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DIFFERENTIAL SUSCEPTIBILITY TO CONTEXT: A PROMISING MODEL OF THE INTERPLAY OF GENES AND THE SOCIAL ENVIRONMENT

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Abstract

The goal of this chapter is to demonstrate the importance of incorporating gene by environment (GxE) interactions into behavioral science theory and research. In pursuit of this aim, the chapter is organized in the following way. First, we provide a brief critique of the behavioral genetics paradigm, noting why one should be skeptical of its suggestion that genes exert large main effects, and only main effects, on social behavior. Second, we describe how the recent mapping of the human genome has facilitated molecular genetic research and the emergence of the new epigenetic paradigm that has begun to supplement and replace the simpler model of genetic determinism. Third, we turn our focus to the explosion of GxE research that has occurred in the wake of this paradigmatic shift. These studies find that genetic variation often interacts with environmental context to influence the probability of various behaviors. Importantly, in many, and perhaps most, of these studies the genetic variable, unlike the environmental variable, has little if any main effect on the outcome of interest. Rather, the influence of the genetic variable is limited to its moderation of the effect of the environmental construct. Such research does not undermine the importance of environmental factors; rather it shows how social scientific explanations of human behavior might be made more precise by incorporating genetic information. Finally, we consider various models of gene - environment interplay, paying particular attention to the differential susceptibility to context perspective. This model of GxE posits that a substantial proportion of the population is genetically predisposed to be more susceptible than others to environment influence. We argue that this model of GxE is particularly relevant to sociologists and psychologists.

Most sociologists and psychologists are not sure how to interpret and incorporate findings from the profusion of studies that have been published in recent years regarding the effect of genes on social behavior. This is especially true of behavioral genetics research reporting heritability estimates of 30%-50% for virtually every human behavior. Indeed, this literature suggests that the heritability of political party affiliation and voting behavior is roughly the same as that for schizophrenia (Alford, Funk, & Hibbing, 2005; Joseph, 2006). Such findings seem implausible and have suggested the need for reconsideration of the methods used to derive these estimates. In addition to the difficulty of incorporating genetic main effects into our theoretical models and research designs, these problems have led many

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sociologists and psychologists to simply ignore the heritability findings reported by behavioral geneticists.

In this chapter, we urge behavioral scientists to reconsider hostile and dismissive attitudes regarding the potential merit of incorporating genetics into their theoretical explanations. Findings from the profusion of molecular genetic studies conducted during the past decade tell a story that is compatible with traditional social science research and identifies variables that can be incorporated more readily into social science research paradigms. This research tests models that include variation in one or more genes, or regulatory elements within genes, as directly measured variables alongside various social and behavior variables. These studies find that genetic variation often interacts with environmental context to influence the probability of particular behaviors (see Moffitt, Caspi, & Rutter, 2006; Rutter, Moffitt, & Caspi, 2006; Shanahan & Hofer, 2011). Importantly, in many instances the genetic variable, unlike the environmental variable, has little if any main effect on the outcome of interest. Rather, its influence is largely through its moderation of the effect of the environmental construct (Moffitt, et al., 2006; Rutter, et al., 2006). Thus such research does not undermine the importance of environmental factors; rather it shows how social scientific explanations of human behavior might be made more precise by incorporating genetic information (Guo, Elder, Cai, & Hamilton, 2009; Guo, Roettger, & Cai, 2008; Pescosolido et al., 2008; Shanahan, Erickson, Vaisey, & Smolen, 2007; Shanahan, Vaisey, Erickson, & Smolen, 2008).

This potential is particularly evident in the recently articulated differential susceptibility to context model of GxE (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Belsky & Pluess, 2009; Ellis et al., 2011), a perspective that has received much support in the past five years. Proponents of this framework posit that a substantial proportion of the population is genetically predisposed to be more susceptible than others to a range of environment influences. Compared to others, individuals with this genetic predisposition show greater vulnerability to adverse social conditions, but also reap more benefit from environmental support. In other words, some people are programmed by their genes to be more sensitive to environmental context, for better or worse (Belsky, et al., 2007). Such a finding would seem to have major implications for behavioral scientists concerned with formulating models of the manner in which the social environment influences human behavior.

The goal of this chapter is to make a case regarding the importance of GxE research for the behavioral sciences. In pursuit of that aim, the chapter is organized in the following way. First, we provide a brief critique of the behavioral genetics paradigm, noting why one should be skeptical of its suggestion that genes exert large main effects on social behavior. Second, we describe how the recent mapping of the human genome has facilitated molecular genetic research and the emergence of the new epigenetic paradigm that provides a more complex understanding of gene-environment interplay, reserving a larger role for the environment and providing one potential mechanism for gene-environment interactions. Finally, the major portion of the chapter focuses on the explosion of GxE research that has occurred in the wake of this paradigmatic shift. We consider various models of gene by environment interplay, paying particular attention to the differential susceptibility perspective. In our view, the differential susceptibility model of GxE is particularly relevant to sociologists and psychologists.

The Equal Environment Assumption: Pulling Back the Curtain on Behavioral Genetics

As noted, molecular genetics studies often fail to find genetic main effects; rather the effect of genes is often limited to their moderation of the impact of social environmental variables.

Indeed, even large scale "successful" efforts to identify genetic main effects by scanning the entire genome have produced modest results that fall far short of the expectations generated by behavioral genetic research (Thomas, 2010). This has come be known as the problem of missing heritability (Maher, 2008). One of several possible explanations advanced for the missing heritability problem is that heritability may have been systematically overestimated in behavioral genetics research both because interaction effects are included in the "main effects" term of the estimate, and because some outcomes do not meet statistical assumptions required for the approach to yield valid estimates. Before turning to a discussion of newer literature that examines interaction effects directly, we feel obliged to provide a brief, simplified explanation for the problem of missing heritability. We suggest that much of the inconsistency between the small to negligible main effects found by molecular geneticists and the large heritabilities found by behavioral geneticists (Plomin, DeFries, McClearn, & McGuffin, 2001; Rowe, 1994; Walsh, 2002) arises from widespread violations of the equal environment assumption (EEA), a topic we explore in some detail in the context of understanding how heritability estimates are derived in behavioral genetics.

Twins are relevant to the investigation of heritability because monozygotic (MZ)twins (those from one fertilized egg) share all of their inherited genetic material, whereas dizygotic (DZ) twins (those from two fertilized eggs) share on average half of their inherited genetic material, the same as two non-twin biological siblings. Given these facts, researchers estimate the extent to which genetic variation contributes to trait variation by comparing two correlations – the correlation between MZ twins and between DZ twins with regard to the outcome of interest. Also calculated from the correlational data are estimates of the shared environment (i.e., all of the shared external influences that lead to trait similarity between individuals such as similar parenting, school experiences, peer relationships, neighborhood context, etc.) as well as the unshared environment (i.e., all of the distinctive external influences that would lead to trait dissimilarity). Note that there is no actual measurement of shared and unshared environment. They are estimated based on differences in concordance on the outcome variable between MZ and DZ twins.

In fairness to this approach, it must be noted that it provided the earliest look at genetic effects on human behavior and provided much of the conceptual foundation for current molecular research. The convergence of findings across the different types of genetically informed designs has provided compelling evidence of the need to consider genetic factors in some form in social and behavioral research. Nonetheless, to the extent that heritability estimates were systematically inflated, this may have produced substantial distortions in later conceptual models and contributed to popular misunderstandings of the nature of genetic effects. Accordingly, it is important to understand the potential source of inflated estimates.

Most contemporary twin studies utilize structural equation modeling to calculate heritability (Medland & Hatemi, 2009). However, the underlying logic remains identical to the simple equations used in the earliest behavior genetics studies. The terms in the equations are squared as they represent the proportion of variance explained.

- $r_{MZ} = h^2 + c^2$ represents the contributions of genes (h^2) and shared environment (c^2) to the correlation (concordance) between members of MZ pairs in a sample.
- $r_{DZ} = h^2/2 + c^2$ represents the contributions of genes and shared environment to concordances between members of DZ pairs in a sample.
- To calculate the heritability statistic, the DZ correlation is subtracted from the MZ correlation: $r_{MZ} - r_{DZ} = (h^2 + c^2) - (h^2/2 + c^2)$.

- Then, by assuming that the contribution of the shared environment is equivalent for MZ and DZ twins, the formula can be simplified to $r_{MZ} - r_{DZ} = h^2 - h^2/2$, and then to $2(r_{MZ} - r_{DZ}) = 2\ (h^2 - h^2/2)$, and then finally $h^2 = 2\ (r_{MZ} - r_{DZ})$.
- To get the equation for shared environment, one returns to the first equation and moves the terms around a bit: $c^2 = r_{MZ} - h^2$

Note that these calculations necessarily assume that the contribution of the shared environment is the same for MZ and DZ twins. This is the *equal environment assumption (EEA)*. Importantly, there is a wealth of evidence that this is not the case. It is well established that MZ twins share a more similar environment than DZ twins. For example, MZ twins are more likely to have the same friends (Cronk et al., 2002; Horwitz, Videon, Schmitz, & Davis, 2003), to be placed in the same classroom (Cronk, et al., 2002; Morris-Yates, Andrews, Howie, & Henderson, 1990), to spend time together (Horwitz, et al., 2003; Rende, Slomkowski, Lloyd-Richardson, & Niaura, 2005), and to go out together (Kendler & Gardner, 1998). Further, MZ twins have greater contact as adults (Heller et al., 1988; Kaprio, Koskenvuo, & Rose, 1990; Rose et al., 1988) and report greater identification, closeness (Joseph, 2004; LaBuda, Svikis, & Pickens, 1997; Segal, 2000), and mutual influence (Ainslie, 1997; Sandbank, 1999).

This rather massive literature indicates that the equal environment assumption is untenable for many aspects of the environment and particularly untenable for the social environment. If MZ correlations for a phenotype are larger than DZ correlations in part due to environmental influences, particularly peer group or other social influences, then heritability calculations will be overestimated. Even slight violations of the EEA will produce a substantial overestimation of heritability (and underestimation of environmental effects). For example, if the shared environmental effect is .3 for MZ twins and .2 for DZ twins, heritability will be overestimated by 20%.

Given the overwhelming nature of the evidence that the environments of MZ twins are more similar than those of DZ twins, behavioral geneticists generally grant that the EEA is incorrect. They go on to argue, however, that violation of this assumption generally does not matter as these environmental differences have little if any impact on the phenotypes being investigated (Kendler, 1983; Morris-Yates, et al., 1990; Wright, 1998). Although this simplifying assumption may be tenable for some physical characteristics, cognitive abilities, or temperamental traits, it is not clear that it can be accepted for any problem in which a large social contribution as been documented.[1] Indeed, the shared environmental factors on which MZ and DZ twins have been shown to differ (e.g., parent, sib, and peer influences) represent variables that past research has shown to be among the most powerful determinants of the outcomes of concern to behavioral scientists. This, along with other critiques of the genetic main effects model (Dodge & Rutter, 2011) suggests the need for an understanding of G-E interplay that allows more room for main effects of the environment and for GxE interactions that may modify environmental main effects. Accordingly, we next briefly discuss newer genetic paradigms that stress epigenetics, i.e. the way that the environments may regulate gene expression and, in turn, behavior. We then go on to discuss newer models that emphasize GxE interactions.

[1]Interestingly, concerns about violations of the EEO may extend all the way to the paradigmatic case of schizophrenia. Davis, Phelps and Bracha (1995) investigated concordance of schizophrenia in monochorionic (same blood supply in the womb) and dichorionic monozygotic twins (different blood supply in the womb), and found that the concordance rate for the former was high, 60% but for the latter was low 10.7%, even though the genetic overlap was the same in each case. So, it may be that the equal environments assumption does not hold even across different types of MZ twins, and differential influences due to the environment may begin to appear already in the womb. In addition, because MZ twins are much more likely to be monochorionic than are DZ twins these effects will reappear in heritability estimates based on twin studies.

The Paradigmatic Shift from Genetic Determinism to Epigenetics

In 1953, Watson and Crick discovered that genes are composed of sequences of 4 nucleotide bases and that these DNA strands represent a code for forming the body's protein molecules. Their discovery ushered in the paradigm of genetic determinism: the belief that genes control all of our traits -physical, behavioral, and emotional. Genes produce RNA which controls the production of proteins which control the functioning of cells and ultimately behavior. This idea became the dominant dogma of molecular biology and it gave rise to much hyperbole over the decades regarding the power of genes (i.e., the main effects, genetic determinism model). This hyperbolic presentation was supported by behavioral genetic studies suggesting that virtually every aspect of human behavior, from disease to political ideology, was determined in large measure by a person's genes. All that was left to be done was to sequence the human genome. This would enable scientists to identify the specific genes that make people vulnerable to physical and emotional illnesses, learning difficulties, obesity, aggression, and all sorts of other undesirable traits and behaviors.

The Human Genome Project (HGP) was launched in 1990 by the National Institutes of Health. The goal was to identify the basis of human traits, both positive and negative, and to foster development of new medical applications around the world. Based upon the assumption that genes control an organism's traits, researchers expected to find a strong correlation between the complexity of an organism and the number of genes that it possesses. With over 100,000 proteins in the human body, and with a blueprint needed to make each protein, the assumption was that the human genome consisted of at least 100,000 genes.

Concomitantly, with the HGP, researchers began mapping the genomes of a variety of other organisms (Lipton & Bhaerman, 2009). In the beginning, this work produced the expected results. Bacteria, nature's most primitive organism, were found to have between 3,000 and 5,000 genes. The barely visible roundworm, an organism with only 960 cells, had 20,000 genes (Holdrege & Wirz, 2001). Then, however, a contradiction was encountered. The more complex fruit fly had only 18,000 genes (Lipton & Bhaerman, 2009). An even bigger surprise came shortly after the turn of the century, when the HGP reported that humans, with over 50,000 trillion cells, had roughly 25,000 genes (Claverie, 2001; Venter et al., 2001), just slightly more than the roundworm. Thus the human body has over 100,000 proteins but only 25,000 genes. This finding was crushing evidence that the one gene-one protein assumption was incorrect (Silverman, 2004), and led to increased attention to gene regulation. Further, the large genome wide association studies that followed on the heels of completion of the HGP largely failed to find strong main effects of genetic variation on physical or emotional illness or behavioral phenotype. In response to the weakness of the "main effects, genetic determinism" paradigm, a new genetics model has begun to emerge. There are continuing efforts to identify solutions to the problem of missing heritability that are consistent with a main effects model. However, the shift to greater attention to factors that influence gene expression is clearly underway.

The new model views genes as a combination of DNA segments that together constitute an expressible unit. Through complex promoters and alternative splicing, the various DNA segments that comprise any particular gene can contribute to the production of a variety of RNA sequences and proteins (Portin, 1993). And what determines how a gene expresses itself? As biologist H. Frederick Nijhout (1990) has noted, a gene cannot turn itself on or off. Rather, "when a gene product is needed, a signal from its environment, not an emergent property of the gene itself, activates expression" (Nijhout, 1990: 443). In other words, the environment controls gene expression (Powell, 2005). The environment includes the external world in which the organism is located or develops, as well as its biochemical

internal world of hormones, metabolism, and the like. In contrast to the old view of the deterministic gene, the new paradigm of epigenetic control places the environment center stage. Environmental circumstances foster gene expression which, through several additional mechanisms, results in behavior. The new view has the advantage of better capturing adaptation to changing environmental circumstances.

At this point the reader might be wondering how this new model is relevant to behavioral science research. If genes simply mediate the effect of environmental context on behavior, and all human beings have the same set of genes, can't behavioral scientists simply ignore the mediating effect of genes and proceed with business as usual (viz., investigating the impact of the environment on behavior)? The answer is "no" in that genes frequently show structural variation and this genetic variation often moderates the impact of the environment on behavior. This is the phenomenon of gene-environment interaction. The next section provides a short primer on the various types of genetic variation as a prelude to discussing research and perspectives on GxE.

A Brief Introduction to Molecular Genetics and Useful Terminology

The genetic code is composed of nucleotide base pairs (bps) that are organized into genes. Genes represent segments of the genome that produce proteins that contribute to particular phenotypes or functions. Many genes are "polymorphic" in that their structure varies somewhat across individuals. Each variant is labeled an "allele." Two common types of variation, length and sequence, are observed. Length type variation involves the number of times that a particular set of base pairs is repeated. This type of variability is referred to as a Variable Number Tandem Repeat (VNTR). VNTRs are important as they often alter the structure of the product (e.g., protein) of the gene if they occur in the coding region or they may influence the amount of the product if they occur in the promoter region. The other type of genetic variation is Single Nucleotide Polymorphisms, frequently called SNPs, which involve variation in a single nucleotide base pair, changing the genetic sequence. Like VNTRs, SNPs can influence the quality and amount of product produced by a gene.[2]

The more common variants of a gene are labeled the major alleles, whereas the less common variants are labeled minor alleles. Individuals carry two copies of a gene as they inherit a copy from each of their parents. Thus for any particular polymorphism, they may be homozygous with regard to the major allele (have two copies of the major allele), heterozygous (have a copy of both the major and minor allele), or be homozygous with regard to the minor allele (have two copies of the minor allele). In most cases, GxE studies examine the way that having one or two copies of the minor allele of some gene changes the way that individuals respond to environmental conditions.

Evidence that Genes Interact with the Environment to Influence Behavioral Outcomes

In 2002, Caspi and colleagues (2002) published an article in *Science* reporting an interaction between child maltreatment and variants of the MAOA gene in predicting the antisocial behavior of young adult males. The results indicated that abusive treatment had a main effect on antisocial behavior whereas MAOA variation did not. Rather, the effect of the

[2]Another source of genetic variation consists of whether a particular gene has been expressed (upregulated) or turned off (downregulated) in response to prior environmental experiences (including intrauterine events). Differences in expression, like VNTR and SNP variability, may impact how individuals respond to an event. However, consideration of gene expression takes us into a discussion of methylation, histone modification, etc. which are beyond the scope of this chapter. Further, measures of such epigenetic effects remain complex and provocative. Thus we limit our discussion to VNTRs and SNPs, the two types of genetic variation that are easily assayed and available in many large secondary data sets (e.g., Adolescent Health).

variation in this gene was limited to its moderation of the impact of child maltreatment. Maltreatment was a strong predictor of subsequent involvement in antisocial behavior for men with MAOA low activity alleles but had little impact on the probability of such behavior for those with high activity alleles. The following year, Caspi and his colleagues (2003) published a second GxE article in *Science*. This paper reported that the association between life stress and depression was stronger for individuals who had the short allele in a polymorphism in the promoter region of the serotonin transporter gene (5-HTT). Again, there was no direct effect of the gene. Its influence was limited to its moderation of the effect of life stress.

These studies stimulated a flurry of research investigating the extent to which various genetic polymorphisms interact with the environment to foster various types of internalizing and externalizing problems. In 2009, Belsky and Pluess published a list containing scores of studies reporting a G×E effect on child and adolescent behavioral and emotional problems. Many more articles concerned with child outcomes have appeared since this publication. These studies have reported GxE effects for developmental outcomes such as prosocial behavior (Bakermans-Kranenburg & van Ijzendoorn, 2011; Knafo, Israel, & Ebstein, 2011), attachment style (van Ijzendoorn & Bakermans-Kranenburg, 2006), sensation seeking (Sheese, Voelker, Rothbart, & Posner, 2007), emotion regulation (Belsky & Beaver, 2011), and substance use (Beach, Brody, Lei, & Philibert, 2010; Brody et al., 2011). This wealth of studies included a meta-analysis confirming the findings of Caspi et al. (2002) regarding the interaction of MAOA and maltreatment in predicting aggression (Kim-Cohen et al., 2006).

In addition to these studies of children, a host of studies has focused upon adults. Among other findings, this research has reported GxE effects in predicting outcomes such as quality of parenting (Beach et al., 2012; van Ijzendoorn, Bakermans-Kranenburg, & Mesman, 2008), negative affective arousal (Beach, et al., 2012), aggression (Simons et al., 2011; Simons et al., 2012), sexual behavior (Kogan et al., 2010), and depression (Beach, et al., 2010). Most of these studies focused upon variants of the genes DRD4, DRD2, MAOA, 5-HTT and GABRA2. In a few instances, the genes in these studies demonstrated a small main effect. In the majority of cases, however, the environmental variable demonstrated a rather strong main effect and the impact of the gene was limited to its moderation of the environmental variable.

Models of GxE

Genetically informed behavioral science requires models of the manner in which genetic variation combines with social context to influence behavioral outcomes. The *diathesis-stress model* utilized in the vast majority of G×E studies assumes that allelic variation in particular genes amplifies the probability that exposure to social adversity (e.g., abusive parenting, racial discrimination, economic hardship) will result in emotional and behavioral problems. Thus the perspective presumes that some individuals are by nature more vulnerable than others as they possess dysfunctional “risk alleles” that foster maladjustment in the face of deleterious environmental conditions.

Support for the diathesis-stress model is evident when a graph of GxE produces a fan-shaped pattern where the effect of the social environment on some outcome becomes greater as the number of copies of a particular risk allele increases. Figure 1 depicts a hypothetical example of such an interaction using delinquency as an outcome. The figure indicates that environmental adversity has an effect on delinquency regardless of genotype but that the effect is weakest for those with no copies of the risk allele, stronger for those with one copy of the risk allele, and strongest for those with two copies of the risk allele. Such a pattern is

consistent with the idea that some individuals are genetically predisposed to be more vulnerable or reactive to adverse conditions than others.

This assumption is contradicted, however, by the fact that over the past several thousand years evolution seems to have conserved these various alleles (Ellis, et al., 2011; Homberg & Lesch, 2011). While truly dysfunctional genetic variants should largely disappear over time, most of the so called risk alleles studied by behavioral science researchers are highly prevalent, often being present in 40 to 50 percent of the members of the populations being investigated (Ellis, et al., 2011). Thus contrary to the negative view usually taken of these alleles, this suggests that, at least in certain contexts, these genetic variants must provide advantages over other genotypes. This view is an essential component of the alternative model of gene by environment interaction recently proposed by Jay Belsky and his colleagues (Belsky, et al., 2007; Belsky & Pluess, 2009; Ellis, et al., 2011).[3]

Belsky and his colleagues (Belsky, et al., 2007; Belsky & Pluess, 2009) argue that the polymorphisms used in most G×E studies to date exert their influence by augmenting susceptibility to social context, whether that environment is adverse or supportive. Thus those persons most vulnerable to adverse social environments are the same ones who reap the most benefit from environmental support. Belsky and company label this view the *differential susceptibility to context* perspective on GxE. Their model assumes that some individuals are programmed by their genes to be more sensitive to environmental influence than others. In other words, they are more *plastic*. Indeed, Belsky and his colleagues often refer to genetic variants thought to enhance sensitivity to social context not as risk alleles but as plasticity alleles.

How would genes cause some individuals to be more susceptible than others to environmental influence? The candidate genes analyzed in most GxE studies involve neurotransmitters concerned with the dopaminergic system (MAOA, DRD2, DRD4, COMT, DAT1), which has been implicated in reward sensitivity and sensation seeking, the serotoninergic system (5-HTT), which has been linked to sensitivity to punishment and displeasure, and the neurotransmitter gamma aminobutric acid or GABA (GABRA2, GABRG1), which influences general levels of disinhibition and excitability in the brain (see Carver, Johnson, & Joormann, 2008; Edenberg et al., 2004; Frank, D'Lauro, & Curran, 2007). These genes also influence a wide variety of other biochemicals within the brain. In general, the low activity or minor alleles associated with these genes tend to increase the activity of the brain's limbic system, especially the amygdala, thereby increasing emotional responsiveness to environmental events. For example, the short allelic variant of the serotonin-transporter polymorphic region (5-HTTLPR), which is linked to reduced serotonin transporter protein availability and function, has been shown in a variety of studies to foster hyper-vigilance to environmental cues, including increased sensitivity to both aversive and rewarding social stimuli (Homberg & Lesch, 2011). Thus the differential susceptibility model assumes that persons with plasticity alleles may be may be more readily shaped by environmental rewards and punishments than other genotypes. Although each of these various genes has been shown to have their own unique biochemical effect upon the brain, there is also reason to believe that each of them, in their own way, influences a person's responsiveness to environmental events.

Support for the differential susceptibility or plasticity argument is evident when the slopes for a gene by environment interaction show a crossover effect with the susceptibility group

[3]An alternative theory of how "risk" alleles might be preserved in some cases focuses on genetic pleiotropy, a wide-spread phenomenon in which one gene has multiple impacts across a range of organ systems or behaviors, creating opportunities for trade-offs between advantages and disadvantages of particular alleles (Sivakumaran et al., 2011).

showing worse outcomes than the comparison group when the environment is negative but demonstrating better outcomes than the comparison group when the environment is positive (Belsky, et al., 2007; Belsky & Pluess, 2009). Figure 2 provides a hypothetical example of such an interaction again using delinquency as an outcome. The figure shows that the social environment influences delinquency regardless of genotype, with those exposed to favorable environments showing less delinquency than those exposed to adverse environments. Most importantly, however, the graph also indicates that what the diathesis-stress model considers to be a risk allele is actually a plasticity or sensitivity allele. This is the case as individuals with one or two copies of the allele show higher levels of delinquency than those with no copy when the environment is adverse but show lower levels of delinquency than those without a copy when the environment is favorable. Further, those with two copies of the allele are more delinquent under conditions of adversity and less delinquency when the environment is favorable, than those carrying one copy of the allele. When the researcher obtains a crossing pattern like that shown in Figure 2, the next step is to test whether the slopes differ from each other at both ends of the graph. Support for the differential susceptibility hypothesis requires that those with the putative plasticity allele show significantly poorer adjustment than other genotypes when the environment is adverse but significantly better adjustment than other genotypes when the environment is supportive.

As is evident in Figure 2, a stringent test of the differential susceptibility model requires that the researcher utilize the full range of the social environment, from very favorable to very adverse (Belsky & Pluess, 2009; Dick, 2011). Most G×E studies only focus upon variation in adversity. This is the case in the hypothetical example shown in Figure 1. When this is the case, the researcher is apt to obtain a fan-shaped pattern in keeping with the diathesis-stress model even when the true effect is that of differential susceptibility. By truncating the measure of the environment, the researcher is essentially eliminating the left half of the graph presented in Figure 2. In many studies, however, the susceptibility effect is so strong that a significant crossing pattern is obtained even when the researcher only assesses variation in adversity (see Belsky & Pluess, 2009). While individuals with plasticity alleles show higher rates of problem behavior than other genotypes when the environment is adverse, they often show better adjustment than other genotypes when the environment becomes less aversive, even if this more benign environment simply involves the absence of adversity and not the presence of a truly supportive milieu (Belsky & Pluess, 2009). Albeit, a stronger and more appropriate test of the differential susceptibility hypothesis requires using the full range of the naturally occurring environment, from favorable to adverse.[4]

In a recent article, Belsky and Pluess (2009) reviewed scores of studies reporting a G×E effect on child or adolescent adjustment. Although these studies appeared to support a stress-diathesis model, Belsky and Pluess concluded that a careful inspection of the results pointed to a different interpretation. All of the studies included in the review showed a cross-over effect. This included the *Science* articles by Caspi et al. (2002, 2003). Since Belsky and Pluess published their review article, a number of additional papers supporting the differential susceptibility perspective have been published. This includes a meta-analysis (Bakermans-Kranenburg & van Ijzendoorn, 2011) of GxE studies focusing on youth externalizing problems and a recent issue of *Development and Psychopathology* (February, 2011) that focused entirely upon research supporting the differential susceptibility perspective.

[4]There are a number of complexities introduced by this position, not the least of which is determining which aspect of the positive environments are most relevant to the outcome of interest. Accordingly, the susceptibility perspective requires strong, validated theories of social causation that can guide genetic research.

If there are several genetic alleles that operate to enhance plasticity or susceptibility to context, it stands to reason that the more plasticity alleles one carries, the more susceptible he or she will be to environmental context. Belsky and Pluess (2009) therefore suggest that researchers create composite scores based on multiple plasticity alleles, in much the same way that that multiple environmental risk factors are often summed to form indices of cumulative environment risk. Several recent papers have reported support for this idea. Belsky and Beaver (2011) formed a cumulative plasticity measure using five genes – DAT1, DRD2, DRD4, 5-HTTLPR, and MAOA. Consistent with the differential susceptibility model, the more plasticity alleles adolescent males carried, the more and less self-control they manifested in response to supportive and unsupportive parenting, respectively. Using two genes – 5-HTT and DRD4 - Simons et al. (2011) found cumulative plasticity enhanced the probability of aggression in response to environmental adversity but decreased the probability of aggression when the environment was supportive. Similarly, Simons et al. (Simons, et al., 2012) reported that cumulative plasticity based on three genes – MAOA, DRD4 and 5-HTT – interacted with variation in various community and family factors to predict involvement in criminal behavior in a manner consistent with the differential susceptibility perspective. Finally, Gibbons et al. (2012) found that a measure of cumulative plasticity created from 5HTT and DRD4 moderated the effect of discrimination on various cognitive schemas in the manner predicted by differential susceptibility. Thus the evidence to date seems to support the idea of summing across genes to formulate measures of cumulative plasticity.

Theoretical Implication for Social Psychology

In large measure, the audience for this volume consists of social psychologists. Social psychology is concerned with the causes and consequences of social interaction. Given this focus, it has never been clear how findings from behavior genetics might be incorporated into the theory and research of the field. This is not the case, however, regarding molecular genetics. Models testing traditional social psychological theories can be elaborated in a conceptually simple manner by incorporating genotypic variation in candidate genes as additional variables. As noted earlier, such research usually finds that the environmental variable of interest has a main effect on social behavior whereas the genetic variable does not. The gene's influence is usually limited to its moderation of the environmental variable of interest (Belsky & Pluess, 2009; Moffitt, et al., 2006; Rutter, et al., 2006). Including this moderating effect provides a more precise prediction of the circumstances under which the environmental variable increases the probability of the focal outcome.

Past research on GxE would seem to be particularly relevant to social psychology as most of the social environmental variables that have been investigated involve social interaction. Studies have investigated, for example, the effects of parent-child interaction (e.g. Beach, et al., 2012; Knafo, et al., 2011), racial discrimination (e.g. Brody, et al., 2011; Gibbons, et al., 2012), criminal victimization (e.g. Gibbons, et al., 2012; Simons, et al., 2011), and peer influences (Larsen et al., 2010; Simons et al., in press). Although the majority of GxE studies only investigate the diathesis-stress hypothesis, most of those that test for differential susceptibility find support for the model.

In addition to its concern with social interaction, the field of social psychology focuses upon the formation and consequences of beliefs, attitudes, and values. This research investigates the processes whereby social experiences give rise to schemas and sentiments that, in turn, influence one's interpretation of and response to subsequent situations (Shanahan & Macmillan, 2008). Recently, Simons and colleagues (2011) argued that one of the implications of the differential susceptibility perspective is that persons with plasticity alleles should learn the lessons inherent in recurrent patterns of interaction more quickly

than other genotypes. These individuals are genetically predisposed to be more sensitive to their social environment than others, and consequently they should learn the skills, schemas, attitudes, and values communicated by environment events more quickly than other genotypes. Several recent studies indicate that this is the case.

Simons et al. (2011) examined three personal characteristics – chronic anger, concern with being tough, and a hostile attribution bias - that criminological theory has identified as mediators of the effect of environmental adversity on aggression. Their findings indicated that individuals with the 7-repeat allele on the dopamine receptor gene (DRD4) and the short allele on the serotonin transporter gene (5-HTT) scored higher on anger, toughness, and hostile view of relationships than other genotypes when the social environment was characterized by discrimination, harsh parenting, criminal victimization and deviant peers. On the other hand, persons with these two plasticity alleles reported less anger and concern with toughness and were more trusting of people than other genotypes when the environment was characterized by supportive parenting, religious affiliation, school involvement, and conventional peers. These finding provide strong support for the differential susceptibility perspective. Further, the analyses indicated that the interaction of genotype and maltreatment on aggression was fully mediated by the effect of G×E on anger, toughness, and hostile view of relationship. In other words, the results supported a mediated moderation model where the effect of G×E on aggression was explained by its impact on mediating emotions and schemas.

In a second study, Simons et al. (2012) focused on adoption of the street code. In his well know ethnographic study of inner city Philadelphia, Elijah Anderson (1999) argued that exposure to community disadvantage, racial discrimination, and criminal victimization leads to adoption of the code of the street, and in turn involvement in criminal behavior. Importantly, however, while the adverse circumstances described by Anderson increase the probability of adopting the code of the street, most of those exposed to these difficult social conditions do not do so. Simons et al. (2012) examined the extent to which genetic variation accounts for these differences. Using longitudinal data from several hundred African American adolescents, they investigated the moderating effect of three genes: 5-HTT, DRD4, and MAOA. Consistent with the differential susceptibility hypothesis, individuals with the minor alleles on these three genes manifested more commitment to the street code and aggression than those with other genotypes when exposed to the adverse community conditions described by Anderson, whereas they demonstrated less commitment to the street code and aggression than those with other genotypes when the social environment was more favorable. And, once again there was evidence of mediated moderation. Much of the effect of G×E on aggression was explained by its impact on street code.

In a third study, Simons and his colleagues (in press) found that variation in the GABRA1 gene interacts with the social environment to influence learning of prototype images of substance users that, in turn, impact the use of substances. The pattern of this interaction was consistent with the differential sensitivity to context hypothesis in that carriers of GABRG1 minor alleles demonstrated significantly more positive images of substance users than other genotypes when the environment was favorable to substance use (viz., substance use prevalent in the community, family, and peer group) but more negative images of substance users than other genotypes when the environment was adverse to substance use (viz., little support for use within the community, family, or peer group). There was also a GxE effect on substance use and it also was consistent with the differential susceptibility perspective. Finally, the GxE effect on substance use was no longer significant once the GxE effect on prototype was taken into account, indicating a pattern of mediated moderation.

Additional support for the idea that genetic variation influences the acquisition of beliefs, values and attitudes comes from a study by Gibbons et al. (2012). The authors of this study found that African American adolescents with minor alleles for either DRD4 or 5HTT, or both, were more responsive to racial discrimination. Consonant with the differential susceptibility perspective, the respondents demonstrated more positive prototype images of persons who engage in various types of deviant behavior than other genotypes when discrimination was high but more negative prototype images of deviant individuals than other genotypes when discrimination was low. These prototype images, in turn, influenced involvement in education, substance use, and risky sexual behavior.

Finally, Belsky and Beaver (2011) recently reported that genetic variation influences level of self-control. This psychological characteristic has been linked to a wide variety of behaviors including conduct problems, substance use, and risky sex (Baumeister & Vohs, 2004; Pratt & Cullen, 2000). Using Add Health data, Belsky and Beaver (2011) examined the extent to which five genes - DAT1, DRD2, DRD4, 5-HTT, and MAOA – moderate the effect of parenting on the self-control of adolescent males. Consistent with the differential susceptibility perspective, they found that the more plasticity alleles that an individual carried, the more and less self-control they manifested in response to supportive and unsupportive parenting, respectively. Past research has provided strong evidence that self-control is a moderately strong predictor of a wide variety of outcomes, including delinquency, substance abuse, intimate partner violence, and risky sexual behavior (Cullen, Unnever, Wright, & Beaver, 2008; Pratt & Cullen, 2000). Therefore the findings of Belsky and Beaver can be seen as providing further support for the idea that plasticity alleles interact with the social environment to influence psychological traits that, in turn, increase the probability of delinquency and crime.

Together, these studies provide rather strong evidence that variants of an assortment of genes operate to intensify sensitivity to the various dimensions and qualities of social interaction. This increased sensitivity enhances responsiveness to both adverse and favorable events, and amplifies the probability that individuals will develop attitudes, values, and schemas that reflect the lessons or tenets implicit in the repetitive patterns of interaction action to which they are exposed. These findings suggest the importance of including genetic variation in social psychological research as a way of increasing theoretical precision.

Conclusion

Social psychology is largely concerned with the effect of social context on people’s behavior. Importantly, genetic variability is a factor that has been shown to influence a person’s response to his or her social environment. We are optimistic that social psychology can incorporate the interplay of genes and social environment into its theoretical perspectives without sacrificing human agency for biological determinism. Although a wide variety of perspectives have emerged regarding the complex manner in which genes and the social environment might interact over the life course (Shanahan & Hofer, 2005, 2011), recent results provide rather strong support for the differential susceptibility model, which posits that a substantial proportion of any population is genetically predisposed to be more responsive to their social environment than those with other genotypes. It has become relatively inexpensive to genotype human subjects and the cost will undoubtedly continue to decline. Further, genetic data is now available in many large-scale secondary data sets (e.g., Adolescent Health). This means that social psychologists are now able to test the differential susceptibility model, as well as a variety of other perspectives, regarding the complex interplay of genes and social context. The consequence will most certainly be a more precise and comprehensive explanation of social processes.

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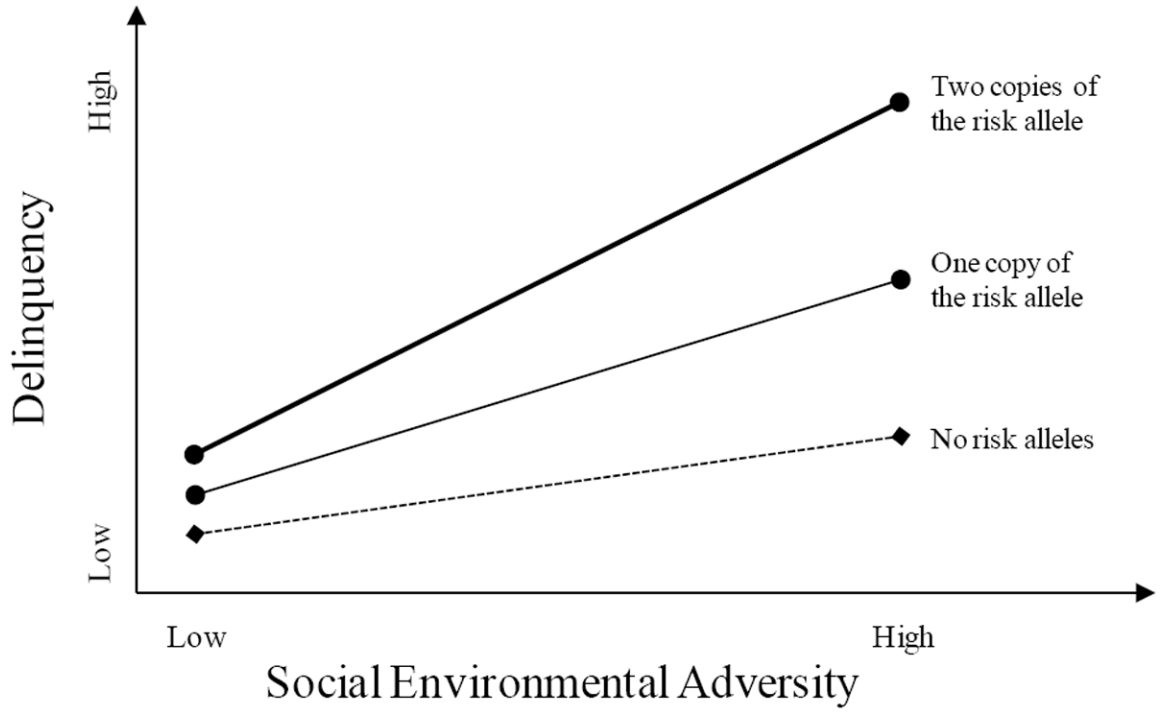

Figure 1.
The diathesis-stress model

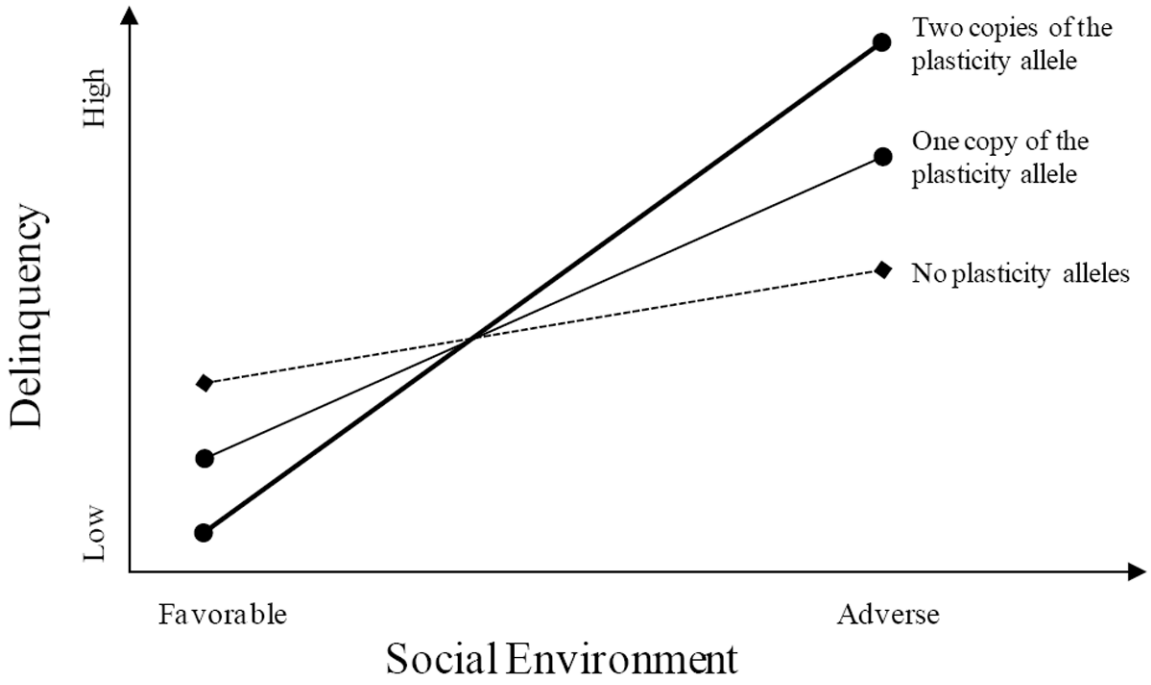

Figure 2.
The differential susceptibility model