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The New Look of Behavioral Genetics in Developmental Psychopathology: Gene–Environment Interplay in Antisocial Behaviors

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This article reviews behavioral–genetic research to show how it can help address questions of causation in developmental psychopathology. The article focuses on studies of antisocial behavior, because these have been leading the way in investigating environmental as well as genetic influences on psychopathology. First, the article illustrates how behavioral–genetic methods are being newly applied to detect the best candidates for genuine environmental causes among the many risk factors for antisocial behavior. Second, the article examines findings of interaction between genes and environments (G × E) associated with antisocial behavior, outlining steps for testing hypotheses of measured G × E. Third, the article envisages future work on gene–environment interplay, arguing that it is an interesting and profitable way forward for psychopathology research.

Despite assiduous efforts to eliminate it, antisocial behavior is still a problem. Approximately 20% of people in the developed world experience victimization by perpetrators of violent and nonviolent illegal behavior each year (U.S. Bureau of Justice Statistics, 2002). The *World Report on Violence and Health* (World Health Organization, 2002) tallies the staggering burden of mortality, disease, disability, and compromised well-being brought about by perpetrators of family violence and other violent crimes. Behavioral science needs to achieve a more complete understanding of the causes of antisocial behavior to provide an evidence base for effectively controlling and preventing it. A new wave of intervention research in the past decade has demonstrated clear success for a number of programs designed to prevent antisocial behavior (Heinrich, Brown, & Aber, 1999; Sherman et al., 1999; University of Maryland, Department of Criminology, 2003; Weissberg, Kumpfer, & Seligman, 2003). Nevertheless, the reduction in antisocial behavior brought about by even the best prevention programs is, on average, modest (Dodge, 2003; Heinrich et al., 1999; Olds et al., 1998; Wandersman & Florin, 2003; Wasserman & Miller, 1998; Wilson, Gottfredson, & Najaka, 2001). The best designed interventions reduce serious juvenile offenders' recidivism by only about 12% (Lipsey & Wilson, 1998). This modest success of theory-driven, well-designed, and amply funded interventions sends a message that the causes of antisocial behavior are not yet well enough understood to prevent it.

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Why Look for Causes of Antisocial Behavior in the Family?

Simultaneous with the new wave of research evaluating interventions is a wave of research pointing to the concentration of antisocial behavior in families. In the 1970s, the astounding discovery that fewer than 10% of individuals perpetrate more than 50% of crimes (Wolfgang, Figlio, & Sellin, 1972) prompted researchers to investigate individual career criminals (Blumstein & Cohen, 1987) and examine the childhood origins of such persistent re-offenders (Moffitt, 1993). This research constructed the evidence base supporting the new wave of preventive intervention trials (Yoshikawa, 1994). Recently, journalists drew public attention to families who across several generations seem to contain far more than their share of criminal family members (Butterfield, 1996, 2002). This familial concentration of crime has been confirmed as a characteristic of the general population (Farrington, Barnes, & Lambert, 1996; Farrington, Jolliffe, Loeber, Stouthamer-Loeber, & Kalb, 2001; Rowe & Farrington, 1997). In general, fewer than 10% of the families in any community account for more than 50% of that community's criminal offenses. The family concentration of antisocial behavior could be explained by a genetic influence on antisocial behavior, but it could just as easily be explained by nongenetic social transmission of antisocial behavior within families. Again, causation is not well understood. Studies that cannot disentangle genetic and environmental influences cannot help.

Antisocial Behavior Research Is Stuck in the Risk Factor Stage

Influential reviewers have concluded that the study of antisocial behavior is stuck in the "risk factor" stage (Farrington, 1988, 2003; Hinshaw, 2002; Rutter, 2003a; 2003b) because so few studies have

used designs that are able to document causality (Rutter, Pickles, Murray, & Eaves, 2001). A variable is called a *risk factor* if it has a documented predictive relation with antisocial outcomes, whether or not the association is causal. The causal status of most risk factors is unknown; researchers know what statistically predicts psychopathology outcomes, but not how or why (Kraemer, 2003; Kraemer et al., 1997). There are consequences to the field's failure to push beyond the risk factor stage to achieve an understanding of causal processes. Valuable resources have been wasted because intervention programs have proceeded on the basis of risk factors without sufficient research to understand causal processes. For example, mentoring programs are based on evidence that poor adult–child bonding is a risk factor for antisocial outcomes. Family preservation programs are based on evidence that family dissolution is a risk factor. Peer-group skills programs are based on evidence that peer delinquency is a risk factor. However, mentoring programs and family preservation have not worked (Wasserman & Miller, 1998), and peer-group programs have been shown to exacerbate adolescent offending (Dishion, McCord, & Poulin, 1999; Klein, 1995). Similarly, Drug Abuse Resistance Education (DARE), gun buybacks, boot camps, outward-bound-type programs, after-school leisure-time programs, youth job programs, and neighborhood watch programs were all originally designed to correct known risk factors for delinquent offending, but formal evaluation has revealed that none of these interventions work to reduce antisocial behavior and some of them have marked iatrogenic effects (Sherman et al., 1999). Simply put, the cost of getting causation wrong is not trivial.

A central barrier to interpreting an association between an alleged environmental risk factor and antisocial outcome as a cause–effect association is the possibility that some unknown third variable may account for the association, and that third variable may be heritable. For example, does the cycle of violence from abusive parent to aggressive child arise from environmental transmission or genetic transmission (DiLalla & Gottesman, 1991)? Perhaps the most pragmatic implication from accumulating evidence that genes influence antisocial behavior is that environmental causation can no longer be assumed. Because much research on intergenerational transmission continues without genetic controls (Serbin & Karp, 2003), this point cannot be made too often. Without control for genetic variation, further risk-factor research remains ambiguous if not uninformative.

During the 1990s, the assumption that "nurture" influences behavior came under fire. Traditional socialization studies of antisocial behavior, which could not separate environmental influences from their correlated genes, were challenged by four empirical discoveries: (a) ostensible environmental measures are influenced by genetic factors (Plomin & Bergeman, 1991), (b) parents' heritable traits influence the environments they provide for their children (Kendler, 1996; Plomin, 1994), (c) people's genes influence the environments they encounter (Kendler, 1996), and (d) environmental influences do not seem to account for the similarity among persons growing up in the same family (Rowe, 1994). It was said that although non–behavioral–genetic studies might show that certain rearing experiences predict young people's antisocial outcomes, theories of causation based on findings from such designs were guilty of a fundamental logical error: mistaking correlation for causation (Scarr, 1992). These challenges culminated in admonishments that, thus far, the evidence for genetic influences outweighed the evidence for environmental influences within the family (Harris, 1998; Pinker, 2002; Rowe, 1994). Many social scientists responded to this claim, reasserting evidence for environmental influences (Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000; Reid, Patterson, & Snyder, 2002; Vandell, 2000). The best way forward to resolving the debate is to reexamine each putative environmental risk factor for antisocial behavior, one by one, while using research methods that are capable of applying explicit controls for genetic effects to test environmental causation (Rutter et al., 2001).

Ordinary studies cannot test whether a risk factor is causal, and it would be unethical to assign children to experimental conditions expected to induce aggression. Instead, researchers can use three other methods for testing causation: (a) natural experiment studies of within-individual change (Cicchetti, 2003; Costello, Compton, Keeler, & Angold, 2003), (b) randomized treatment experiments (Howe, Reiss, & Yuh, 2002), and the focus of this review, namely, (c) behavioral–genetic designs. None of the three alone can provide decisive proof of causation, but if all supply corroborative evidence by ruling out alternative noncausal explanations about a risk factor, then a strong case for causation can be made.

How Can Behavioral–Genetic Research Help?

Behavioral–genetic designs are a useful addition to a toolkit for testing environmental causation. It seems counterintuitive to think about using behavioral–genetic designs to control for and rule out genetic influences while highlighting environmental influences in bas relief, but, paradoxically, this is one of their strongest applications. Behavioral genetics disentangles genetic from nongenetic aspects of familial transmission and, thereby, can rule out one of the most serious challenges to environmental causation: that a heritable third variable accounts for the correlation between a putative environmental risk factor and antisocial outcome. Behavioral genetics also offers methods for putting genetic and nongenetic influences back together again in a systematic and controlled way, to work out how they jointly cause behavior. Behavioral genetics has been rapidly moving beyond the initial question of heritability (Dick & Rose, 2002; Kendler, 2001) to apply its methods to a broad array of causal questions. Concurring evidence from behavioral–genetic methods, natural experiments of within-individual change, and treatment experiments will move the study of antisocial behavior beyond the risk-factor stage, where it has been stuck, to inform strong etiological theory.

Before reviewing studies that have applied behavioral–genetic designs to testing environmental causation, it is important to ask whether estimates of environmental influence from behavioral–genetic samples apply to the general population (Rutter, 2002). The assumption of generalizability is probably defensible for twin studies because twin-versus-singleton comparisons have not yielded differences in the prevalence rates of antisocial behavior or antisocial personality traits (Gjone & Novik, 1995; Johnson, Krueger, Bouchard, & McGue, 2002; Levy, Hay, McLaughlin, Wood, & Waldman, 1996; Moilanen et al., 1999; Simonoff et al., 1997; van den Oord, Koot, Boomsma, Verhulst, & Orlebeke, 1995; van der Valk, Verhulst, Stroet, & Boomsma, 1998). Adoptees do show elevated rates of antisocial outcomes, although the distribution of these outcomes has the same skewed shape within adoptee samples as in the general population (Hutchings & Mednick, 1973;

Sharma, McGue, & Benson, 1998). It is important to note that the effect sizes for associations between risk factors and psychopathology outcomes have been found to be similar across behavioral–genetic and nongenetic studies (Moffitt & the E-Risk Study Team, 2002).

Testing Hypotheses About Environmental Causation: Behavioral Genetic Studies of Parenting Effects on Children's Aggression

To illustrate how behavior-genetic designs are helping to move the study of antisocial behaviors from the risk-factor stage to causal understanding, I next review research investigating one risk factor, bad parenting, and one antisocial outcome, children's aggression. I use the term *bad parenting* as shorthand for a variety of alleged environmental risks to children's behavior thought to emanate from parental treatment. This review includes risk factors ranging from mothers' smoking heavily during pregnancy to inconsistent or unskilled discipline to frank child neglect and abuse. The outcome, "children's physical aggression," includes hitting, fighting, bullying, cruelty, and related antisocial behaviors. It has already been established that bad parenting statistically predicts children's aggression and that bad parenting plays a central causal role in leading theories of antisocial behavior (Lahey, Moffitt, & Caspi, 2003; Thornberry, 1996). The aim of the research reviewed here is to determine whether the relation between bad parenting and children's aggression is a true cause–effect relation such that interventions that stop bad parenting can reasonably be expected to prevent aggression from emerging. This aim is fundamental because studies of adoptions have documented the dispiriting fact that aggression emerges in adopted children despite the fact that they were separated from their at-risk biological parents at birth and reared by skilled and loving adoptive parents.

The current review systematically tackles five questions in turn. First, is there evidence that children's aggression cannot be wholly explained by genetic factors and must have nongenetic environmental causes as well? Second, do parents' genes influence bad parenting? Third, does the influence of parents' genes on parenting confound a cause–effect interpretation of the association between bad parenting and children's aggression? Fourth, does a genetic child effect evoke bad parenting to further confound a cause–effect interpretation of the association between bad parenting and children's aggression? Fifth, after both genetic confounds are controlled, does bad parenting have an environmentally mediated causal effect on children's aggression? Each question is presented in a separate section, first describing relevant research designs and then reviewing findings to date. Table 1 summarizes the text. The research designs covered here are not intended to be exhaustive but are intended to illustrate what kinds of studies can be done using the logic of behavioral–genetic methods.

Question 1: Is Children's Aggression Wholly Accounted for by Genetic Factors, or Does It Have Nongenetic Causes as Well?

More than 100 studies have addressed the question of genetic influence on antisocial behavior (Moffitt, in press), and meta-analyses conclude that genes influence 40% to 50% of population variation in antisocial behavior (Miles & Carey, 1997; Rhee & Waldman, 2002). This research unequivocally proves that environmental influences account for variation. This fact constitutes a remarkable contribution to the understanding of causation (Plomin, 1994). In addition, it is recognized that the heritability coefficient indexes not only the direct effects of genes but also the effects of interactions between genes and family-wide environments (Boomsma & Martin, 2002; Rutter & Silberg, 2002). In such interactions, the effect of an environmental risk may be even larger than previously reported among the subgroup of individuals having a vulnerable genotype. This is the case for antisocial behaviors.

One useful feature of behavioral–genetic research designs is that they offer two powerful methods for documenting the importance of environmental effects (Plomin, DeFries, McClearn, & McGuffin, 2001). One of these methods of detecting environmental influence tests whether any of the family members in a study sample are more similar than can be explained by the proportion of genes they share. For instance, monozygotic (MZ) twins' genetic similarity is twice that of dizygotic (DZ) twins and, therefore, if nothing but genes influenced antisocial behavior, MZ twins' behavior ought to be at least twice as similar as that of DZ twins. If that is not the case, then it can be assumed that something environmental has influenced the twins and enhanced their similarity. For almost all human behavioral traits studied thus far, environmental factors shared by family members (variously labeled the "family-wide," "common," or "shared" environment) have not been found to make family members similar (Rowe, 1994). Antisocial behavior is a marked exception. A comparison of shared environment effects across 10 psychiatric disorders revealed that such effects were stronger for antisocial personality and conduct disorder than for affective, anxiety, or substance disorders (Kendler, Prescott, Myers, & Neale, 2003).

Estimates of shared environment effects on population variation in antisocial behavior are about 15% to 20%, as reported by meta-analyses (Miles & Carey, 1997; Rhee & Waldman, 2002). The small size of this shared environment estimate should not be too surprising, because the twin-study coefficient indexing the shared environment does not include environmental effects involved in gene–environment interactions. The shared environment coefficient can be thought of as a residual effect of shared environment that remains after controlling for gene–environment interactions. As most human behavior involves nature–nurture interplay, it is remarkable that as much as 20% of the population variation in antisocial behavior can be attributed to direct environmental effects not conditional on genetic vulnerability.

The second method of detecting the presence of environmental influence is to test whether family members are less similar than expected from the proportion of genes they share (Plomin & Daniels, 1987). For instance, if twins in an MZ pair are not perfectly identical in antisocial behavior, despite sharing all their genes, this indicates that experience has reduced their behavioral similarity. After estimates of the influences of heritability (50%) and shared family environment (20%) on antisocial behavior are calculated, the remainder of population variation (30%) is assumed to reflect environmental influences not shared by family members (variously labeled "unique," "person-specific," or "nonshared" experiences). These experiences might include criminogenic experiences unique to the individual and not shared with his or her sibling, such as sustaining a head injury, being the unique target of

Table 1
Study Designs for a Program of Research Into the Interplay Between the Influences of Genes and a Candidate Environmental Measure (X_{env}) on Measures of a Behavioral Outcome (Y_{beh})

The research question	Useful designs	Selected exemplary studies from research on the association between parenting and children's antisocial behavior
1. Are individual differences in the behavioral phenotype Y_{beh} under the influence of nongenetic factors?	Yes, if Y_{beh} is not wholly explained by twins' genetic similarity.	See Rhee and Waldman (2002)
	Yes, if adoptees' Y_{beh} is not wholly explained by genetic transmission from biological parents.	See Rhee and Waldman (2002)
2. Is the putative candidate environmental variable X_{env} under the influence of parents' genes?	Yes, if biological parents' X_{env} predicts adoptees' X_{env}	No studies
	Yes, if MZ twins reared apart are similar on X_{env} as parents.	Plomin et al. (1989)
	Yes, if MZ twin parents are more similar on X_{env} than DZ twin parents.	Perusse et al. (1994), Wade and Kendler (2000)
3. Passive rGE: Does the influence of parents' genes on X_{env} confound a cause–effect interpretation of the association between X_{env} and outcome Y_{beh}?	Yes, if biological parents' X_{env} predicts adoptees' Y_{beh}.	No studies (For a study of socioeconomic status, see VanDusen et al., 1983)
	Yes, if the correlation between parents' X_{env} and children's Y_{beh} is larger in natural families than in adoptive families.	No studies (For a study of temperament, see Plomin, 1994)
	Yes, if a parent's X_{env} predicts her natural child's Y_{beh} more strongly than her adoptive child's Y_{beh}.	McGue et al. (1996)
	Yes, if an MZ aunt's X_{env} predicts her nephew's Y_{beh} as strongly as does his MZ mother's X_{env}.	No studies (see D'Onofrio et al., 2003; Silberg & Eaves, 2004)
	Yes, if the correlation between X_{env} and Y_{beh} decreases when genetic influence on Y_{beh} is controlled in a twin design.	Turkheimer and Waldron (2000), Table 3
4. Active rGE: Does peoples' genetically influenced Y_{beh} lead them to evoke, create, seek, or end up in X_{env} and thus confound a cause–effect interpretation of the association between X_{env} and outcome Y_{beh}?	Yes, if MZ twins' X_{env} is more similar than DZ twins' X_{env}.	Hur and Bouchard (1995), Plomin and Bergeman (1991), Reiss et al. (2000)
	Yes, if adoptees' Y_{beh} predicts their adoptive parents' X_{env}, and the adoptees' Y_{beh} is genetically influenced (i.e., predicted by their biological parents' Y_{beh}).	Ge et al., (1996), O'Connor et al. (1998), Riggins-Caspers et al. (2003)
	Yes, if Twin A's Y_{beh} predicts Twin B's X_{env} and more strongly in MZ than DZ pairs.	Jaffee et al. (2004a), Neiderheiser et al. (1999)
5. If both genetic confounds are ruled out, does X_{env} have an environmentally mediated association with outcome Y_{beh}?	Yes, if adoptive parents' X_{env} increases Y_{beh} over and above the influence from biological parents' Y_{beh}.	Cadoret et al. (1995), Mednick et al. (1984)
	Yes, if an MZ twin mother's X_{env} predicts her child's Y_{beh} better than does her MZ sister's X_{env}.	No studies (see D'Onofrio et al., 2003; Silberg & Eaves, 2004)
	Yes, if the shared experience of X_{env} is associated with greater twin similarity on Y_{beh} than could be explained by the twins' genetic relatedness.	Burt et al. (2003), Caspi et al. (2000), Jaffee et al. (2002), Meyer et al. (2000)
	Yes, if differences in exposure to X_{env} make MZ twins different on Y_{beh}.	Caspi et al. (2004), Pike et al. (1996)
	Yes, if a longitudinal natural experiment shows that exposure to X_{env} is followed by within-individual change in Y_{beh} from baseline.	Campbell et al. (1996), Costello et al. (2003), Farrington (1988), Nagin et al. (2003), Thornberry et al. (1993)
	Yes, if a randomized treatment experiment that changes X_{env} reduces Y_{beh}.	Dodge (2003), Olds et al. (1998)
6. G × E: Does the influence of genes on Y_{beh} depend on exposure to X_{env}? Does the influence of X_{env} on Y_{beh} depend on genetic vulnerability or resilience?	Yes, if adoptive parents' X_{env} increases Y_{beh} more among adoptees whose biological parents had Y_{beh} (signaling high genetic load) than among adoptees' Y_{beh} whose biological parents did not have Y_{beh} (low genetic load).	Cadoret et al. (1995), Riggins-Caspers et al. (2003)
	Yes, if X_{env} increases Y_{beh} more among MZ twins whose co-twin has a diagnosis of Y_{beh} (signaling high genetic load) than among MZ twins whose co-twin does not have Y_{beh} (low genetic load).	Jaffee et al. (2005)
	Yes, if the effect of a randomized treatment depends on patients' genetic status.	No studies (See Howe et al., 2002)
	Yes, if a measured gene interacts with a measured X_{env} to affect individuals' outcome on Y_{beh}.	Caspi et al. (2002), Foley et al. (2004)

Note. MZ = monozygotic; DZ = dizygotic; rGE = gene–environment correlations.

sexual abuse, or living with an antisocial spouse. There are two caveats about estimates of the effect of nonshared environments. First, measurement error inflates these estimates because random mistakes in measuring behavior will result in scores that look different for twins in an MZ pair, and it is not easy to differentiate such faux MZ differences from true MZ differences caused by the twins' nonshared experiences. The second caveat is that the coefficient for nonshared environmental effects indexes not only direct effects of nonshared experiences but also effects of interactions between nonshared environments and genes (Boomsma & Martin, 2002; Rutter & Silberg, 2002). Thus, some portion of the nonshared environment effect is attributable to error or genes, and the size of this portion is unknown.

It is highly unlikely that any behavior disorder is wholly determined by genes, but it is important to begin any program of research into causal processes by ascertaining what effect sizes can be expected for both genetic and environmental influences under natural conditions, in the absence of intervention. For overall population variation in antisocial behavior, these effects are 50:50. Therefore, quantitative behavioral–genetic research has shown that the answer to Question 1, "Does children's aggression have any nongenetic causes?" is a definite yes; there is strong evidence that environmental causes must exist.

Question 2: Do Parents' Genes Influence Bad Parenting?

It is important to know the size of the contribution of parents' genotypes to their bad parenting, because if parenting is substantially influenced by parents' genotype, then its correlation with children's aggression cannot be confidently interpreted as a cause–effect relation. But how much do people's genes influence their parenting? Answering this question requires researchers to treat parenting as a phenotype in behavioral–genetic research.

What research designs can be used to answer this question? Three designs are relevant. Adoptions can be studied to test whether biological parents' bad parenting (of the children they did not give up for adoption) predicts that their adopted-away child will also engage in bad parenting when she becomes a parent. This study would show that bad parenting is genetically transmitted, in the absence of social transmission. However, this study has not been conducted, because of the difficulty of obtaining parenting data from two generations of adults separated by adoption.

Adult MZ twins reared apart can be studied to test whether they are similar in parenting their children. The Swedish Adoption Twin Study of Aging used this design, by asking 50 pairs of adult MZ twins reared apart to report their own parenting styles on the Moos Family Environment Scale (Plomin, McClearn, Pederson, Nesselroade, & Bergeman, 1989). Results indicated that 25% of the variation in parenting was genetically influenced.

Adult twin parents can be studied to ascertain how much variation in their bad parenting is attributable to genetic versus environmental sources. The aforementioned Swedish twin study carried out this design, studying 386 adult twin pairs, and again results indicated that 25% of the variation in the Family Environment Scale was genetically influenced (Plomin et al., 1989). In another study, 1,117 pairs of midlife twin volunteers who had reared, on average, three children reported their own parenting styles. The heritability estimate for an overall measure of parenting, referred to as "care," was 34% (Perusse, Neale, Heath, & Eaves, 1994). A Virginia sample of 262 pairs of adult twin mothers reported their own parenting styles, and the heritability estimates were 21% for physical discipline, 27% for limit setting, and 38% for warmth (Kendler, 1996; Wade & Kendler, 2000). An Oregon sample of 186 pairs of adult twin mothers and adoptee mothers reported their own parenting styles, and the heritability estimates ranged from 60% for positive support to 24% for control (Losoya, Callor, Rowe, & Goldsmith, 1997). These findings were echoed by a study of 236 pairs of adult twin mothers reporting their own parenting, in which genetic effects were found for positivity and monitoring (Neiderhiser et al., 2004; Towers, Spotts, & Neiderhiser, 2001). Finally, a study of 1,034 adult twin mothers estimated heritability over 50% for smoking during pregnancy, which is a known prenatal parenting risk factor for children's aggression (D'Onofrio et al., 2003).

What research is needed? This very small literature is a good beginning, but a number of limitations need to be overcome. First, the studies have relied on the twin design, and twin-design weaknesses ought to be complemented by the strengths of the adoption design (see Deater-Deckard, Fulker, & Plomin, 1999). Second, measurement has relied on parents' self-reports, and thus the findings are a mix between genetic influences on actual parenting behavior and genetic influences on self-perception and self-presentation (Kendler, 1996; Plomin, 1994). As a third limitation, studies have tended to focus on mothers and excluded fathers, for the obvious reason that fathers' nonparticipation in research disproportionately characterizes families of aggressive children. However, fathers' antisocial behavior in the home is a central aspect of bad parenting that predicts children's aggression (Jaffee, Moffitt, Caspi, & Taylor, 2003). Fourth, and most serious for the purpose of investigating antisocial behavior, the samples underrepresent families at serious risk, and the parenting measures do not address the most powerful risk factors for children's aggression, such as exposure to domestic violence, child neglect, maternal rejection, and child abuse. These serious forms of bad parenting themselves constitute antisocial acts, and as a result researchers should anticipate that the influence of parents' genes on them is much stronger than the genetic influences found for parenting styles within the normative range, such as spanking, monitoring, or limit setting. It is not unreasonable to expect genetic influence on serious bad parenting to resemble genetic influence on other antisocial behaviors (50%).

The answer to Question 2, "Do parents' genes influence bad parenting?" seems to be probably. It may seem surprising that little research has been done on the question of a genetic contribution to bad parenting. The question has been neglected because behavioral–genetic researchers have not often viewed parenting as a phenotype. Moreover, developmental researchers who are interested in parenting as an outcome almost never adopt behavioral–genetic research methods. It is quite likely that bad parenting is under some degree of genetic influence because parenting styles are known to be associated with parents' personality traits (Belsky & Barends, 2002; Spinath & O'Connor, 2003) and personality traits are known to be under genetic influence (Plomin & Caspi, 1999). Bad parenting should be treated as a phenotype in future behavioral–genetic research (McGuire, 2003).

Question 3: Does the Influence of Parents' Genes on Parenting Confound a Cause–Effect Interpretation of the Association Between Bad Parenting and Children's Aggression?

The technical term for the association referred to in the question posed here is *passive correlation* between genotype and an environmental measure, often abbreviated as rGE (Plomin, DeFries, & Loehlin, 1977). A passive rGE confound occurs when a child's behavior and the environment his or her parents provide are correlated because they have the same origins in the parents' genotype (i.e., not because bad parenting itself causes children's aggression). Parents may transmit to their child a genetic liability for aggression and simultaneously provide an environment of violent, abusive maltreatment that is symptomatic of the parents' genetic liability for aggression. To the extent that such parenting is under genetic influence, the observed association between bad parenting and child aggression could be a spurious artifact of a third variable that causes both, namely, genetic transmission. This is why it is important to study passive rGE.

It is important to note that the mere evidence that bad parenting is under the influence of parents' genes (Question 2) is not sufficient to conclude that this genetic influence goes on to mediate the connection between bad parenting and children's aggression. Rutter and Silberg (2002) have made this point, explaining that mothers' genes influence whether they have low birth-weight babies, but the babies' birth weights are wholly determined by environmental conditions, not by any genes inherited from their mothers. To take this point to an extreme, genes influence which breeds of dog bite readily, but once a dog bites, injury to the victim is wholly environmentally mediated. Therefore, despite the fact that antisocial behavior is concentrated in families and this concentration is known to be under the influence of parental genes, it remains entirely possible that the pathway from bad parenting to children's aggression is wholly environmentally mediated. For this reason, it is important to disentangle (a) the genetic origins of bad parenting from (b) the genetic and environmental mechanisms by which bad parenting produces children's aggression.

Nonetheless, the pairing of bad parenting with children's aggression as risk factor and outcome intuitively raises the question of genetic mediation, because both bear a relation to the antisocial trait. Bad parenting and juveniles' aggression both violate the rights and safety of victims, and both are criteria for antisocial personality disorder (American Psychiatric Association, 1994). Moreover, aggressive children followed up to adulthood often become bad parents (Fagot, Pears, Capaldi, Crosby, & Leve, 1998; Jaffee, Caspi, Moffitt, Taylor, & Dickson, 2001; Serbin & Karp, 2003). If bad parenting and children's aggression are age-heterotypic expressions of the same genetically influenced trait, this could constitute an rGE that rules out any causal status for bad parenting.

What research designs can be used to answer this question? There are at least four appropriate research designs, but to my knowledge none of them has been carried out. Adoptions can be studied to test whether the biological parents' bad parenting predicts the adopted-away children's aggression, even if parent and child never have contact. This study has not been conducted because of the difficulty of obtaining parenting data from adopted children's biological parents. Correlations between bad parenting and children's aggression in natural families versus adoptive families can be compared. If the correlation is stronger in natural families (which have both genetic and environmental processes of transmission) than in adoptive families (which have only environmental transmission), then genetic transmission is taking place (Plomin, 1994). However, this design is biased toward finding evidence of an rGE confound, because greater variation in bad parenting among natural than adoptive families could produce larger correlations with children's aggression in natural families (Stoolmiller, 1999). To avoid such bias, researchers can conduct a study within adoptive families to test whether rearing parents' bad parenting is more strongly correlated with their natural children's aggression than with their adoptive child's aggression (Rutter & Silberg, 2002). The within-family design holds constant variation in bad parenting across natural versus adoptive parent–child pairs but requires a sample of families having both an adopted and a natural child, not too far apart in age. I am not aware of a study that has compared the correlations between bad parenting and natural children's aggression versus adoptive children's aggression. However, a study of 667 adoptive families found adoptive parents' reports of "family functioning" to be more strongly correlated with self-reported antisocial behavior in their natural child than in their adopted child (McGue, Sharma, & Benson, 1996).

A particularly promising method studies the families of adult MZ twins who are mothers to test if MZ aunts' bad parenting predicts their nephews' aggression. In this twin-mothers design, both MZ sisters are genetic mothers to each other's birth children. However, the MZ aunt does not provide the rearing environment for her nieces and nephews; only the children's birth mother is an environmental mother to them. If the MZ aunts' and the MZ mothers' parenting predicts the children's aggression to the same extent, this would be strong evidence of a complete rGE confound. But, if the MZ mother's parenting predicts the children's aggression better than does the MZ aunt's parenting, this would show that bad parenting has an environmental effect. This elegant design offers unprecedented capacity to disentangle sources of bad parenting from mechanisms of risk for the children of bad parents, particularly when DZ twin mothers as well as MZ twin mothers are sampled (D'Onofrio et al., 2003; Silberg & Eaves, 2004). This children-of-twins design is newly being applied to the question of causes of children's aggression by Silberg (2002), but findings were not available at the time of this writing.

The aforementioned methods test the hypothesis that genetic transmission explains the observed association between bad parenting and child aggression by looking for an effect of parenting on behavior over and above genetic influence on behavior. Another method is to compare the effect size of the association between bad parenting and children's aggression before versus after genetic influences are controlled. Any shrinkage estimates the extent to which the association is mediated by genetic transmission. This method is an instance of the familiar test for mediation (Baron & Kenny, 1986). In their meta-analysis of studies of differential treatment of siblings, Turkheimer and Waldron (2000; see their Table 3) showed that the effect sizes for associations between risk factors and behavior outcomes tended to shrink by at least half when genetic confounds were controlled. However, this meta-analysis compared effect sizes across two groups of studies, those with genetic designs versus those without such designs, and the groups of studies differed on design features such as sample

composition or sample size. Comparisons of effect sizes for parenting predicting children's aggression before versus after genetic controls within the same sample would be informative (see Question 5, below).

What research is needed? Researchers have neglected the questions of whether genes contribute to parenting and whether genetic transmission confounds interpretation of the link between bad parenting and children's aggression. As such, research applying any of the designs described here to parenting is needed. However, a comparison of effect sizes in studies with genetic controls versus those without such controls suggests that genetic transmission might explain as much as half of the connection. The answer to Question 3, "Are cause–effect interpretations of the connection between bad parenting and children's aggression confounded by genetic transmission?" seems to be probably.

Question 4: Does a Genetic Child Effect Evoke Bad Parenting to Confound a Cause–Effect Interpretation of the Association Between Bad Parenting and Children's Aggression?

The technical term for the association referred to in the question posed here is *evocative correlation* between genotype and an environmental measure, and it is also abbreviated as rGE (Plomin, DeFries, & Loehlin, 1977). Evocative rGE occurs when a child's behavior and the parenting the child receives are correlated because they have common origins in the child's genotype (i.e., not because bad parenting itself causes children's aggression). The evocative rGE is a conceptual extension of the child effect discussed by Bell (1968), who pointed out that children influence their parents' behavior. The child effect hypothesis has been shown to apply to the question at hand here, namely, whether children's aggression can elicit bad parenting (e.g., Lytton, 1990). Behavioral geneticists add the hypothesis that the child's parent-provoking behaviors may be under genetic influence. Like passive rGE, evocative rGE confounds interpretation: To the extent that bad parenting is elicited by a child's genetically influenced behavior, the observed association between bad parenting and child aggression could be a spurious artifact of a third variable that causes both, namely, the child's genotype.

What research designs can be used to answer this question? A large number of studies have ascertained twins' recollections of how they were treated by their parents during childhood, with the finding that MZ twins' ratings of their parents' child rearing are more similar than DZ twins' ratings, suggesting an influence of children's genotype on parents' parenting (Hur & Bouchard, 1995; Kendler, 1996; Rowe, 1983). This literature has been reviewed elsewhere (e.g., Plomin, 1994; Plomin & Bergeman, 1991). There is a basic difficulty with this literature, however. Although it seems reasonable to interpret the findings as evidence for a child effect on bad parenting, studies of twins' self-reports about their parents' treatment of them do not rule out the alternative interpretation of a genetic effect on perceptual bias, according to which MZ twins are more alike than DZ twins in how they interpret their parents' treatment or how they revise their childhood memories (Krueger, Markon, & Bouchard, 2003). Nonetheless, the body of studies is generally interpreted as evidence for genetic child effects on parenting because several other studies have shown genetic child effects using adoption and sibling family designs instead of twin designs and using observational or multi-informant measures of parenting instead of twins' self-reports (Braungart, Plomin, & Fulker, 1992; Deater-Deckard et al., 1999; Neiderhiser et al., 2004; O'Connor, Hetherington, Reiss, & Plomin, 1995; Reiss, Neiderhiser, Hetherington, & Plomin, 2000; Rende, Slomkowski, Stocker, Fulker, & Plomin, 1992). These numerous studies decidedly demonstrated that a genetic child effect on parenting exists, but they did not demonstrate what it is that children do to provoke bad parenting. In other words, these studies did not include children's aggression as a measured variable.

Another research design involves studying adoptions, to test whether adoptees' aggression predicts their adoptive parents' bad parenting while establishing that the adoptees' aggression has a genetic basis (i.e., that it is predicted by their biological parents' antisocial behavior). Three studies have used this compelling design. The first study examined 41 adolescent adoptees, defined genetic risk as the biological parent's official diagnosis, measured adoptee antisocial behaviors using multiple sources, and measured adoptive parents' hostility, warmth, nurturant involvement, and harsh-inconsistent parenting with multiple methods, including observations (Ge et al., 1996). The second study examined 56 to 80 child adoptees (depending on the analysis), defined genetic risk by biological mother's self-report, and measured adoptee antisocial behaviors and adoptive parents' negative control by adoptive parent self-report (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). The third study examined 150 adult adoptees, defined genetic risk as biological parents' diagnosis, measured adoptee conduct problems by adoptees' retrospective self-reports, and measured adoptive parents' harsh discipline with adoptees' retrospective reports (Riggins-Caspers, Cadoret, Knutson, & Langbehn, 2003). All three studies reported that adoptees at high genetic risk for psychopathology received more discipline and control from their adoptive parents than adoptees at low genetic risk. Furthermore, unlike prior research, the three studies demonstrated that the link from a child's genetic risk to adoptive parents' parenting is mediated by the child's genetically influenced aggressive behavior problems. Individual studies among these three were limited by a small sample or by single-source retrospective data, but as a set the studies provide robust evidence for a genetically mediated child effect in which the causal arrow runs from children's aggression to parenting. However, adoption samples are not well suited to ascertaining whether the child effect applies to parenting outside the normal range. As a result of self-selection by older, better educated, higher income applicants and subsequent screening by adoption agencies, adoptive parents are better prepared than nonadaptive parents, and they tend to have unusually high motivation for parenting and responsibility for few children (Stoolmiller, 1999). Designs other than adoption designs are needed to test whether the evocative genetic child effect extends to the sorts of bad parenting (e.g., child neglect, psychological abuse, physical maltreatment) found in families whose members exhibit serious, persistent antisocial outcomes.

A third design for testing genetic child effects involves studying twin children, asking whether Twin A's aggression predicts the bad parenting received by Twin B and vice versa. This is an application of bivariate twin modeling. Its basic logic involves the premise that if the correlation between Twin A's aggression and Twin B's experience of bad parenting is higher among MZ pairs than DZ pairs, this would indicate that the same set of genetic

influences causes children's aggression and provokes bad parenting. Bad parenting must be measured separately for each twin so that it can be used as a phenotype similar to each twin's aggression. Two studies of several hundred sibling pairs taking part in the study of Nonshared Environment in Adolescent Development (NEAD) have applied variations of this bivariate approach using multisource measures of adolescents' and parents' behavior. A genetic child effect accounted for most of the correlation between adolescents' antisocial behavior and parents' negativity assessed cross-sectionally (Pike, McGuire, Hetherington, Reiss, & Plomin, 1996) and longitudinally after accounting for the continuity of adolescent antisocial behavior (Neiderhiser, Reiss, Hetherington, & Plomin, 1999).

As noted earlier, it is important to know whether the genetic child effect for ordinary parenting (as indicated by previous adoption studies and the NEAD study) also applies to extreme forms of bad parenting associated with serious, persistent antisocial behavior. The bivariate modeling approach was applied to this question in the E-Risk longitudinal study of 1,116 British families with young twins (Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004a). To do this, the E-Risk study incorporated two innovations (Moffitt & the E-Risk Study Team, 2002). First, the study assessed a birth cohort in which one third of families were selected to oversample families who were at high risk (findings were weighted back to represent the population of British families having babies in the 1990s). Second, the study interviewed mothers about parenting that was beyond normal limits (physical maltreatment: neglectful or abusive care resulting in injury, sexual abuse, registry with child protection services) as well as about parenting in the normative range (frequency of corporal punishment: grabbing, shaking, spanking). Children's genes influenced which children received corporal punishment, explaining 24% of the variation in the cohort, but children's genes were unrelated to becoming a victim of maltreatment. Bivariate twin modeling of the cross-twin, cross-phenotype correlations revealed that children's genes accounted for almost all of the correlation between corporal punishment and children's aggression, indicating that most of the observed association between this often used form of parenting and children's aggression is a genetic child effect. However, children's genes did not account for the correlation between physical maltreatment and children's aggression. Although difficult children can and do provoke their parents to use frequent corporal punishment in the normal range, factors leading to injurious maltreatment lie not within the child but within the family environment or the adult abuser. There are limits to child effects.

What research is needed? Taken together, the adoption and twin studies reviewed in this section provide evidence to answer Question 4: Yes, the observed association between normative parenting and child aggression is in large part a spurious artifact of a third variable that causes both, namely, the child's genotype. The child-to-parent effect strongly outweighed any parent-to-child effect in five of the six studies (Ge et al., 1996; Jaffee et al., in press; Neiderhiser et al., 1999; Pike et al., 1996; Riggins-Caspers et al., 2003). A provocative deduction from this group of studies is that Scarr (1991) may have been correct when she argued that improving parenting in the normal range will not produce significant changes in children because the associations between ordinary parenting and child outcome are not causal. "There is no evidence that family environments, except the worst, have any significant effect on the development of conduct disorders, psychopathy, or other common behavior disorders" (Scarr, 1991, p. 403). Scarr (1992) further argued that environmental conditions outside the expected range will have causal influences on children quite apart from genetic influences and, in keeping with this notion, one study showed that maltreatment causes children to be aggressive apart from any influence of their genotypes. This distinction between normative versus extreme forms of parenting has implications for future research. Most genetically informative studies to date have assessed parenting using omnibus measures (e.g., family functioning, negativism, control) because the goal has been to ascertain whether genetic child effects exist. However, interventionists try to change specific well-defined forms of parental behavior. To inform interventions, research needs to query genetic versus environmental mediation of specific features of parenting. Furthermore, the aspects of parenting that correlate with children's aggression are probably quite different in early childhood, later childhood, and adolescence. Genetically informative studies of samples at different ages are needed to inform parenting interventions tailored to developmental stages.

The specific question of whether children's genotype evokes bad parenting has been considered here, but it is useful to note that the evocative type of rGE is a subset of a larger class referred to as active rGE (Scarr & McCartney, 1983). Active rGE encompasses at least three different processes, when people's genetically influenced behavior leads them to "(1) create, (2) seek, or (3) otherwise end up in environments that match their genotypes" (Rutter & Silberg, 2002, p. 473). Antisocial behavior can bring about each of these three processes at any point in the life course, and these active rGE processes are of enormous importance in understanding the continuity of antisocial behavior (Caspi & Moffitt, 1995; Laub & Sampson, 2003). Once genetically influenced behavior has brought a person into contact with an environment, the environment may have unique causal effects of its own, cutting off opportunities to develop alternative prosocial behaviors, promoting the persistence of antisocial behavior, and exacerbating its seriousness (Moffitt, 1993). Research is needed to test for active rGE processes involved in antisocial behavior at all developmental stages.

Question 5: After Both Genetic Confounds Are Controlled, Does Bad Parenting Have Any Environmentally Mediated Effect on Children's Aggression?

The new generation of research designs that can evaluate whether a risk factor has an environmentally mediated effect on children's aggression has three key features. First, the studies must use a genetically sensitive design to control for the confounding effects of parents' genes or children's genes on putative environmental measures. As this review shows, these confounding effects are at least small to moderate and, in the case of child effects, may be large, so they must be controlled.

The second key feature is that designs must include an observed measure of the construct alleged to have environmental effects on children, in the case here, bad parenting. Traditional behavioral–genetic studies have reported latent environmental variance components but not observed measures. This has been problematic because even very large twin studies are underpowered to detect

environmental influence on twin similarity as a latent variance component, whereas statistical power to detect such influence is increased if a putative environmental variable is measured so that its effects can be estimated empirically (Kendler, 1993; Kendler, Neale, Kessler, Heath, & Eaves, 1992).

The third key feature is that genetically informative samples must accurately represent the full range of families' environmental circumstances (Taylor, 2004). Many behavioral–genetic samples suffer substantial biases in recruitment and attrition, inadvertently restricting their range of participating families to primarily middle-class populations. Contemporary theories of psychopathology implicate experiences outside the normal range, such as exposure to domestic violence or child maltreatment, which are generally concentrated in the poorest segment of the population, the segment not sampled by most behavioral–genetic studies. (Scandinavian national twin registers of psychiatric hospital and court records accurately represent variation in the population, but such register studies have been unable to measure children's environments directly.)

What research designs can be used to answer this question? Four basic behavioral–genetic methods can be used to rule out gene–environment correlation confounds while testing putative environmental risk factors. Although the focus here is on genetically sensitive studies, some such studies have incorporated natural-experiment analyses showing within-individual change that also contributes evidence for environmental causation.

Adoptions can be studied to test whether the adoptive parents' bad parenting increases adoptees' aggression over and above the genetic influence from the biological parents' aggression. The large adoption studies of antisocial behavior that emerged from Scandinavia and the United States in the 1970s and 1980s were primarily cited for their innovation of demonstrating genetic influences; they showed that adoptees' criminal offending was significantly associated with the antisocial behavior of their biological parents, although these parents did not rear the adoptees. However, some of these same studies examined whether adoptees' criminal offending was also associated with the antisocial behavior of the adoptive parents who did rear them (Bohman, Cloninger, Sigvardsson, & von Knorring, 1982; Cadoret, Cain, & Crowe, 1983; studies by Mednick and colleagues e.g., VanDusen, Mednick, Gabrielli, & Hutchings, 1983). To my knowledge, a study of antisocial behavior was the first in the behavioral sciences to apply behavioral–genetic methods to control for genetic confounds while testing an environmental hypothesis (VanDusen et al., 1983). It was well established that low socioeconomic status is a risk factor for offending, but Mednick and colleagues were concerned that some dysfunctional genetic susceptibilities transmitted within families might account for the coincidence of fathers' low-status occupations with sons' antisocial activities. As such, they used the Danish Adoption Study data to disentangle the socioeconomic status in which adoptees were conceived (their biological father's occupational status) from the socioeconomic status in which they were reared (adoptive father's status). Results showed that biological inheritance could not explain the majority of the class–crime connection; the social class in which people grew up had a direct environmental effect on their probability of criminal offending (VanDusen et al., 1983).

Twin children can be studied to test whether the shared experience of bad parenting makes children more similar on aggression than could be predicted on the basis of their degree of genetic relationship. A basic approach is to conduct ordinary behavioral–genetic modeling that apportions genetic versus environmental effects on child behavior and then add a measured putative environmental risk factor to assess whether the children's shared experience of that risk factor accounts for any of the shared environmental variation in their behavioral phenotype. The first twin study to apply this approach to problem behavior reported that living in a deprived neighborhood explained a significant 5% of the shared environmental variation in 2-year-olds' behavior problems (Caspi, Taylor, Moffitt, & Plomin, 2000). Another study applied this approach to examine 5-year-old's exposure to their mothers' experience of domestic violence (Jaffee, Moffitt, Caspi, Taylor, & Arseneault, 2002). Exposure to domestic violence over the first 5 years of the children's lives was particularly relevant for children who developed both externalizing and internalizing problems simultaneously; such co-occurring problems are associated with poor prognosis. Domestic violence exposure explained a significant 13.5% of the shared environment variance in children's comorbid outcomes. A third, unpublished study reports that measured parental monitoring accounted for 15% of the shared environment variance in behavior problems in a large sample of 11- to 12-year-old Finnish twins (described in Dick & Rose, 2002). A caveat about this approach is in order. Inference of environmental causation is compromised if parent and child share genes that simultaneously influence both the measure of parenting and the measure of child aggression.

The basic twin design can be improved on by adding indicators of mothers' and fathers' behavioral phenotype to the usual indicators of twin behavior. This approach, referred to as the extended twin-family design (Kendler, 1993), estimates the effect of the putative environmental risk factor on child behavior while controlling for genetic effects on both parents and children. An assumption of the design is that parental phenotype measures carry genetic information parallel to that assessed in the child phenotype measures. (Although this assumption is seldom fulfilled perfectly it seems not unreasonable for antisocial behavior, which has strong child-to-adult continuity.) The first twin study to apply this approach to parenting was reported from the Virginia Twin Study of Adolescent Behavioral Development (Meyer et al., 2000). Antisocial conduct problems were assessed for adolescent twins and their parents in 1,350 families. The measured parenting variables were marital discord and family adaptability. No effect was found for marital discord, but measured family adaptability accounted for 4% of the variance in adolescents' conduct problems.

A complementary approach to testing whether a risk factor has a causal (vs. noncausal) role in the origins of antisocial behavior has been used by studies that rule out passive rGE through statistical controls for parental antisocial behavior. This approach does not differentiate whether the risk factor is influenced at the genotype versus phenotype level of parental antisocial behavior. However, it does offer the advantage that it can be used in nontwin samples, if phenotypic data are collected for all family members. In the above-mentioned E-Risk longitudinal twin study of 1,116 families, the effect of fathers' bad parenting on young children's aggression was examined (Jaffee et al., 2003). Mothers' antisocial behavior was statistically controlled, to make clear that the findings applied specifically to fathers' behavior. As expected from the literature on single mothers, a prosocial father's absence predicted

more aggression by his children. However, the study also revealed a new finding: An antisocial father's presence predicted more aggression by his children, and this harmful effect was exacerbated by the more years a father lived with the family and the more time each week he spent taking care of the children. Inference of environmental causation was supported because the finding for conventional fathers (less involvement predicts more child aggression) was opposite that for antisocial fathers (more involvement predicts more child aggression), and the latter association held after ruling out passive rGE by statistically controlling for both parents' antisocial histories. Obtaining data from fathers is challenging (Caspi et al., 2001), but because fathers are often a target of social policies, a better evidence base about their parenting is needed.

In another report, the E-Risk study evaluated the hypothesis that maternal depression promotes children's aggression (Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). Research has shown that the children of depressed mothers are likely to develop conduct problems. However, it has not been clear that this correlation represents environmental transmission, because women's depression is under genetic influence (Kendler et al., 1992); it often co-occurs with a girlhood history of antisocial conduct, which is also under genetic influence (Moffitt, Caspi, Rutter, & Silva, 2001); and depressed women often mate assortatively with antisocial men (Moffitt et al., 2001). The study controlled for antisocial behavior in the twins' biological father and for the mothers' own antisocial history. Although the connection between mothers' depression and children's conduct problems decreased after this stringent control for familial liability, it remained statistically significant. A concern in the study was the possibility that depressed women might exaggerate ratings of their children's problem behaviors, but the pattern of findings remained the same when teachers' ratings of child behavior were substituted as the outcome measure. A temporal analysis showed that the effect of maternal depression on children's aggression depended on the timing of the depression episodes (a type of natural experiment design). If E-Risk mothers experienced depression, but only before their children's birth and not after, the children were not unusually aggressive. In contrast, only if mothers suffered depression while rearing their children were the children likely to develop aggression. Finally, the possibility that a child effect (in which children's aggression provoked mothers' depression) explained the association was ruled out by documenting within-individual change. After controlling for each child's aggression up to age 5 years, the children exposed to an episode of maternal depression between ages 5 and 7 years became more aggressive by the age 7 assessment. Taken together, these four results are not consistent with a genetic account of the association between maternal depression and children's aggression.

The E-Risk study also examined the effects of physical maltreatment on young children's aggression (Jaffee, Caspi, Moffitt, & Taylor, 2004b) using twin-specific reports of maltreatment. This study satisfied six conditions that together supported the hypothesis that physical maltreatment has an environmentally mediated causal influence on children's aggression: (a) Children's maltreatment history prospectively predicted aggression, (b) the severity of maltreatment bore a dose-response relation to aggression, (c) the experience of maltreatment was followed by increases in aggression from prior levels within individual children, (d) there was no child effect provoking maltreatment, (e) maltreatment predicted aggression while mothers' and fathers' antisocial behavior was statistically controlled, and (f) modest but significant effects of maltreatment on aggression remained present after controlling for genetic transmission of liability to aggression in the family. A similar analytic approach using twin-specific measures of risk was taken by the Minnesota Twin Family Study (Burt, Krueger, McGue, & Iacono, 2003), which studied 808 11-year-old twin pairs. Models revealed that measured parent–child conflict accounted for 12% of the variance in the externalizing syndrome of oppositional, conduct, and attention-deficit-hyperactivity disorders (23% of the common environment variation in this syndrome).

A potential challenge to the findings from the aforementioned studies of parenting effects on twin children is that some of the findings may arise from child effects provoking bad parenting. The finding about parental monitoring is susceptible to this challenge because parental monitoring is known to be subject to strong child effects (Kerr & Stattin, 2000). It seems less plausible that children provoke their mothers' domestic violence experience, or their fathers' antisocial history. Ill-behaved children might provoke maternal depression, but the study took this into account by showing that children exposed to maternal depression subsequently developed new antisocial behavior. Finally, the possibility that a child effect accounted for the influence of maltreatment and parent–child conflict on children's aggression was ruled out by modeling twin-specific measures.

Researchers can study the children of adult MZ twin mothers. As described earlier in this article, in this children-of-twin-mothers design, the MZ aunt constitutes a genetic mother to the child but not an environmental mother (Silberg & Eaves, 2004). Thus, if an MZ mother–son correlation is larger than its companion MZ aunt–nephew correlation, this provides evidence that environmental mothering influences children, over and above genes. Such research is underway (D'Onofrio et al., 2003; Silberg, 2002).

As a final design, researchers can study MZ twin children to test whether differences between siblings' exposure to bad parenting makes them different on aggression. The fact that MZ twins are not perfectly concordant for aggression opens a window of opportunity to examine whether a nongenetic cause specific to one twin has produced the behavioral difference. A number of studies have tested whether differential parental treatment can account for antisocial behavior differences between siblings and cousins within a family (e.g., Conger & Conger, 1994; Reiss et al., 2000; Rodgers, Rowe, & Li, 1994). Most of these studies have already been reviewed by Turkheimer and Waldron (2000). However, comparing the parenting experiences of discordant MZ twins allows the least ambiguous interpretation of results. Three studies have reported that MZ-twin differences in bad parenting are correlated with MZ-twin differences in antisocial behavior (Asbury, Dunn, Pike, & Plomin, 2003; Caspi et al., 2004; Pike, Reiss, Hetherington, & Plomin, 1996).

The E-Risk study reported that within 600 MZ twin pairs, the twin who received relatively more maternal negativity and less maternal warmth developed more antisocial behavior problems (Caspi et al., 2004). Negativity and warmth were measured by coding voice tone and speech content in mothers' audiotaped speech about each of their twins separately, according to the "expressed emotion" paradigm. This study provided evidence that the effect of mothers' emotional treatment of children causes

aggression by ruling out five alternative explanations of the finding. First, using MZ twin pairs ruled out the possibility that a genetically transmitted liability explained both the mother's emotion and her child's antisocial behavior. Second, using MZ twins also ruled out the possibility that a genetic child effect provoking maternal emotion accounted for the finding. Third, the study included a longitudinal natural experiment to rule out the possibility that any nongenetic child effect accounted for the finding by controlling for prior child behavior that could have provoked maternal negative emotion; individual children whose mothers were negative toward them at age 5 evidenced a subsequent increase of antisocial behavior between ages 5 and 7. Fourth, the study controlled for twin differences in birth weight in an effort to rule out the possibility that twins with neurodevelopmental difficulties had more behavior problems that elicited more negative emotion from mothers. Fifth, the study measured the children's behavior using teacher reports to rule out the possibility that a mother's negativity toward a child led her to exaggerate her report of the child's behavior problems. Effect sizes for the influence of maternal emotion on children's aggression ranged from large (r = .53) to small (r = .10), depending on the number of controls that were applied.

Not all tests of putative environmental risk factors confirm environmental effects. Lest readers assume that application of behavioral–genetic methods to a putative environmental risk factor will necessarily affirm environmental mediation, it is useful to mention that some known risk factors do not appear to be causal. First, as noted above, children's genes accounted for virtually all of the association between their corporal punishment (i.e., spanking) and their conduct problems. This indicated a child effect, in which children's bad conduct provokes their parents to use more corporal punishment, rather than the reverse (Jaffee et al., 2004a).

Second, studies have reported that mothers' smoking during pregnancy is correlated with children's conduct problems, but pregnancy smoking is known to be concentrated among mothers who are antisocial, have mental health problems, mate with antisocial men, and rear children in conditions of social deprivation. When the liability for transmission of antisocial behavior from E-Risk parents to children was taken into account through statistical controls for the parents' antisocial behavior, mental health, and social deprivation, even the effect of heavy smoking during pregnancy disappeared (Maughan, Taylor, Caspi, & Moffitt, 2004). Subsequently, this inference received further support in an extended twin-family model (Caspi, 2004). A similar finding was reported by Silberg et al. (2003). These studies suggest that although pregnancy smoking undoubtedly has undesirable effects on outcomes such as infant birth weight, it is probably not a cause of conduct problems.

A third finding of nil environmental influence concerned father absence. In families having absent fathers, the children are known to have more conduct problems. However, absent fathers are more antisocial on average than fathers who stay with their children, and antisocial behavior can be genetically transmitted. When parents' antisocial history was controlled for, the association between father absence versus presence and children's conduct problems disappeared. This finding also held in an extended twin-family model (Caspi, 2004). This work suggests that father absence is not a cause of conduct problems but rather is a proxy indicator for familial antisocial liability (Jaffee et al., 2003).

What research is needed? To date, Question 5, "Does bad parenting have an environmentally mediated effect on children's aggression?" has been answered in the affirmative by reports from several twin samples, finding such effects for, for example, family adaptability, parent–child conflict, bad fathering, maternal depression, physical maltreatment, and mothers' negative expressed emotions. However, these studies share two Achilles' heels: First, because different forms of parenting risk are concentrated in the same families, the particular parenting measure targeted in a study reviewed here may be a proxy for some other, correlated type of parenting. Research is needed that isolates the effects of one risk factor from its correlates. Second, the findings came from twin studies, and it is reasonable to ask whether such studies can provide a fair assessment of environmental effects. In twin studies, estimates of genetic influence could be biased upward and environmental effects biased downward if the equal environments assumption were violated (Kendler et al., 1994). However, the opposite bias could be produced by parental assortative mating, prenatal factors affecting intrauterine growth, and inactivation of genes on one of each girl's two X chromosomes (Galbaud du Fort, Boothroyd, Bland, Newman, & Kakuma, 2002; Jorgensen et al., 1992; Krueger, Moffitt, Caspi, Bleske, & Silva, 1998; Rutter, 2002). It has been suggested that any bias arising from these factors is likely to be very small, and they bias heritability upward as often as they bias it downward, perhaps canceling each other out (Miles & Carey, 1997; Rutter, 2002). The bottom line is that it is important for tests of environmental risk to exploit a variety of designs and not rely on twins alone.

All of the studies testing measured environmental variables were conducted very recently, illustrating that such testing is a new direction in behavioral–genetic research (Dick & Rose, 2002; Kendler, 2001). In keeping with this article's focus, I reviewed only studies measuring examples of "bad parenting," but the methods illustrated here can be applied to any known risk factor for antisocial behavior, ranging from neighborhood deprivation (Cleveland, 2003), to school classmates' behavior (Rose et al., 2003), to child sexual abuse (Dinwiddie et al., 2000). The choice of the construct bad parenting allowed me to cover the majority of studies published to date that have looked at measured risk factors for antisocial behavior using genetically sensitive designs. This small set of studies signals a research initiative that will grow to encompass environmental factors ranging from prenatal teratogens to prison sanctioning of adult offenders.

The environmental effects reported in studies that ruled out alternative explanations were uniformly small. It may surprise some to learn that when familial liability and child effects are controlled, parents' influences on children drop to small effect sizes. However, small effects ought to be expected, for three reasons. First, it must be remembered that these small effects reflect true environmental associations after they have been purged of the confounding influences that inflate effect sizes in nongenetic studies. Associations between risk factors and behavior outcomes tend to shrink by at least half when genetic confounds are controlled (Turkheimer & Waldron, 2000). This shrinkage suggests that the risk–outcome correlations that social scientists are accustomed to seeing are inflated to about double their true size. Second, small effects for any particular risk factor make sense, in view of evidence that clear risk for antisocial behavior accrues only when a person accumulates a large number of risks (Rutter, Giller, &

Hagell, 1998), each of which may individually have only a small effect (Daniels & Plomin, 1985). A third reason why small effects should not be too surprising is that they represent the main effects of measured environments apart from any environmental effects involved in gene–environment interactions. However, genetic risk and bad parenting are not usually disentangled in real life as they are in behavioral–genetic studies. In ordinary lives, genetic and environmental risks often coincide. It is possible in theory that environmental effects conditional on genetic vulnerability could be quite large. I next turn to the question of Gene × Environment interactions influencing antisocial behavior.

Testing the Hypothesis of Interaction Between Genes and Environments

The study of gene–environment interaction (G × E) entails substantial methodological challenges. It requires measured environments that are truly environmental, measured genetic influence, some means of separating them from each other, and enough statistical power for a sensitive test of interaction (Rutter & Silberg, 2002). Despite the challenges, theory-driven hypotheses of G × E interaction are well worth testing, because where measured G × E interactions are found to influence behavior disorders, both specific genes and specific environmental risks can conceivably have moderate to large effects, as opposed to the very small effects expected from prior quantitative genetic research. Specific genes revealed to be stronger in the presence of environmental risk would guide strategic research on those genes' expression, possibly leading to genetic diagnostics and improved pharmacological interventions (Evans & Relling, 1999). Specific environmental effects revealed to be stronger in the presence of genetic risk would prompt a new impetus for specific environmental prevention efforts and would help identify who needs the prevention programs most. The study of G × E is especially exciting in antisocial behavior research, where investigations have pioneered the way. Studies of antisocial behavior were first to report evidence of interaction between latent, anonymous genetic risk and latent environmental risk, as ascertained in adoption studies, and also first to report evidence of an interaction between a measured genetic polymorphism and a measured environmental risk. Four research designs have been used.

Adoption Studies of Latent G × E

The first suggestion that genetic and environmental risks might interact to influence antisocial behavior came from studies of Danish, U.S., and Swedish adoption registers (Cadoret, Cain, & Crowe, 1983; Cloninger, Sigvardsson, Bohman, & von Knorring, 1982; Mednick & Christiansen, 1977). The findings did not represent statistically significant cross-over interaction terms, but they did illustrate clearly that the effects of genetic and environmental risk acting together were greater than the effects of either factor acting alone.

Adoption Studies of Latent G × Measured E

In a pool of 500 adoptees from the Iowa and Missouri adoption studies, adoptees had the most elevated antisocial behaviors when they experienced adverse circumstances in their adoptive homes in addition to having birth mothers with antisocial personality problems or alcoholism (Cadoret et al., 1983). This landmark study documented that the interaction was statistically significant and replicated across two independent samples. This finding was replicated and extended in another Iowa adoption cohort of 200 families (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995). Adoptive parents' adversity was defined according to the presence of marital problems, legal problems, substance abuse, or mental disorder, and it interacted significantly with biological parents' antisocial personality disorder to predict elevated rates of childhood aggression, adolescent aggression, and diagnosed conduct disorder in the adoptees. This same Iowa adoption study was creatively analyzed to demonstrate that adversity in the adoptive home can moderate the genetic child effect in which children's aggression provokes bad parenting (Riggins-Caspers et al., 2003). Adoptees' genetic liability for antisocial behavior (defined as biological parents' psychopathology) provoked more harsh discipline from the adoptive parents in homes where the adoptive parents suffered adversity (marital, legal, substance or psychopathology problems). There is one problem with studying G × E in adoption designs, and that is that adoption itself breaks up the naturally occurring processes of rGE that characterize the nonadopted majority population, thereby precluding the possibility of natural G × E. This separation allows the empirical study of G × E, but paradoxically probably results in an underestimate of the influence of G × E on antisocial outcomes in the general population. For this reason, adoption G × E studies should be complemented with twin studies.

A Twin Study of Latent G × Measured E

The E-Risk twin study also yielded evidence that genetic and environmental risks interact (Jaffee et al., 2005). Because it was previously established that conduct problems were highly heritable in the E-Risk twin sample at age 5 years (Arseneault et al., 2003), each child's personal genetic risk for conduct problems could be estimated by considering whether his or her co-twin had already been diagnosed with conduct disorder and whether he or she shared 100% versus 50% of genes with that diagnosed co-twin. This method's usefulness was demonstrated previously in a landmark G × E study showing that the risk of depression following life-event stress depends on genetic vulnerability (Kendler et al., 1995). For example, an individual's genetic risk is highest if his or her co-twin sibling already has a diagnosis of disorder and the pair is monozygotic. Likewise, an individual's genetic risk is lowest if his or her co-twin has been free from disorder and the pair is monozygotic. Individuals in dizygotic twin pairs fall between the high- and low-genetic-risk groups. In this study, an interaction was obtained such that the effect of maltreatment on conduct problem symptoms was significantly stronger among children at high genetic risk than among children at low genetic risk. (Because there was no genetic child effect provoking maltreatment, the genetic risk groups did not differ on concordance for maltreatment or the severity of maltreatment). In addition, the experience of maltreatment was associated with an increase of 24% in the probability of diagnosable conduct disorder among children at high genetic risk but an increase of only 2% among children at low risk.

Studies of Measured G × Measured E; Testing a Measured Gene

The aforementioned adoption and twin studies established that genotype does interact with bad parenting in the etiological processes leading to antisocial behavior. However, the studies did not implicate any particular genes. One study tested the hypothesis of G × E using a measured environmental risk, child maltreatment, and an identified gene, monoamine oxidase A (MAOA) promoter polymorphism (Caspi et al., 2002). The MAOA gene was selected as the candidate gene for four reasons (supporting research is cited in Caspi et al., 2002). First, the gene encodes the MAOA enzyme, which metabolizes the neurotransmitters linked with maltreatment victimization and aggressive behavior by previous research. Second, drugs inhibiting the action of the MAOA enzyme have been shown to prevent animals from habituating to chronic stressors analogous to maltreatment and to dispose animals toward hyperreactivity to threat. Third, in studies of mice having the MAOA gene deleted, increased levels of neurotransmitters and aggressive behavior were observed, and aggression was normalized by restoring MAOA gene expression. Fourth, an extremely rare mutation causing a null allele at the MAOA locus was associated with aggression among men in a Dutch family pedigree, although no relation between MAOA genotype and aggression was detected in the general population.

The decision to select maltreatment for this study was made for four reasons (supporting research is cited in Caspi et al., 2002). First, childhood maltreatment is a known predictor of antisocial outcomes. Second, not all maltreated children become antisocial, suggesting that vulnerability to maltreatment is influenced by heretofore unstudied individual characteristics. Third, the abovementioned twin research established that maltreatment's effect on children's aggression is environmentally mediated, that is, the association is not an artifact of a genetic child effect provoking maltreatment or of transmission of aggression-prone genes from parents. As such, maltreatment can serve as the environmental variable in a test of G × E. Fourth, research suggests that maltreatment in early life alters neurotransmitter systems in ways that can persist into adulthood and can influence aggressive behavior.

On the basis of this logic to support the hypothesis of G × E, childhood maltreatment history (8% severe, 28% probable, 64% not maltreated) and MAOA genotype (37% low-activity risk allele, 63% high-activity allele) were measured in the 442 Caucasian male participants of the longitudinal Dunedin Multidisciplinary Health and Development Study. Maltreatment history and genotype interacted to predict four different measures of antisocial outcome: an adolescent diagnosis of conduct disorder, personality assessment of aggression at 26 years of age, symptoms of adult antisocial personality disorder reported by informants who knew the study members well, and court conviction for violent crime up to age 26, the latest age of follow-up. Among boys having the combination of the low-MAOA-activity allele and severe maltreatment, 85% developed some form of antisocial outcome. Male participants having the combination of the low-activity allele and severe-to-probable maltreatment constituted only 12% of the male birth cohort but accounted for 44% of the cohort's violent convictions because they offended at a higher rate on average than other violent offenders in the cohort.

Replication of this study was of utmost importance, because the study reported the first instance of interaction between a measured gene and a measured environment in the behavioral sciences and because reports of connections between measured genes and disorders are notorious for their poor replication record (Hamer, 2002). One initial positive replication, and extension, has emerged from the Virginia Twin Study for Adolescent Behavioral Development (Foley et al., 2004). This team studied 514 Caucasian male twins and measured environmental risk with an adversity index composed of parental neglect, interparental violence, and inconsistent discipline. MAOA genotype and adversity interacted significantly such that 15% of boys having adversity and the high-MAOA-activity allele developed conduct disorder, in comparison with 35% of boys having adversity plus the low-activity allele. This study went a step further, controlling for maternal antisocial personality disorder to rule out the possibility that passive rGE might have resulted in the co-occurrence of environmental and genetic risk. This study thus replicated the original G × E, extended it to other forms of parental treatment, and showed that it is not an artifact of passive rGE.

Research Implications of the Nil Main Effect of the MAOA Polymorphism on Behavior

One important finding from these two studies of a measured gene was that, in contrast to the G × E interaction's marked effects on antisocial outcomes, the unique effects of the MAOA polymorphism apart from its role in the G × E interaction were virtually nil. The MAOA genotype was statistically unrelated to antisocial outcomes in the full cohorts, its effects were revealed only in the presence of maltreatment or adversity. Moreover, this pattern of a significant G × E in the presence of an initial nil main effect of the measured gene has now emerged from a number of other G × E studies (Moffitt, Caspi, & Rutter, 2005). This pattern of nil main effects for measured genes appears to be widespread and, if this is the case, has an implication for gene hunters: Gene-to-disorder connections may be diluted across all the individuals in a sample if the connection is apparent only among individuals exposed to specific environmental risks.

The expectation that simple direct paths will be found from gene to disease has not proved fruitful for complex psychiatric disorders (Hamer, 2002). The MAOA G × E finding suggests three possibilities for future genetics research. First, a major source of error in linkage pedigrees, incomplete gene penetrance, could occur if a gene's effects are expressed only among family members exposed to environmental risk. Linkage studies should ascertain pedigree members' environmental risk exposure. Second, candidate gene studies will not replicate each other if G × E is operating and there are differences between research samples on risk exposure. Where possible, candidate-gene association studies should measure and take into account participants' environmental risk exposure. Third, most psychiatric genetics research, including genome-wide scans, aims to identify genes having main effects (i.e., to find genes that show associations with behavior irrespective of the environment), but this main effects approach will not be efficient for detecting genes whose effects are conditional on environmental risk. (Interactions are independent of main effects, so main effects of risk factors are not a prerequisite for interactions between them.) Genome-wide scans might be more powerful if gene-hunters de-

liberately recruit samples selected for known exposure to environmental risks for the disorder they wish to study.

Genes as Protective Factors Promoting Resilience

An intriguing finding from the two MAOA G × E studies was that, in contrast to the G × E interaction's marked effects on antisocial outcomes, the unique effects of maltreatment apart from its role in the G × E interaction were very modest. Maltreatment initially predicted antisocial outcomes in the full cohorts, but within the high-MAOA-activity genotype group its effects were reduced by more than half (Caspi et al., 2002; Foley et al., 2004). This pattern is in keeping with the findings from relevant adoption and twin studies, all of which found that measured bad parenting had relatively little effect on children who were at low genetic risk (Cadoret et al., 1983, 1995; Cloninger et al., 1982; Jaffee et al., in press; Mednick, Gabrielli, & Hutchings, 1984). Taken together, these findings suggest the novel notion that genotype can be a protective factor against adversity. Some people respond poorly to adversity whereas others are resilient to it, and the reason for this variation has been a holy grail of developmental research. The search for sources of resilience has tended to focus on social experiences thought to protect children, overlooking a potential protective role of genes. The E-Risk twin study asked whether genes influenced children's resilience against the detrimental effects of socioeconomic deprivation (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). Resilience was defined in terms of children who developed fewer conduct problems than expected on the basis of the level of socioeconomic deprivation their family suffered. MZ twins were more alike on resilience than DZ twins ($r = .72$ vs. .26), and model fitting revealed that genetic influences explained 71% of the variation in resilient status in the E-Risk cohort. The potential protective effect of genes deserves more attention (Insel & Collins, 2003).

Strategy for Future G × E Studies Using Measured Genes

In the future, many more tests for G × E are likely to be developed using measured genes and measured environments. There are statistical models to test for G × E variance components (Andrieu & Goldstein, 1998; Eaves & Erkanli, 2003; Purcell, 2002), but such unspecified "black box" variance components do not go as far toward informing diagnostic and therapeutic research and development as do findings about measured variables. This difference arises because quantitative analyses yield population statistics, whereas studies of measured genes yield information about specific genotypes. What is needed is careful, deliberate, theory-guided G × E hypothesis testing of plausible triads of a genetic polymorphism, an environmental risk, and a behavioral phenotype (Moffitt et al., 2005). Toward this aim, this section briefly enumerates strategic steps for G × E tests using measured variables.

Step 1 is to consult quantitative genetic models of the behavior in question derived from twin and adoption research. The estimate of genetic influence (i.e., the A term) in part represents gene–environment interplay, as does the estimate of unique environmental influence (i.e., the E term; Purcell, 2002). Moderate to large quantitative estimates of A and E encourage hypotheses about potential G × E interaction effects.

Step 2 is to identify candidate environmental risks for the behavior in question. It is necessary to glean from the literature the candidate environmental risk factors having the strongest predictive efficacy. Fortunately for the study of antisocial behavior, a large pool of candidate environmental risk factors is available (Loeber & Farrington, 1998). The best candidate environmental risks are those having evidence of a plausible effect on biological systems involved in psychopathology; maltreatment, for example, fills this requirement (DeBellis, 2001). Once candidate risks have been identified, it is important to go a step further to test whether each candidate risk factor has effects that are actually environmentally mediated. Why must G × E researchers prove environmental mediation? If an alleged environmental risk factor's association with psychopathology is wholly genetically mediated, then a putative G × E is really only an interaction between one specific gene and other unidentified genes. That could be interesting in itself, but it would lack the implications of a G × E finding.

Step 3 is to measure the environmental risk as well as possible. Measuring environmental risk exposure precisely and reliably can be costly, but simulations show that reliable risk measurement can substantially enhance power to detect G × E, thus reducing the need for large samples (Luan, Wong, Day, & Wareham, 2001; Wong, Day, Luan, & Wareham, 2003).

Step 4 is to identify candidate susceptibility genes for a G × E hypothesis. I resisted the temptation to name candidate genes associated with antisocial behavior in this article, because gene detection advances so rapidly that any list made now will be outdated shortly; by the time the article comes to press, today's list would feature disappointing replication failures and omit newly found hot possibilities (Insel & Collins, 2003). I can, however, propose three guidelines for choosing which candidate genes are best for a G × E hypothesis, as new possibilities emerge. First, good candidate genes for G × E will be those whose polymorphic variants are relatively common in the population. If a potentially damaging variant is maintained at a high prevalence rate, this might imply (but certainly does not guarantee) that natural selection has not eliminated the variant because it is only expressed under particular environmental conditions or perhaps because it confers advantage under particular conditions (Hill, 1999; Searle & Blackwell, 1999). As a second guideline for gene selection, if the gene has already been shown to have a replicated main effect association with the psychiatric disorder, it will be an easy candidate choice. However, it is important to appreciate that the endeavor cannot rely on such rare replicated main effect associations, because of the following paradox: Logically, if a gene's effects are conditional on the environment, this has the natural consequence of diminishing the capacity to detect a main effect! As a final guideline for Step 4, the soundest logical basis for selecting a candidate gene for G × E is evidence that the gene is related not to a disorder but rather to organisms' responses to environmental risk. This evidence is necessary to frame a biologically plausible hypothesis that the gene moderates responses to an environmental risk (i.e., G × E). As one example, the serotonin transporter polymorphism (5-HTTLPR) is a good candidate for G × E research into psychopathology (Caspi et al., 2003) because its two variants have been shown to affect physiological responsiveness to stressful environmental conditions in three experimental para-

digms, including knockout mice (Murphy et al., 2001), stress-reared rhesus macaques (Bennett et al., 2002), and a human functional neuro-imaging paradigm (Hariri et al., 2002). Experimental assignment of subjects to environmental risk is an advantage because it rules out the possibility of any confounding gene–environment correlation. I hope for a new wave of experimental investigations examining whether genotype influences responsiveness to emotion-eliciting stimuli or laboratory stress paradigms. These studies will use psychophysiological phenotypes in G × E experimental designs, such as electrodermal reactivity or reactivity of the brain as measured by the electroencephalograph and functional neuro-imaging tools. The results of such studies will provide an evidence base for nominating gene candidates in G × E hypotheses. Until now, researchers have put most of their efforts into the search for direct connections between genes and disorders, whereas the search is only beginning for connections between genes and responsiveness to stress or other environmental risk factors (cf. Kaiser, 2003, for a major research initiative on genetic variability in response to environmental chemical toxins).

Step 5 is to test for an interaction between the candidate gene and the environmental risk factor. The most informative design begins with a representative population-based cohort. For example, in the case of dichotomous genotypic and environmental variables, groups would include the following: (a) low genotypic- and environmental risk to establish the baseline level of psychopathology associated with factors apart from the hypothesis, (b) high-genotypic but low environmental risk to ascertain any effect of the gene in isolation, (c) high environmental but low genotypic risk to ascertain any effect of risk environment in isolation, and (d) high genotypic and environmental risk to ascertain whether their joint association with psychopathology is additive or interactive (for more discussion of design issues and statistical approaches see Moffitt et al., 2005; Ottman, 1990; van Os & Sham, 2003; Yang & Khoury, 1997). Cohort designs allow researchers not only to report statistical significance but to characterize the size of the G × E effect in the population as well, which is prerequisite for evaluating the potential clinical validity and utility of a finding.

Step 6 ensues if and only if the hypothesized G × E interaction is obtained. Step 6 is to evaluate whether the resulting associations (a) show specificity to the initially hypothesized triad of gene, environmental risk factor, and disorder or (b) extend beyond that triad. Work at this step systematically ascertains whether the interaction holds when the gene is replaced with other relevant candidate genes, when the environmental risk is replaced with the disorders' other risk factors, and when the disorder is replaced with other related disorder phenotypes. Whereas it is vital to frame a specific hypothesis of G × E prior to analyzing any data, once an initial hypothesis has been tested in the affirmative, it is also responsible scientific practice to ascertain how far beyond the original hypothesis the G × E may extend (Licinio, 2003).

Step 7 is replication, which is particularly vital because of the known difficulty of detecting interaction terms between any two factors, including genes.

A finding of G × E is too crude to be an answer in and of itself; rather, it is interesting because it brings up new questions. A G × E interaction's main value lies in revealing much stronger connections with a behavioral disorder than anyone previously thought. Knowledge that a genetic polymorphism has strong connections with a disorder kick-starts a fresh round of experimental work into what the polymorphism does, its relations with surrounding parts of the gene and with adjacent genes, its place in multi-gene causal systems, the conditions surrounding its expression, and why it is associated with responsiveness to the environmental risk factor. Likewise, knowledge that an environmental risk factor has stronger connections with a disorder among a biologically vulnerable subgroup ought to kick-start new research into what brain mechanisms convert environmental experiences into the symptoms of psychopathology. Applied research might address the relevance of the G × E for clinical diagnostics and therapeutics. The 2002 report that maltreatment and the MAOA polymorphism interacted to predict antisocial outcomes stimulated investigations in ethics, law, and even theology (e.g., Nuffield Council on Bioethics, 2002; Peters, 2003; Ross & Shestowsky, 2003; Sankar, 2003; Stone, 2003).

The Way Forward to Studying Gene–Environment Interplay in Psychopathology

This article reviewed new work to show how behavioral–genetic studies are documenting that many putative environmental risk factors do have environmentally mediated effects on antisocial behavior and that some of these risk factors interact with genetic vulnerability. The sum total of such studies is fewer than 20 publications and, thus far, only one measured gene has been studied. Obviously this work is in its infancy. This section offers rationales focusing future research on the interplay between environments and genes.

1. Main effects of G and E are small, but effects in G × E interactions are bigger. The residual main effects of environmental risk factors appear small after controlling for genetic transmission and child effects. However, emerging evidence about gene–environment interactions suggests that environmental risks can affect people more strongly than previously appreciated, within genetically vulnerable segments of the population. Parallel to this, genetic association studies reveal only small or nil main effects of measured genes on behavior, but G × E studies suggest that potentiated effects of genes can be larger when interacting with environmental risk exposure. Thus, the question is reframed from "Are there causal effects?" to "Who is at greatest risk?"

2. Gene–environment interplay has real-world authenticity. Genetic and environmental risks for psychopathology often coincide in the same families and are concentrated together in the same segment of the population, specifically, the segment where psychopathology outcomes also concentrate. Because of this demographic fact, studies of developmental processes originating where genetic and environmental risks coincide are the most relevant for prevention, and findings from such studies will generalize to real-world circumstances where interventionists usually find their clients.

3. Longitudinal gene–environment research could solve the riddle of continuity. Although genes bring children into contact with environmental risk via processes of passive and active gene–environment correlation, once contact is made, it is reasonable to expect the environment to have consequences of its own, cutting off opportunities to develop healthy behaviors, promoting the persistence of pathological behavior, and exacerbating its seriousness. The remarkable continuity of antisocial behavior has been attributed to such "cascade" processes (Caspi & Moffitt, 1995), but

the empirical evidence is sparse. More psychopathology research integrating behavioral–genetic samples and longitudinal methodology are needed.

4. Gene–environment studies should address the most potent risk factors for pathological behavior. Much of the behavioral–genetic research to date has studied environments in the normal range and samples in the normal range. But there were hints in this review that causal environmental effects might emerge if factors outside the normal range are studied, such as poverty, child neglect and abuse, or exposure to domestic violence. Gene–environment interplay research should address forms of risk known to predict serious, recurrent, and persistent forms of psychopathology. Moreover, it is not good enough to include a measure of serious risk in a study unless the sample includes families who can be scored at the serious extreme on the measure. Recruitment and retention of genetically informative samples that accurately represent the whole population is vital.

5. Gene–environment interplay research is valuable outside the family crucible at every point in the life course. This article highlighted studies of bad parenting and children's aggression because thus far that is where the research is. If the aim is to explain the etiology of serious and persistent antisocial behavior, then the focus on childhood and the family environment is appropriate, because that is when and where life-course persistent behavior begins. However, gene–environment interplay research ought to embrace other risk factors, in other age periods. As an example, gene–environment interplay research into the role of peers in adolescent antisocial behavior is underway (e.g., Carey, 1992; Iervolino et al., 2002; Plomin, 1994; Rose et al., 2003; Rowe, 1985; Rowe & Osgood, 1984; Rowe, Rodgers, & Meseck-Bushey, 1992).

6. Gene–environment interplay and endophenotypes for antisocial behavior. Crime is not inherited, so what is? Endophenotypes are phenotypic traits or markers thought to represent biological systems underlying a behavioral disorder and are assumed to be under greater genetic influence than the disorder itself (Gottesman & Gould, 2003). For some disorders such as schizophrenia and autism, attention is shifting from the search for connections between genes and the disorder to the search for connections between genes and endophenotypes, such as eye tracking or working memory. This shift offers statistical advantages because endophenotypes are generally better distributed than disorders, and they can be studied in nonpatients. However, the promise of endophenotypes must be tempered by cautions that each underlying biological variable is as likely to be a consequence as a cause and may well be subject to the same gene–environment interplay processes as are disorders themselves (as opposed to representing a purer genetic etiology). That said, endophenotype studies might illuminate how genes increase the probability that people will commit antisocial acts because "notions such as genes for crime are nonsense" (Gottesman, Goldsmith, & Carey, 1997, pp. 117). One edited volume suggested a starting list of endophenotypes for antisocial behavior: sensation seeking; overactivity; fearlessness; low self-control; negative emotionality; callous, unemotional style; weak verbal ability; poor memory; executive dysfunction; frontal lobe hypoarousal; serotonergic dysfunction; testosterone imbalance; and even large toddler body mass index (Lahey et al., 2003). Bringing these traits into research on gene–environment interplay involves several steps. First, such traits can be examined in quantitative twin studies to ascertain whether they are under genetic influence. Second, an endophenotype can be entered with antisocial behavior into a quantitative bivariate model to determine how much of the correlation between endophenotype and disorder arises from genes predisposing to both. Third, traditional mediation models can determine whether the endophenotype mediates the pathway between measured genes and antisocial outcomes.

7. Epigenetic processes as outcome variables in gene–environment interplay. A colleague recently remarked that it must be satisfying to study a measured gene because one can be certain that a gene is a root cause, given that it is present from conception. However, it bears highlighting here that in future work on gene–environment interplay, the proverbial causal arrow will point toward genes as well as away from them. The relatively new science of epigenetic processes is revealing how environments can affect genes' capacity to influence phenotypes (Pray, 2004). Theorists are putting forward conceptualizations of genes as mediating variables that carry out developmental processes (Belsky, 1997; Gottlieb, 2003) or as dependent variables "switched on or off" by nongenetic influences (Johnston & Edwards, 2002; Ridley, 2003). For example, compelling experiments are beginning to suggest that variation in the quality of parental care can alter gene expression in offspring (Meaney, 2001). Considering gene function as an outcome variable represents a paradigm shift in the way behavioral science views genes and offers exciting opportunity for the gene–environment interplay research of the future.

8. Quantitative twin and adoption studies will play an important role in the study of gene–environment interplay. In the aftermath of the announcement that the human genome had been solved, many pundits speculated that the need for quantitative behavioral–genetic twin and adoption studies had ended (but see Plomin, DeFries, Craig, & McGuffin, 2003). To the contrary, this article has spelled out many essential roles for quantitative analyses, even as researchers work more with measured genes. Quantitative studies will be needed to inform decisions about which phenotypes are strong candidates for molecular studies. Designs that can control for genetic influence will be essential for showing whether a putative environmental variable can serve as a bona fide "E" in $G \times E$ hypotheses. Bivariate quantitative models will be needed to ascertain which alleged endophenotypes are associated with disorder phenotypes for genetic reasons and whether an endophenotype is under greater genetic control than the disorder it predicts. Traditional quantitative designs will have applications beyond quantitative variance estimates. DZ twins are ideal for testing whether polymorphic allelic differences can explain behavioral differences between siblings matched for age, sex, ethnic background, and rearing experiences. Discordant MZ twins are ideal for studying variation in gene expression in patients versus nonpatients, matched for genotype. Twin and adoption designs are likely to prove very useful for a long time.

9. Mouse and other animal models should become more important in the study of gene–environment interplay. Nonhuman animal models of behavioral disorders offer undeniable scientific advantages, but the world of animal research has remained somewhat apart from the world of psychological research into human psychopathology, primarily as a result of skepticism about the validity of animal models for human mental disorders. However, animal models of disorders are not necessary for making a contribution to future gene–environment research. Instead, there is huge

potential for developing new animal models of environmental risk mechanisms (Maxson, 2000; Suomi, in press). Once a G × E interaction is discovered in humans, clarifying the mechanisms behind it requires experimental inducement of environmental risk exposure, studies of the consequences for gene expression in brain tissue, and experimental manipulation of the genome (Crabbe, 2003; Flint, 2003; Francis, Insel, Szegda, Campbell, & Martin, 2003). Such manipulations cannot be accomplished with humans, but analogues are available, particularly in mice (Tecott & Wehner, 2001). Animal models of environmental risk will prove to be invaluable tools for unpacking many elements of gene–environment interplay.

10. Gene–environment interplay research requires social and behavioral scientists as well as geneticists. A focus on gene–environment interplay will bring about a stimulating multidisciplinary fusion between experts in genetics and experts in nongenetic risk factors for pathological behavior. Experts in child and family development, clinical psychologists, epidemiologists, sociologists, and criminologists have knowledge that is vital to the success of the enterprise; they know which risk factors are relevant and how to measure them well. The Website of the American Psychological Association (2003) gives information about training opportunities in genetics for psychologists: http://www.apa.org/science/genetics/teaching.html

11. Gene intervention interplay? Interventions are environments, and true randomized intervention trials are environments disentangled from any control by genetic influence. As such, harnessing interventions brings the power of experimental manipulation to the study of human G × E. Do individuals having particular genotypes respond better than others to psychosocial interventions? This research is the focus of pharmaco-genetics, which explores genetic individuality in drug response to improve the efficacy and safety of prescribing (Evans & Relling, 1999; Wolf, Smith, & Smith, 2000). Given the known genetic influence on antisocial behavior, how far can interventions go to prevent the expression of genetic risk; just how powerful can the environment be when it is under deliberate control? Integrating prevention research and behavioral–genetic research offers unprecedented opportunities to test etiological theories (Howe, Reiss, & Yuh, 2002).

Behavioral genetics has a new look. It is working hard to integrate with the wider research agenda on abnormal behaviors and is expanding the agenda to embrace gene–environment interplay. The results thus far look very promising for antisocial behavior, where gene–environment studies are well underway. The same agenda can be applied to other abnormal behaviors, and I look forward to seeing the results.

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