizophrenia: Early and late developmental models. In E. F. Walker (Ed.), *Schizophrenia: A life-course developmental perspective.* New York: Academic Press.

Raiha, I., Koskenvuo, M., Kaprio, J., Rajala, T., & Sourande, L. (1994, April). *Occurrence of dementia in the Nationwide Finnish Twin Cohort.* Presented at the International Symposium on Genetic Epidemiology of Twins and Twinning, Amsterdam.

Reiss, D. (1995). Genetic influence on family systems: Implications for development. *Journal of Marriage and the Family, 57,* 1–18.

Rose, R. J. (1995). Genes and human behavior. *Annual Review of Psychology, 46,* 625–654.

Rowe, D. C. (1981). Environmental and genetic influences on dimensions of perceived parenting: A twin study. *Developmental Psychology, 17,* 203–208.

Rowe, D. C. (1983). Biometrical genetic models of self-reported delinquent behavior: A twin study. *Behavior Genetics, 13,* 473–489.

Rutter, M. (1995). Relationships between mental disorders in childhood and adulthood. *Acta Psychiatrica Scandinavica, 91,* 73–85.

Rutter, M., MacDonald, H., LeCouteur, A., Harrington, R., Bolton, P., & Bailey, A. (1990). Genetic factors in child psychiatric disorders—II. Empirical findings. *Journal of Child Psychology and Psychiatry, 31,* 39–83.

Salthe, S. N. (1985). *Evolving hierarchical systems—Their structure and representation.* New York: Columbia University Press.

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype–environment effects. *Child Development, 54,* 424–435.

Schmitz, S., Cherny, S. S., Fulker, D. W., & Mrazek, D. A. (1994). Genetic and environmental influences on

https://doi.org/10.1017/S0954579497002095 Published online by Cambridge University Press

early childhood behavior. *Behavior Genetics, 24,* 25–34.

Silberg, J. L., Erickson, M. T., Meyer, J. M., Eaves, L. J., Rutter, M. L., & Hewitt, J. K. (1994). The application of structural equation modeling to maternal ratings of twins' behavioral and emotional problems. *Journal of Consulting and Clinical Psychology, 62,* 510–521.

Sing, C. F., Zerba, K. E., & Reilly, S. L. (1994). Traversing the biological complexity in the hierarchy between genome and CAD endpoints in the population at large. *Clinical Genetics, 46,* 6–14.

Slutske, W. S., Heath, A. C., Dinwiddie, S. H., Madden, P. A. F., Bucholz, K. K., Dunne, M. P., Statham, D. J., & Martin, N. G. (in press). Genetic and environmental influences in the etiology of conduct disorder: A study of 2682 adult twin pairs. *Journal of Abnormal Psychology.*

Tanksley, S. D. (1993). Mapping polygenes. *Annual Review of Genetics, 27,* 205–233.

Trumbetta, S. L., Gottesman, I. I., & Turkheimer, E. N. (1995). There are no genes for divorce; there is genetic variance in stable, heterosexual pair-bonding. *Behavior Genetics, 25,* 291 [abstract].

Turkheimer, E., Goldsmith, H. H., & Gottesman, I. I. (1995). Commentary on G. Gottlieb's, "Some conceptual deficiencies in 'developmental' behavior genetics." *Human Development, 38,* 142–153.

Turkheimer, E., & Gottesman, I. I. (1991). Individual differences and the canalization of human behavior. *Developmental Psychology, 27,* 18–22.

Van Den Oord, E. J. C. G., Verhulst, F. C., Boomsma, D. I., & Orlebeke, J. F. (1993). A genetic study of maternal and paternal ratings of problem behaviors in 3-year-old twins. In E. Van Den Oord (Ed.), *A genetic study of problem behaviors in children* (pp. 69–85). Doctoral dissertation, Erasmus Universiteit Rotterdam.

Yeo, R. A., & Gangestad, S. W. (1993). Developmental origins of variation in human hand preference. *Genetica, 89,* 281–296.

https://doi.org/10.1017/S0954579497002095 Published online by Cambridge University Press