# *Nature-Nurture Interplay*

## *Genetically Informative Designs Contribute to Understanding the Effects of Trauma and Interpersonal Violence*

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*The past two decades have seen an explosion in research in the fields of violence and trauma and behavior genetics. These two fields came into direct conflict when Lisabeth Fisher DiLalla and Irving I. Gottesman outlined a fundamental conceptual limitation of trauma and violence research: that rather than being causal, the well-documented relationship between exposure to trauma or violence and later negative outcomes could be explained by gene-environment correlation. In the past decade, researchers have addressed this limitation by studying the effects of trauma and violence using genetically informative designs. This report briefly discusses the gains made from this research approach and the promising future for genetically informative trauma and violence research.*

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### WHAT IS THE MOST IMPORTANT THING WE HAVE LEARNED ABOUT VIOLENCE AND TRAUMA IN THE PAST 20 YEARS?

The past two decades have seen an explosion in research in two fields—violence and trauma and behavior genetics. These fields came into direct conflict in the early 1990s when two behavior geneticists, Lisabeth Fisher DiLalla and Irving I. Gottesman (1991), wrote a response to an article by Cathy Spatz Widom (1989) that had critically examined the evidence for the "cycle of violence hypothesis," the widely held proposition that abused children become antisocial, violent adults. DiLalla and Gottesman (1991) argued that Widom's (1989) otherwise insightful and thorough review had over-

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looked a critical mechanism in the cycle of violence: that antisocial parents genetically transmit antisocial tendencies to their children.

DiLalla and Gottesman's critique outlined a fundamental conceptual limitation of trauma and violence research—that the association between exposure to trauma or violence and later negative outcomes had been assumed to be environmentally mediated (i.e., adult antisocial behavior is caused by exposure to child abuse). They specifically made the case that it is incorrect to presume that the correlation between child abuse and antisocial behavior indicates causation, because another variable may explain the association: children exposed to trauma may be at genetic risk for antisociality. Parental antisocial behavior prospectively predicts abuse of offspring and offspring antisocial behavior (e.g., Moffitt, Caspi, Harrington, & Milne, 2002). Antisocial behavior is moderately heritable (Rhee & Waldman, 2002). Thus, antisocial parents are more likely to abuse their children and also to transmit increased genetic risk for antisocial behavior. This tendency for children to inherit family environments that are correlated with their genetic propensities is referred to as a gene-environment correlation (Plomin, DeFries, & Loehlin, 1977). DiLalla and Gottesman's (1991) critique was part of a larger movement in the field of behavior genetics demonstrating that individual differences in environmental experiences are influenced by genetic propensities.

DiLalla and Gottesman's (1991) critique challenged trauma and violence researchers to show that the association between trauma and violence exposure and adverse outcomes was a causal, environmentally mediated effect and not merely a function of gene-environment correlation. The hypothesis that trauma or violence causes an adverse outcome could be tested by experimental studies exposing individuals to trauma or violence (which are unethical) or by longitudinal studies giving outcome assessments before and after exposure to trauma or violence to assess within-individual change (which are impractical). This causal hypothesis can also be tested via a twin design (Rutter, Pickles, Murray, & Eaves, 2001). Twin studies offer a natural experiment that can test whether trauma or violence has an environmentally mediated effect on outcomes. Specifically, two types of twin studies have been used in this manner: the co-twin control design and the extended classical twin design.

The co-twin control design examines the relationship between a traumatic event, such as childhood sexual abuse, and an outcome, such as substance abuse by selecting monozygotic (MZ) or identical twin pairs discordant for traumatic exposure. MZ twins share 100% of their genes and 100% of the family-wide or shared environment; therefore, any difference between MZ twins must be due to nonshared environmental factors uncorrelated between

twins. Thus, the member of an MZ pair who has not been exposed to trauma serves as the control for the trauma-exposed member of the MZ pair. Because MZ twins are genetically identical and share the same family environment, they are therefore matched on a number of important variables that cannot otherwise be controlled. The design also eliminates gene-environment correlation as an explanation for any association between the trauma exposure and adverse outcome. This design was used to support a causal, environmentally mediated relationship between childhood sexual abuse and a wide range of psychopathology and other adverse outcomes (Bulik, Prescott, & Kendler, 2001; Kendler et al., 2000; Nelson et al., 2002).

The classical twin method relies on the different level of genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twin pairs to estimate the contribution of genetic and environmental factors to individual differences in an outcome of interest. Population variance on a behavioral phenotype (e.g., antisocial behavior) may be partitioned into an additive genetic component and two types of environmental components: a shared or family-wide environmental effect that serves to make individuals growing up in the same family similar to each other, and a nonshared environmental effect that is uncorrelated among siblings. In the extension of the classical twin design, researchers have added measured environmental variables (such as neighborhood deprivation, parent-child conflict, and parental separation) to twin models to test the hypothesis that their influence on a phenotype is environmentally mediated (Burt, Krueger, McGue, & Iacono, 2003; Caspi, Taylor, Moffitt, & Plomin, 2000; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Recently, this method has been used to show that childhood physical abuse has an environmentally mediated, causal effect on the development of antisocial behavior (Jaffee, Caspi, Moffitt, & Taylor, 2004).

## WHAT IS THE MOST IMPORTANT THING WE NEED TO LEARN IN THE NEXT 10 YEARS?

By integrating measures of trauma and violence into genetically informative designs, trauma and violence researchers have answered the critique posed by DiLalla and Gottesman (1991) and other behavior geneticists. In the past 10 years, this research has demonstrated that exposure to trauma and violence has a causal, environmentally mediated, adverse effect on risk for outcomes such as antisocial behavior, substance abuse, and a wide range of adult psychopathology. The relationship between trauma and violence and these adverse outcomes is not merely accounted for by gene-environment correlation. In the next 10 years, we need to focus on the interplay between

trauma and violence exposure and genetic variation in the development of psychopathology and other adverse outcomes. Researchers continue to be puzzled about why only some individuals are adversely affected by exposure to trauma or violence. Research on genotype-environment interaction and gene expression may provide a piece of that puzzle.

Work in the trauma and violence field on genotype-environment interaction or "genetic control of sensitivity to the environment" (Kendler & Eaves, 1986) has been pioneered by Avsholam Caspi, Terrie E. Moffitt, and their colleagues (Caspi et al., 2002; Caspi et al., 2003). Using a longitudinal epidemiologic design, they examined the effect of genotype on the well-documented relationship between child maltreatment and adult antisocial behavior. The results replicated the finding that child maltreatment increased risk for adult antisocial behavior. However, the effect of child maltreatment was dependent on genotype. Individuals were at increased risk of developing antisocial behavior only if they had experienced child maltreatment and had a genotype conferring low levels of monoamine-oxidase (MAOA) expression. The presence of either maltreatment or the MAOA low expression genotype did not increase risk of antisocial behavior (Caspi et al., 2002).

Research on genotype-environment interaction will eventually lead to studies of gene expression in humans. Put simply, research on gene expression examines how genes respond to environmental inputs. New methodologies now enable researchers to measure gene expression in animal models. Such research has demonstrated that in rats, environmental factors such as variation in maternal care cause specific genetic changes that can then be inherited (Robinson, 2004). The development of similar technologies in humans will completely reframe our understanding of issues such as the intergenerational transmission of violence.

## WHAT IS THE MOST PROMISING METHODOLOGICAL INNOVATION IN THE PAST 20 YEARS FOR THE STUDY OR TREATMENT OF TRAUMA OR INTERPERSONAL VIOLENCE?

The compelling findings from Caspi et al. (2002; Caspi et al., 2003) are likely to spur a growing number of studies on how trauma and violence interact with genotype to produce adverse outcomes. Such studies will use a candidate gene approach whereby investigators have an a priori reason to hypothesize an interaction between trauma or violence and a specific genetic variant in the etiology of an outcome of interest. Large-scale candidate gene studies have been made possible by methodological innovations allowing for the painless and inexpensive collection of genetic material. DNA can be

extracted from cheek swabs or mouthwash, which makes its collection more feasible and palatable to a wide range of populations including young children. The methods for such DNA collection are straightforward and can be performed by research participants in their homes; materials can then be mailed back to the investigators (Freeman et al., 1997). In addition, extracting DNA from cheek swab or mouthwash samples is relatively inexpensive (about $10-15 per sample), can be stored indefinitely under controlled conditions, and produces adequate amounts of genetic material for most candidate gene studies.

The development of new methodologies will cause the cost of DNA extraction, genotyping, and expression in humans to decline further over the next decade. Such methodological innovations will allow trauma and violence researchers to routinely collect and analyze genetic data. Rather than being in conflict, trauma and violence researchers and behavior geneticists will have the opportunity to collaborate in the larger goal of understanding the complex interplay between trauma and violence and genetic variation in the development of adverse outcomes. This research will contribute to our understanding of the mechanisms by which exposure to trauma and violence exerts their adverse effects, aid in identifying individuals who are at risk, and facilitate the prevention of adverse effects in these individuals.

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