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Resilience and measured gene–environment interactions

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Abstract

The past decade has witnessed an exponential growth in studies that have attempted to identify the genetic polymporphisms that moderate the influence of environmental risks on mental disorders. What tends to be neglected in these Gene × Environment (G × E) interaction studies has been a focus on resilience, which refers to a dynamic pattern of positive adaptation despite the experience of a significant trauma or adversity. In this article, we argue that one step toward advancing the field of developmental psychopathology would be for G × E research to consider resilience instead of focusing almost exclusively on mental disorders. After providing an up-to-date summary on the expanding definitions and models of resilience, and the available evidence regarding measured G × E studies of childhood maltreatment, we discuss why resilience would be a worthwhile phenotype for studies of measured G × E. First, although G × E hypotheses require that there be an environmental risk (e-risk) involved in a causal process that leads to psychopathology, e-risks are typically not included in the diagnostic criteria for most psychiatric disorders. In contrast, resilience by definition includes an e-risk. Second, G × E hypotheses require that there is evidence of variability in response to an environmental stressor, and resilience often represents the positive end on this continuum of adaptation. Third, both resilience and G × E are best understood from a developmental perspective. Fourth, although resilient outcomes are not public health concerns, the types of adversities (e.g., childhood maltreatment, poverty, or exposure to natural disasters) that are often investigated in studies of resilience certainly are. Understanding how some individuals, perhaps because of their genetic makeup, are able to withstand such adversities can inform prevention and intervention efforts to improve mental health.

Developmental psychopathologists tend to agree that resilience is not a fixed trait within an individual, nor is it the equivalent of competence. Instead, resilience is defined as a dynamic process by which individuals adapt successfully to an adverse experience (Cicchetti, 2010; Luthar, Cicchetti, & Becker, 2000; Masten, 2011; Masten & Obradovic, 2006; Rutter, 1985, 2012). It is an interactive concept (Rutter, 1987) that is not directly measured but is inferred by the two key components of its definition: exposure to adversity and evidence of "good" functioning (Luthar et al., 2000). Resilience is *dynamic* and *interactive* in that it is a process stimulated by the presence of adversity rather than simply the balance of risk versus protective factors (Rutter, 2012). "Good" adjustment to adversity does not necessarily require superior levels of functioning, but it is important to consider the domains of functioning that are likely to be most important in response to a particular stressor (Luthar et al., 2000). That is, the specific way in which resilience is operationally measured in any given study depends on the risk exposure of interest and on the way in which "positive adaptation" is defined. Moreover, it is possible that competence in one domain may be maintained while functioning in another domain declines. In this article, we discuss various ways in which resilience can be conceptualized, including stress inoculation and posttraumatic growth (PTG), and include how notions of differential susceptibility to environment influences relate to resilience. After reviewing G × E studies pertaining to childhood maltreatment and emerging G × E studies of resilience, we present several reasons why focusing on resilience rather than just psychopathology in G × E studies would be beneficial.

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Varieties of Resilience and Related Phenotypes

Typically, resilience has been operationally defined as the absence of psychopathology or the presence of competence in the context of significant adversity. Masten and Narayan (2012) recently mapped a variety of patterns of adaptation that might be expected in response to two general types of stressors: severe and chronic adversity and acute trauma. For severe, chronic adversity, typically there is a decline in functioning with a restoration of adaptation once the adversity has been removed and good conditions are established. For acute trauma, there are three types of resilience patterns: (a) resistance or maintenance of function, (b) decline in functioning followed by recovery, and (c) functioning that improves over baseline as a result of the stressful experience. Not everyone agrees that recovery after an initial drop in well-being should be considered a type of resilience. For instance, Bonanno, Westphal, and Mancini (2005) argue that recovery after the initial decline is often incomplete. However, Luthar and Brown (2007) state that there is no good evidence to suggest that "resistance" and "recovery" groups of resilient individuals are qualitatively different, or that these groups have distinct antecedents or consequences. Of course,

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this distinction depends on the time frame one uses to characterize resilience. As the time frame increases, it is more likely that many, and even most, individuals will recover, which is why longitudinal designs are essential for studies of resilience (Rutter, 2012). There is also growing recognition that individuals with serious mental disorders can function quite well given a well-established repertoire of coping strategies (Carey, 2011), which is one reason why resilience should not solely be defined by the absence of psychopathology criterion.

Early research on the predictors of resilience identified what has been called a "triad of protective factors": (a) characteristics of the individual, such as IQ and temperament; (b) characteristics of the family environment and parenting quality; and (c) characteristics of the social environment outside the home, such as school and relationships with extended family members (Cicchetti, 2010; Masten & Garmezy, 1985; Werner & Smith, 1982, 1992). Although individual traits play a significant role in promoting resilience, the systems that surround the child, including family members, schools, and neighborhoods are also crucial (Bowes, Maughan, Caspi, Moffitt, & Arseneault, 2010; Hanson & Gottesman, 2012). More recently, resilience researchers have emphasized the importance of incorporating multiple levels of analysis from molecules to neighborhoods, including genes (Cicchetti, 2010; Cicchetti & Blender, 2004, 2006; Curtis & Cicchetti, 2003; Kim-Cohen, 2007, Kim-Cohen & Gold, 2009; Luthar & Brown, 2007). Genes may be implicated in resilience in a number of ways. First, resilience, like other psychological constructs, is heritable (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). Second, if resilience is characterized by the supportive systems surrounding the child, then gene–environment correlation may be at play. That is, a child's genetic makeup may influence how well she can harness the supportive potential of resources in her environment by eliciting help or actively seeking it out. Third, epigenetic processes can be activated by stress (Champagne, 2010; Oberlander et al., 2008; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). Fourth, and the primary focus of this article, G×E studies have demonstrated that genetic variation may moderate the impact of adversity on psychological outcomes (Moffitt, Caspi, & Rutter, 2006).

In the following sections, we review emerging evidence for two resilience-related phenotypes: stress inoculation and PTG. In addition, we include a discussion of differential susceptibility to stress (DS) and biological sensitivity to context (BSC) models in order to highlight how they differ from notions of resilience.

Resilience as stress inoculation

Stress and adversity are threats to positive adaptation when they are severe, chronic, and/or occur during sensitive periods in development. However, moderate amounts of stress exposure, when managed successfully, may be a source of resilience against future adversity and may lead to what has been termed "steeling," "toughening," or "stress-inoculation" effects (Dienstbier, 1989; Garmezy, 1991; Meichenbaum, 1985, 2007; Rutter, 1985, 1993, 2006b; Seery, 2011). Similar to the process of building immunity against a pathogen after vaccination or building muscle strength after exercise, stress inoculation is hypothesized to result from the experience of effectively coping with adversity that is neither too low nor too high. When stressful life events are numerous and severe, they may overwhelm a person's capacity to adapt and lead to poor psychological functioning. In contrast, when stressors are mostly absent, individuals may miss the opportunity to test and build their capacity for overcoming challenges. When a major adversity is eventually encountered, these individuals may be more likely to struggle and show nonresilient functioning than those who have already had moderate levels of stress exposure. Stress-inoculation theory suggests that the optimal environment for developing effective and adaptive coping skills is one in which the individual encounters a moderate amount of stress. Thus, the concept of stress inoculation predicts an inverse U- or J-shaped curve, which represents the relationship between stress exposure and adaptive functioning (Seery, 2011).

Empirical evidence for stress-inoculation effects is accumulating and comes primarily from studies of nonhuman primates and a few human observational and intervention studies. Contemporary research on squirrel monkeys shows a "developmental cascade" of inoculating effects resulting from moderate levels of early life stress (Lyons, Parker, Katz, & Schatzberg, 2009). In prospective longitudinal studies (Lyons et al., 2009; Parker, Buckmaster, Schatzberg, & Lyons, 2004; Parker & Maestripieri, 2011), a randomly selected group of infant squirrel monkeys were intermittently separated from their social group for brief periods. Compared to nonseparated monkeys, monkeys who had experienced separation showed less anxiety-like behavior and better engagement with novel situations than nonseparated monkeys (Parker et al., 2004). Neuroimaging investigations indicate that having coped with the early life stress of intermittent separations leads to greater white matter myelination of the ventromedial prefrontal cortex, a region involved in arousal regulation (Katz et al., 2009). It is important that these researchers have also shown that improved regulation is indeed a result of having experienced the challenge of separation rather than an increase in maternal care after reunion, which is a mechanism in studies of handled rats (Parker, Buckmaster, Sundlass, Schatzber, & Lyons, 2006).

Human evidence for stress inoculation is scant, but emerging studies demonstrate that moderate stress exposure may lead to increased capacity for future resilience. Intriguing data from a study of international children adopted into the United States showed that patterns of cortisol reactivity to a lab-based social stress induction significantly differed among three groups of 10- to 12-year-old children (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009). The "severe" stress group had lived in orphanages for an extended period of time and had been adopted late, the "moderate" stress group had spent less than 2 months in an orphanage and had been adopted by the age of 8 months, and the "low" stress group had lived con-

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tinuously with their biological parents in the United States. Whereas the severe and low stress groups did not differ from one another in cortisol reactivity, the "moderate" stress group showed lower cortisol reactivity, which the authors interpreted as reflecting resilience (Gunnar et al., 2009). Given that a similar study by this group using a sample of children adopted from Romania showed no significant differences in hypothalamus–pituitary–adrenal axis reactivity between the "moderate" and "low" stress-exposed children (Gunnar, Morison, Chisholm, & Schuder, 2001), replication of these results is needed before making stronger conclusions about possible stress-inoculation gains in children. However, similar stress-inoculation results were found in another study of 7-year-old children (Ellis, Essex, & Boyce, 2005). Children who had experienced intermediate levels of familial stress in infancy and the preschool period showed the lowest levels of autonomic reactivity to laboratory stress tasks, although it is not clear whether lower stress reactivity necessarily correlates with emotional, behavioral, or cognitive competence. Moreover, in a study of adolescents living in a runaway crisis shelter, a quadratic relationship between stress exposure and depressive symptoms emerged, such that individuals in both the high and low environmental risk groups exhibited more depressive symptoms than individuals in the moderate risk group (Erdem & Slesnick, 2010).

Available data on adults indicate that moderate stress leads to positive adjustment not seen in individuals with either no exposure or severe exposure. For instance, adults who had self-reported their cumulative lifetime exposure to adverse events were asked to report on new exposures to stressful life events during a 6-month follow-up period (Seery, Holman, & Silver (2010). It is not surprising that recent adversity showed a significant linear association with mental health as measured by self-reports of global distress, functional impairment, posttraumatic stress symptoms, and life satisfaction. Significant quadratic associations were also found such that the most favorable mental health outcomes were observed in individuals who had had a moderate amount of lifetime exposure to adversity (Seery et al., 2010). In a longitudinal study of adolescents (Mortimter & Straff, 2004), having a job in high school predicted lower self-esteem, more depressive affect, and higher levels of stress in high school. However, at follow-up in early adulthood, high school employment had a positive effect on feelings of self-efficacy and self-esteem and predicted less depressed mood. In a study examining the effects of stressful childhood events on women's depressive symptoms, the authors found that having experienced mild stressors during childhood was significantly related to having fewer depressive symptoms in adulthood if the women had also recently experienced stressful life events (Forest, Moen, & Dempster-McClain, 1996). As these studies demonstrate, negative correlations between stress and good adjustment revealed in longitudinal investigations may not be apparent in cross-sectional analyses.

The quality of care in early life is likely to be the primary context for establishing a biological basis for resilient functioning (Luthar & Brown, 2007), and it has been shown to influence behavior through variations in gene expression (Francis, Szegda, Campbell, Martin, & Insel, 2003). The very earliest life experiences are thought to establish a foundation for resilience that will have implications for coping later in life. In infancy, optimal mutual regulation between the infant and the primary caregiver can develop through everyday stresses associated with basic biological needs (e.g., hunger, elimination) and the challenges of achieving developmental milestones (DiCorcia & Tronick, 2011). Resilience in the infant is thought to build each time there is a moment of parent–infant "mismatch" and subsequent "reparation." Interactions are never perfect, and, thus, there is a constant transition from periods of match and mismatch between infant and caregiver. In this model, too much or too little sensitivity by the caregiver is hypothesized to lead to outcomes that are less optimal than those that result from having a moderate amount of sensitivity. During periods of mismatch, levels of stress increase, but during reparation and return to regulation, infants develop resilience. Therefore, some degree of stress and mismatch is critical for providing opportunities for successful coping. The "quotidian resilience" that results from successfully managing mundane everyday stressors may be considered a type of stress inoculation.

Resilience and PTG

Researchers who study PTG are careful to point out that, although related, PTG and resilience are not the same (Kilmer & Gil-Rivas, 2010). PTG involves a process of coping with a traumatic experience that results in significant positive transformation in domains such as the quality of relationships, feelings of personal strength, appreciation for life, and new life possibilities and spirituality, as measured by open-ended questions and structured questionnaire items (Kilmer et al., 2009; Tedeschi & Calhoun, 1996). It is important that, in PTG, symptoms of distress may not only co-occur with positive psychological growth, but the distress is thought to be a "key catalytic element" in the change process (Kilmer & Gil-Rivas, 2010, p. 1214). The degree of self-reported PTG has been shown to differ by the type of life event and, in studies of adults, has been associated most strongly with life-threatening or major life-changing experiences (Tedeschi & Calhoun, 1996). For instance, in a study of urban teenage girls, the experience of pregnancy and motherhood was associated with the highest levels of PTG across domains, whereas interpersonal problems were associated with the lowest levels (Ickovics et al., 2006). Although PTG is sometimes positively correlated with posttraumatic symptoms (e.g., Kilmer et al., 2009), it is sometimes associated with a decrease in emotional distress (Ickovics et al., 2006).

PTG and resilience are both similar and dissimilar. Resilience researchers have also acknowledged that symptoms and competencies are not mutually exclusive and that overtly competent children can at the same time covertly experience mental health symptoms (Luthar & Zigler, 1991; Luthar,

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1993). Whether the presence of symptomatology should disqualify a competent child from being classified as "resilient" depends on several factors, such as the type of adversity experienced (i.e., symptoms may co-occur with competencies more frequently in response to severe events) and the research question at hand (Luthar et al., 2000). Unlike resilience, PTG is concerned with self-perceptions of change from pre- to posttrauma. Therefore, any "personal best" in the life domains of PTG is considered growth, even though in absolute terms, a person's interpersonal relationships or level of personal strength may be low compared to other individuals. PTG and stress inoculation also share some commonalities. If coping with a traumatic experience leads to improvements in relationship quality or outlook on life, the chances that the individual will have better success in dealing with future stressors should increase.

BSC and DS

BSC (Boyce & Ellis, 2005) and DS (Belsky & Pluess, 2009; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007) models address factors that may influence an individual's susceptibility to environmental influences, and, therefore, can inform research on resilience and G × E. The BSC model proposes that there may be an endophenotype that predisposes children to be particularly susceptible to the influences of both negative and positive early environments, such that children who possess the susceptibility endophenotype are not only more likely to suffer from the effects of a risky early environment, but also more likely to benefit from the effects of a positive early environment (Boyce & Ellis, 2005). The DS model posits that there is a subset of individuals who are *genetically* predisposed to be susceptible to early environmental influences (Belsky & Pluess, 2009). These variations in susceptibility to early childhood environments have emerged as an evolutionary "bet-hedging strategy against an uncertain future" (Ellis & Boyce, 2011), where the susceptible subset of the population would flourish in a positive rearing environment or fail in a negative environment, and the less susceptible subset would survive regardless of the quality of the environment.

These theories emerged to explore developmental vulnerability to early environmental influences, positing that individual differences moderate the effects of early experience, rendering a subset of the population especially susceptible to the benefits and risks of early rearing environments. Both theories propose a "flip side of the coin" explanation to counter previous research on the risks of negative early environments, asserting that individuals once thought *vulnerable* to risks may be more appropriately described as *susceptible* to environmental effects, "for better *and* for worse" (Belsky et al., 2007).

Both the BSC and DS models are pertinent to resilience research, because they offer explanations for why some children are more resilient than others. If resilience is defined as the maintenance of prior levels of competence, or the absence of psychopathology in the context of stress, then the subset of children who are less susceptible to environmental risk would be the subset of the population that is more likely to be resilient to adversity. Both models explain that, although these nonsusceptible children are better off in negative environments, it is actually children who do not display resilience to adversity that benefit the most *when the environment is supportive.*

In addition, the BSC theory informs stress inoculation research by proposing that exposure to both extremely negative environments *and* extremely positive environments yield highly physiologically reactive children (Boyce & Ellis, 2005), creating the curvilinear (i.e., U-shaped) relationship between reactivity and quality of early life experiences that defines the stress inoculation hypothesis. This high reactivity emerges in highly positive environments because it is actually *advantageous* for a child to be highly reactive and responsive when the environment is supportive. In highly stressful environments, high reactivity is advantageous, or was advantageous in the past, because it heightened vigilance to threat.

Although there is not a great amount of empirical support of the BSC theory at present, there are several compelling findings that support the connections between stress reactivity, early environment, and later outcomes. These studies show evidence of the U-shaped curve, which suggests that extremely positive *and* extremely negative early environments are risk factors for demonstrating a high physiological reactivity to stress. Ellis et al. (2005) assert that individual differences in stress reactivity are related to variation in susceptibility to early environmental influences. They found that early exposure to both acutely stressful *and* highly protective environments yielded increased physiological reactivity to stress in school-age children. It was children who experienced moderately stressful early environments that experienced the lowest levels of reactivity. Obradovic, Bush, Stamperdahl, Adler, and Boyce (2010) provide evidence for why high physiological reactivity (previously conceptualized as maladaptive) may develop from highly protective early environments. The authors found that school-aged children who were highly reactive to stressors actually experienced more adaptive outcomes (as measured by prosocial behavior, the absence of externalizing symptoms, academic competence, and school engagement) *if* they had experienced and were experiencing low levels of adversity. Although high levels of stress reactivity may be a risk factor if the child later faces high adversity later in life, it is actually *adaptive* in the context of extremely positive environments.

Several studies have found support for DS theory. Empirical studies of DS theory often examine "plasticity alleles," which are alleles of candidate genes that are thought to contribute to the vulnerability or susceptibility to environmental influences. Belsky and Beaver (2011) found that adolescent males who carried more plasticity alleles of candidate genes and experienced supportive parenting during their youth exhibited more self-regulation, defined here as the capacity to control one's emotions, cognitions, and behavior. However,

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males who carried more plasticity alleles and experienced *unsupportive* parenting environments exhibited less self-regulation. In other words, males carrying plasticity alleles were more competent than males who carried fewer plasticity alleles when exposed to a beneficial environment, but less competent when exposed to a harmful environment. Beaver and Belsky (2011) provide further empirical support for DS theory when examining the relationship between genetic plasticity, early parenting support, and current parenting stress. Adult respondents who carried the most plasticity alleles had the highest levels of parental stress if they had experienced negative parenting in adolescence, but the lowest levels of parental stress if they had experienced positive parenting in adolescence. Although not originally conducted as an exploration of DS theory, Taylor, Way, Welch, Hilmert, Lehmans, and Eisenberg's (2006) study of the interaction between stressful life events and the serotonin transporter promoter polymorphism is often cited as strong evidence for DS. The authors found that individuals who were homozygous for the short allele of the serotonin transporter gene, compared to those with one or more long allele, *and* who experienced a stressful early family environment, had significantly higher depressive symptomatology, as predicted. However, those individuals who were homozygous for the short allele also exhibited significantly *less* depressive symptomatology if they had experienced a supportive early environment. This supports the notion that if they are exposed to a positive early environment, individuals thought to be *vulnerable* to environmental risk and thus less resilient, may also express more competence than those thought to be resilient.

Measured G × E Interactions, Childhood Maltreatment, and Resilience

Each year, numerous children are victims of maltreatment. In 2007 alone, 3.5 million children in the United States were investigated for maltreatment by child welfare agencies, and an estimated 794,000 cases were substantiated (US Department of Health & Human Services, 2007). It is not surprising that many children who experience physical abuse, sexual abuse, and neglect are at increased risk of mental health problems over the life course, including aggression and violent crime, depression, substance abuse, posttraumatic stress disorder, and suicide (Cicchetti & Toth, 2005; Widom, Dumont, & Czaja, 2007). In addition to increased risk for psychopathology, maltreated individuals are also at risk for other unfortunate outcomes, such as poor peer relations, lower academic achievement, negative economic consequences, and biological disease markers (Cicchetti & Toth, 2005; Currie & Widom, 2010; Danese & McEwen, 2012; Miller, Chen, & Parker, 2011). However, humans show a wide variability in their response to adverse experiences (Rutter, 1985), and maltreatment is no exception: some maltreated individuals are resilient and have positive developmental outcomes despite their experience of significant adversity as children (Cicchetti, 2010; Dumont, Widom, & Czaja, 2007; McGloin & Widom, 2001). Although prevalence rates of resilience are difficult to estimate because different studies define resilience in different ways, a recent review indicated that, based on stringent criteria, approximately 10%–25% of maltreated children and adolescents can be considered resilient (Walsh, Dawson, & Mattingly, 2010).

As of 2007, biology had been "notably absent" in resilience research (Luthar & Brown, 2007, p. 939), but, currently, there is rapidly growing interest in the biological bases of resilience (Charney, 2004; Cicchetti, 2010; Cicchetti & Blender, 2006; Curtis & Cicchetti, 2003; Feder, Nestler, & Charney, 2009; Luthar, 2006; Luthar & Brown, 2007; Masten & Obradovic, 2006; Sapienza & Masten, 2011), including gene–environment interactions (Cicchetti, 2010; Kim-Cohen & Gold, 2009). There is no logical reason why genes involved in moderating the impact of environmental risks would predict psychopathology any more than they would predict resilience. The vast majority of polymorphic genes have not been evolutionarily selected to cause mental disorders (Kendler, 2005), but they are likely to have been selected to confer greater vulnerability or protection against the positive and negative environments that individuals tend to encounter (Belsky & Pleuss, 2009). Genetic factors that support resilience or vulnerability may be hidden and revealed only when stress is present (Hanson & Gottesman, 2012). For instance, this phenomenon is a likely explanation for monozygotic twin discordance for highly heritable conditions such as schizophrenia (Gottesman & Bertelsen, 1989).

A rapidly growing literature indicates that genes may play a critical role in moderating the influence of adverse experiences, including childhood maltreatment, on the risk for psychopathology. G × E studies involving maltreatment began with the seminal articles published by Caspi and colleagues on the monoamine oxidase A (Caspi et al., 2002) and the serotonin transporter linked polymorphic region (*5-HTTLPR*; Caspi et al., 2003) polymorphisms, and have recently expanded to include evidence of moderation by alleles of the corticotropin releasing hormone receptor 1 (*CRHR1*; Bradley et al., 2008; Polanczyk et al., 2009; DeYoung, Cicchetti, & Rogosch, 2011), FK506 binding protein 5 (Binder et al., 2008; Xie et al., 2010; Appel et al., 2011), and endocannabinoid receptor 1 (Agrawal et al., in press) genes. Moreover, a handful of G × E studies now include more than a single gene and show evidence of G × G × E interactions (Cicchetti, Rogosch, & Oshri, 2011; Kaufman et al., 2006; Wichers et al., 2008; Cicchetti, Rogosch, & Sturge-Apple, 2007; Ressler et al., 2010). Together, the emerging data indicate that multiple gene/biology systems are implicated in whether some individuals, as a function of their genotype, are relatively more vulnerable or resilient to the negative consequences of maltreatment for mental health, which makes sense given that abuse and neglect can trigger a cascade of physiological reactions that lead to the "biological embedding" of adverse experiences and a multifinality of physical and mental health outcomes (Danese & McEwen, 2012; McCrory, De Brito, & Viding, 2011).

A handful of studies have investigated G × E hypotheses specifically in relation to resilience against childhood adver-

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sities. However, with one exception (Cicchetti & Rogosch, 2012), these studies used a self-report questionnaire (Connor & Davidson, 2003) to measure resilience as a personal trait (Carli et al., 2011; Das, Cherbuin, Tan, Anstey, & Easteal, 2011; Stein, Campbell-Stills, & Gelernter, 2009). Carli and colleagues (2011) used a sample of male prisoners and Stein and colleagues (2009) a sample of college undergraduates to investigate the role of *5-HTTLPR*, and they reported results in the opposite direction. In the prison sample that had high levels of stress exposure, the short allele was associated with higher resilience scores (Carli et al., 2011), whereas in the college sample the short allele predicted lower resilience scores (Stein et al., 2009). Das et al. (2011) utilized a representative sample of adults and found increased levels of resilience to childhood adversity in the presence of the 7-repeat allele of the dopamine receptor D4 (*DRD4*) exon III. Although it is encouraging that G×E research is now branching out to consider resilient outcomes rather than only psychopathology, studies that conceptualize and measure resilience as an individual trait may be problematic (Rutter, 2006b). This is because, as discussed above, resilience is theorized to result from a dynamic interplay among multiple factors that threaten adaptive functioning, as well as multilevel factors that protect against adversity and promote positive adjustment (Cicchetti & Blender, 2006; Luthar & Brown, 2007; Masten, 2012; Rutter, 2006b). Although the Connor–Davidson Resilience Scale (Connor & Davidson, 2003) is considered to be among the most psychometrically sound resilience scales available (Windle, Bennett, & Noyes, 2011), it is still limited by the fact that it views resilience as an individual trait.

In contrast to these studies, Cicchetti and Rogosch (2012) conducted a G×E study that involved a composite measure of resilience in a sample of nearly 600 maltreated children and nonmaltreated controls. The resilience composite included seven indicators of children's functioning in developmentally salient domains, such as social competence, externalizing and internalizing symptoms, and school functioning, based on self-reports, peer nominations, and counselor reports. Polymorphisms in four genes, *5-HTTLPR, CRHR1, DRD4–*521C/T, and oxytocin receptor, were all found to significantly moderate the impact of maltreatment on the resilient functioning score, which the authors interpreted as support for DS (Belsky & Pleuss, 2009; Ellis & Boyce, 2008). For instance, two copies of the *5-HTTLPR* short allele was associated with the lowest resilience scores in the presence of maltreatment, but the highest resilience scores in the absence of maltreatment. A similar pattern emerged for zero copies of the *CRHR1* TAT haplotype, the TT genotype for the *DRD4* gene, and the AA or AG genotypes for the oxytocin receptor gene. That is, a specific genotype for each of the four genes of interest predicted the greatest degree of plasticity such that outcomes were worst under maltreatment exposure but best when no maltreatment had been experienced. Cicchetti and Rogosch (2012) concluded that, "the genes included in this investigation appear to be minimally related to resilient functioning in maltreated children" (p. 425).

It is possible, however, that the data may be interpreted as showing some evidence for a G × E effect on resilience. Cicchetti and Rogosch (2012) also analyzed their data by adding up the number of "differentiating" or plasticity genotypes, and found that children with three or four of these genotypes showed low resilience scores in the presence of maltreatment but high scores in the absence of maltreatment. In contrast, maltreated and nonmaltreated children with zero differentiating genotypes did not differ in their resilience scores, which were at or above the sample mean and indicated what the authors had defined as a "medium" level of resilient functioning. Moreover, maltreated children with zero differentiating genotypes appeared to have higher resilience scores than maltreated children with three or four differentiating genotypes. Therefore, although no genotypes predicted high levels of resilient functioning in maltreated children, certain genotypes appear to be associated with relatively higher resilience in maltreated children.

Three points are especially noteworthy regarding G×E research involving childhood maltreatment. First, it is not surprising that the genes identified thus far are all involved, in one way or another, in modulating stress responses. Second, genetic influences on vulnerability or resilience to maltreatment appear to show some disorder specificity. For instance, the majority of G × E studies of the monoamine oxidase A gene have found links to antisocial behavior (Kim-Cohen et al., 2006) and the majority of studies of *5-HTTLPR* and *CRHR1* have found links to depression and depression-related constructs, such as suicidality and neuroticism. Further research, including meta-analyses, will be needed to ascertain whether these current trends hold, and if they do, these results can lead to better understanding the biological pathways by which childhood maltreatment can lead to mental disorders or resilience. Third, the vast majority of G×E studies of maltreatment focus on predicting psychopathology, which means that the understanding of resilience can only be inferred by the absence of psychopathology.

Conclusions

Resilience and G×E research are a natural pairing for a number of reasons.

An e-risk is a necessary element in G×E and in resilience phenotypes

Among the list of guidelines for programmatic G×E research by Moffitt et al. (2005, 2006) is one that calls for the identification of a candidate environment "pathogen." For strong G×E hypotheses, the candidate e-risk should meet three conditions: (a) there must be variability across individuals in response to the e-risk, (b) there must be evidence for a plausible effect of the environmental risk factor on a biological system involved in the disorder, and (c) there should be an environmentally mediated causal association.

Variability in response to stress tends to be the rule: ". . . large individual differences in response to stress and adversity

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are a universal feature of empirical studies following all manner of research strategies" (Rutter, 1985, p. 599). Although many succumb to the deleterious effects of stress, as described earlier, many also resist or recover from those effects, or, under certain circumstances, emerge stronger, wiser, and more resilient than before. If G × E hypotheses depend on good candidate e-risks that affect people differently, why should they be limited only to one end of the continuum on only one dimension (i.e., symptoms and not competencies)?

For several common psychiatric conditions, such as antisocial behavior, depression, and even schizophrenia, etiological research has yielded a robust and reliable set of risk factors, some of which may be causally related to these disorders. Such factors have usefully informed G × E studies, most notably the early studies by Caspi, Moffitt, and colleagues, by showing an interaction between a specific genetic polymorphism and childhood maltreatment for antisocial behavior (Caspi et al., 2002) and depression (Caspi et al., 2003), and early and heavy cannabis use for the onset of psychosis (Caspi et al., 2005). However, with the exception of posttraumatic stress disorder and adjustment disorder *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association, 2000), diagnostic criteria do not specify any precipitating events for the onset of symptoms. Understanding the mechanisms that lead to resilience is as important as understanding the mechanisms that lead to disorder. In fact, understanding mechanisms involved in resilient functioning may be even more advantageous in advancing our knowledge of developmental mechanisms, because, unlike most psychiatric diagnoses, it is an outcome measured in response to a particular risk exposure.

Candidate G × E genes for responsiveness to the environment are likely to play a role in resilience

Developmental psychopathologists have long recognized that genetic factors are likely to operate through influences on susceptibility to environmental conditions (Rutter, 1985), which is why candidate genes for G × E hypotheses should be those involved in influencing susceptibility to environmental pathogens (Moffitt et al., 2006). So-called "plasticity" genes have allelic variants that confer protection or less sensitivity to adverse environments and would therefore, predict resilience. However, there is a lack of knowledge regarding susceptibility genes in psychiatry because ". . . gene-discovery studies have been searching for genetic effects on disease rather than for genetic effects on vulnerability to environmental causes of disease" (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010, p. 520).

Both resilience and G × E are best understood as developmental processes

Resilience is conceptualized as dynamic with the understanding that adjustment can fluctuate over time in response to a stressor (Masten, 2011; Masten & Narayan, 2012). That is, not only are multiple *outcomes* possible after exposure to trauma (i.e., multifinality), but also multiple *pathways of adaptation* over time. Nonresilient pathways may be immediate or delayed, but both result in maladaptation following exposure to adversity. Despite recognition of the developmental nature of psychopathology, we know of no G × E studies that have measured phenotypes in a temporally dynamic fashion, and only one recent study that investigated direct gene-to-disorder trajectories for depressive symptomatology from adolescence to young adulthood (Adkins, Daw, McClay, & van den Oord, 2012). Integrating developmental perspectives into G × E hypotheses by utilizing temporal, pathway measures of phenotypes may be one promising direction for advancing the field.

Clearly, mental disorders place a great burden on patients, their families, and the public, whereas resilient outcomes do not. However, children confront major adversities on a daily basis that we as a society have not been able to effectively eradicate, despite knowing, for instance, that poverty or child maltreatment or war harm healthy development. These adversities are of public health concern, and understanding both genetic and nongenetic processes by which a proportion of exposed children cope well can and should lead to interventions that can eventually help others cope more successfully.

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