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Gene by Environment Interaction and Resilience: Effects of Child Maltreatment and Serotonin, Corticotropin Releasing Hormone, Dopamine, and Oxytocin Genes

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Abstract

In this investigation, gene-environment interaction effects in predicting resilience in adaptive functioning among maltreated and nonmaltreated low-income children (N = 595) were examined. A multi-component index of resilient functioning was derived and levels of resilient functioning were identified. Variants in four genes, 5-HTTLPR, CRHR1, DRD4 -521C/T, and OXTR, were investigated. In a series of ANCOVAs, child maltreatment demonstrated a strong negative main effect on children's resilient functioning, whereas no main effects for any of the genotypes of the respective genes were found. However, gene-environment interactions involving genotypes of each of the respective genes and maltreatment status were obtained. For each respective gene, among children with a specific genotype, the relative advantage in resilient functioning of nonmaltreated compared to maltreated children was stronger than was the case for nonmaltreated and maltreated children with other genotypes of the respective gene. Across the four genes, a composite of the genotypes that more strongly differentiated resilient functioning between nonmaltreated and maltreated children provided further evidence of genetic variations influencing resilient functioning in nonmaltreated children, whereas genetic variation had a negligible effect on promoting resilience among maltreated children. Additional effects were observed for children based on the number of subtypes of maltreatment children experienced, as well as for abuse and neglect subgroups. Finally, maltreated and nonmaltreated children with high levels of resilience differed in their average number of differentiating genotypes. These results suggest that differential resilient outcomes are based on the interaction between genes and developmental experiences.

Resilience is a dynamic process that encompasses the attainment of positive adaptation within the context of exposure to significant adversity that typically exerts major assaults on biological and psychological development (Cicchetti, 2010; Egeland, Carlson, & Sroufe, 2003; Luthar, Cicchetti, & Becker, 2000; Masten, 2001; Rutter, 1987, 2012). Resilient functioning is among the most intriguing and adaptive phenomena of human development. Prior to the advent of theorizing and research on adaptive functioning in the face of significant adversity, investigations of risk and psychopathology generally portrayed the developmental process as somewhat deterministic, eventuating in adverse and maladaptive outcomes. Investigations ranging from genetic and biological predispositions to psychopathology, to assaults on development associated with inadequate caregiving, conveyed the multiplicity of risks that eventuate in pathology (Cicchetti & Garmezy, 1993).

Beginning in the 1970s, the publication of the early writings on resilience by major systematizers in the field contributed to a burgeoning of research on the determinants of resilient functioning (Garmezy, Masten, & Tellegen, 1984; Luthar et al., 2000; Masten, Best, & Garmezy, 1990; Rutter, 1987; Werner & Smith, 1982). The major progenitor of this movement was Norm Garmezy, whose early writings on the topic were among the first exemplars of efforts to stress the importance of investigating protective factors in “at-risk” populations.

In discussing the merits of undertaking prospective longitudinal research with the offspring of schizophrenic parents, Garmezy asserted that these risk studies had the potential to “provide a developmental psychopathology that can produce a conceptual advance over a too dormant child psychiatry” (1974b, p. 116). Garmezy believed that such investigations could portray a compensating picture of a healthy normality in the midst of adversity and disadvantage, rather than the then prevalent notion of omnipresent disorder in such “at-risk” individuals (Garmezy, 1974b). Garmezy (1971) also noted that by examining the processes that help to impel such disadvantaged individuals to function adaptively, it would be possible to construct models of primary prevention that could promote adaptation and decrease maladaptation in vulnerable individuals.

Garmezy’s publications (1971, 1974a, 1974b, 1974c; Garmezy & Rutter, 1983) laid the groundwork for the conduct of future theoretical and empirical work on resilience. Efforts to comprehend the processes and mechanisms contributing to resilient functioning were spearheaded by Michael Rutter (1987) and by other investigators conducting research from a developmental psychopathology perspective (Luthar, 2006; Luthar et al., 2000; Masten, in press; Masten et al., 1990). Through discovering the mechanisms and processes that eventuate in resilient functioning despite the presence of adversity, both normal development and psychopathology could become better understood (Cicchetti, 1984, 2003; Masten et al, 1990; Rutter, 1986; Rutter & Garmezy, 1983).

Although Garmezy (1970, 1974a, b) certainly recognized that genetic liability contributed to the development of maladaptation and serious psychopathology, his work on the factors that contributed to resilience was psychosocial in nature. Specifically, Garmezy delineated three sets of factors that were implicated in the development of resilience: 1) attributes of the individual children; 2) aspects of their families; and 3) characteristics of their broader environments (Masten & Garmezy, 1985; see also Werner & Smith, 1982, 1992). In fact, until recently, the vast majority of research on the development of resilient functioning in humans eschewed the study of genetic and biological contributors. Because self-righting, one of the basic mechanisms contributing to the development of resilient adaptation, has historical roots that are embedded in the fields of genetics and embryology (Sameroff, 1983; Waddington, 1957), the paucity of biological measures in research on resilience has been an unfortunate circumstance.

The artificial distinction among genetics, neurobiology, and behavior in research on the determinants of resilience contradicts years of developmental research demonstrating co-actions among all levels of analysis, from the molecular to the environment broadly construed (Gottlieb, 1992; Gottlieb & Halpern, 2002). For the past decade, there have been calls for incorporating genetic and biological assessments into the research armamentaria of researchers investigating resilience (see, e.g., Charney, 2004; Cicchetti, 2003; Cicchetti & Curtis, 2006; Curtis & Cicchetti, 2003; Feder, Nestler, & Charney, 2009; Masten, 2007). The scientific and technological advances that have taken place in recent years have begun to provide researchers with the means for investigating the biological processes that underlie the development of resilient functioning (see, e.g., Curtis & Cicchetti, 2003; Feder et al., 2009).

Research on resilience in maltreated individuals

Child maltreatment represents one of the most deleterious and stressful challenges that confront children (Cicchetti & Lynch, 1995). The vast majority of abused and neglected children are adversely affected by their maltreatment experiences. Thus, child abuse and neglect may represent the greatest failure of the caregiving environment to provide opportunities for normal development (Cicchetti & Lynch, 1995; Cicchetti & Valentino, 2006). However, not all children who have been maltreated manifest maladaptive development and/or psychopathology (Cicchetti, 2010; Cicchetti & Lynch, 1995; Cicchetti & Toth, 1995). Accordingly, investigating the pathways to resilient functioning among children who have experienced maltreatment has the potential to uncover the multilevel dynamic processes that eventuate in a multiplicity of child developmental outcomes in abused and neglected children, as well as in nonmaltreated children.

As is true for the field of resilience research more broadly, investigations of the factors and processes contributing to adaptive functioning within the face of adversity in abused and neglected individuals have focused predominantly on psychosocial variables (Collishaw, Pickles, Messer, Rutter, Shearer, & Maughan, 2007; Dumont, Widom, & Czaja, 2007; Herrenkohl, Herrenkohl, & Egolf, 1994; Jaffee & Gallop, 2007; McGloin & Widom, 2001; Moran & Eckenrode, 1992; Wingo, Fani, Bradley, & Ressler, 2010). The psychosocial factors implicated in the development of resilience in maltreated children and adults include neighborhood characteristics, personality variables, secure attachment relationships, self-regulatory processes, close friendships and adolescent peer relationships, supportive parenting, high quality, and adult love relationships, among others (Beeghly & Cicchetti, 1994; Haskett, Nears, Ward, & McPherson, 2006).

In a longitudinal study on processes leading to resilience conducted in our laboratory, we, too, examined psychosocial determinants (Cicchetti & Rogosch, 1997). For the maltreated children, the major predictors of resilient functioning were the personality characteristics of ego overcontrol (i.e., the ability to monitor and control impulses and regulate affect) and ego resiliency (i.e., the degree of relative flexibility in regulating affect and behavior to meet situational demands) (Block & Block, 1980), and positive self-esteem. Promotion of resilience among nonmaltreated resilient children, in contrast, was more strongly related to positive relationships with adults and high levels of ego-resiliency, irrespective of nonmaltreated children's level of ego-control.

Thus, personality characteristics and self-system processes were more important in achieving resilient adaptation in maltreated children. Through the personality process of resilient overcontrol, maltreated children who function in a resilient fashion may be more attuned to what is necessary for successful adaptation in their adverse home environments. In contrast, the more affectively expressive style of resilient undercontrollers may not be well suited for successful adaptation in maltreating environments, because such personality styles may provoke attention and reaction from others that could result in greater risk for maltreatment (Cicchetti et al., 1993; Cicchetti & Rogosch, 1997).

Additional cross-sectional research on the psychosocial determinants of resilience in maltreated and nonmaltreated children conducted in our laboratory has revealed that personality and self processes play prominent roles in the development of adaptive functioning in maltreated children (Cicchetti, Rogosch, Lynch, & Holt, 1993; Flores, Cicchetti, & Rogosch, 2005; Kim & Cicchetti, 2004).

In keeping with calls for a multiple levels of analysis perspective in the investigation of the development of psychopathology and resilience (Cicchetti & Curtis, 2007; Cicchetti & Dawson, 2002; Curtis & Cicchetti, 2003; Masten, 2007), we conducted two multilevel

investigations that moved our work beyond a single level focus on psychosocial predictors of resilient adaptation. In the first study, emotion regulation and hemispheric EEG asymmetry were investigated as joint contributors to resilient functioning in maltreated and nonmaltreated children. EEG activity indexes a neural system that has emotion-specific influences whereby the two hemispheres of the cerebral cortex have been found to be differentially involved in emotion (Davidson, 2000). The left hemisphere is associated with positive emotions/approach behavior and the right hemisphere is linked with negative emotions/withdrawal behavior. Positive emotion and good emotion regulatory abilities have been associated with resilient adaptation (Davidson, 2000; Masten, 1986). We found that a neural-level phenomenon, hemispheric EEG asymmetry, was an independent contributor to resilient functioning in maltreated children (Curtis & Cicchetti, 2007). Specifically, maltreated children who were functioning in a resilient fashion exhibited left hemispheric activation asymmetry. Moreover, an adult behavioral rating of emotional regulation, based on 35 hours of child observation, also significantly predicted resilient adaptation in both maltreated and nonmaltreated children.

In a second multilevel investigation we found that ego resiliency and ego overcontrol and the adrenal steroid hormones associated with stress (i.e., cortisol and dehydroepiandrosterone [DHEA]) made independent and noninteractive contributions to resilience, even though they were operating at different levels of analysis (Cicchetti & Rogosch, 2007). We discovered that higher morning levels of cortisol were related to lower levels of resilient strivings for the nonmaltreated children. Physically abused children with high morning cortisol had higher resilient functioning than physically abused children with lower levels of morning cortisol.

In contrast, we found that higher morning levels of cortisol were related to lower levels of resilient strivings for the nonmaltreated children. Within the group of maltreated children, differences in cortisol regulation were found as a function of the subtype(s) of maltreatment experienced. Physically abused children with high morning cortisol had higher resilient functioning than physically abused children with lower levels of morning cortisol.

Prior research on neuroendocrine regulation has indicated that physically abused children generally exhibit lower levels of morning cortisol secretion (Cicchetti & Rogosch, 2001). It may be that the subgroup of physical abused children who were able to elevate cortisol to cope with the life stressors were demonstrating a greater striving for resilient adaptation. In contrast, the larger subgroup of physically abused children with lower levels of morning cortisol may have developed hypocortisolism over time in response to chronic stress exposure (i.e., allostatic load) (Cicchetti, Rogosch, & Oshri, 2011). As a result, for these children there may be a diminished capacity to mobilize the hypothalamic pituitary adrenal (HPA) axis to promote positive adaptation under conditions of ongoing stress. Additionally, we found that the very low level of resilience among sexually abused children with high basal cortisol may be a product of their different traumatic experiences and consequences of chronic excessive vigilance and preoccupation, with commensurate HPA axis hyperarousal.

Finally, we also discovered that maltreated children with high resilient functioning exhibited a unique atypical pattern of a relative DHEA diurnal increase. Maltreated children who have the capacity to elevate DHEA over the course of the day may be better equipped to cope with the demands of high chronic exposure to stress and to adapt competently. In contrast, the nonmaltreated children who functioned resiliently did not exhibit the pattern of diurnal DHEA increase; instead they displayed the lowest levels of DHEA across the day.

Gene-Environment interactions: Implications for resilience

Research on gene-environment interactions has demonstrated that child maltreatment is a strong candidate environmental pathogen (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Karg, Burmeister, Shedden, & Sen, 2011). Maltreatment is an objectively measured, well-defined stressor and meta-analyses have shown that robust findings in GxE investigations are more likely to occur when a specific stressor is identified (cf. Karg et al., 2011). Most GxE research that is relevant to resilience has focused on how genes also may serve as protective factors against developing psychopathology in individuals who have experienced maltreatment (e.g., Bradley et al., 2008, 2011; Caspi et al., 2002, 2003; Cicchetti, Rogosch, & Oshri, 2011; Polanczyk et al., 2009).

Now that gene-environment interaction (GxE) studies of psychopathology have been accorded great attention in the literature (Caspi et al., 2010; Duncan & Keller, 2011; Karg et al., 2011; Risch et al., 2009), several investigators have asserted that empirical studies of genetic contributors to resilience be undertaken (Cicchetti & Blender, 2006; Curtis & Cicchetti, 2003; Feder et al., 2009; Kim-Cohen & Gold, 2009). To date, to the best of our knowledge, there have been no empirical studies that have investigated whether there are particular gene variants that may be related to the development of resilience in individuals who have experienced significant adversity such as child maltreatment (Kim-Cohen & Gold, 2009). It is unlikely that genes act in isolation in explaining such a complex, multiply influenced developmental process as resilience.

According to the differential susceptibility to environmental influence hypothesis proffered by Belsky and Pluess (2009; Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams, 2009), genes that confer risk in harsh environments may confer benefits in normal or nurturing environments. In other words, the characteristics of individuals (including their genotypes) that render them disproportionately more vulnerable to experiencing adversity may also make them disproportionately more likely to benefit from supportive contexts (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011).

In this, the first investigation of the contributions that molecular gene variants may make to the development of resilience in maltreated and nonmaltreated children from low-SES backgrounds, we chose to investigate the separate and cumulative contributions of four candidate genes: the serotonin transporter gene (5-HTT); the oxytocin receptor gene (OXTR); the dopamine receptor D4 (DRD4, -521 C/T SNP) gene; and the corticotropin releasing hormone receptor 1 (CRHR1) gene. Each of these genes was chosen because of their associations with aspects of behavior found to be predictive of resilience in single level psychosocial studies.

5-HTT has been shown to be involved in brain development and in individual differences in mood and emotion regulation (Caspi et al., 2010), which have been demonstrated to be related to resilience in behavioral and biological research (Curtis & Cicchetti, 2007; Davidson, 2000). CRHR1 is the key activator of the HPA axis, binding to receptors that initiate the stress response and culminating with release of cortisol from the adrenal cortex. The ability to regulate stress has long been associated with resilient functioning (Masten & Garmezy, 1985; Rutter, 2012). DRD4, in combination with the -521 C/T SNP, has been shown to be related to quality of attachment organization in some, but not all, studies (see Cicchetti, Rogosch, & Toth, 2011). Secure attachment with an adult figure has been shown to be related to resilience (Beeghly & Cicchetti, 1994). The oxytocin receptor gene (OXTR) has been linked to individual differences in psychological resources that are predictive of physical and psychological health (Saphire-Bernstein, Way, Kim, Sherman, & Taylor,

2011). Psychological resources such as self-esteem, optimism, and mastery have been found to be protective factors in the development of resilient functioning (Cicchetti & Rogosch, 1997; Masten, in press; Seligman & Csikszentmihalyi, 2000). OXTR also has been shown to be related to attachment and relationship quality which are valuable resources for resilient functioning (Bakermans-Kranenburg & van IJzendoorn, 2008) as well as social behavior (Inoue, Kimura, Azuma, Inazawa, Takemura et al., 1994). In this first investigation of genetic influences on resilience in maltreated children, we have selected these candidate genes because of their potential to influence processes known to be associated with resilience. However, it is clear that a diversity of other candidate genes also could be considered, and our selection is by no means exhaustive.

Hypotheses

This investigation was guided by the following hypotheses and research questions.

1. Nonmaltreated children will have higher mean levels of resilient functioning than maltreated children and a higher percentage of children in the high resilience group. Nonetheless, high resilient maltreated children will exist.
2. We will examine whether genetic variation in four candidate genes, 5-HTTLPR, CRHR1, DRD4 -521C/T, and OXTR, contributes to variation in resilient functioning in low-income children. Based on prior evidence in the literature, we do not expect the independent main effect of each gene to be strong.
3. We will investigate the potential for Gene X Environment interactions among each of the four candidate genes and child maltreatment experience, in order to determine potential genetic moderation of the impact of maltreatment on resilient strivings in low-income children. Different genes may be related to resilient strivings based on maltreatment experiences. Based on the paucity of research on the role of Gene X Environment interactions in resilience, we did not posit a priori expectations about specific genotypes that could show differential effects for maltreated and nonmaltreated children.
4. We expect that the collective influence of variants from multiple genes, in interaction with child maltreatment experience, will increase prediction of variation in resilient functioning among maltreated and nonmaltreated children.
5. Among the group of children who have *high* levels of resilient functioning, maltreated and nonmaltreated children will differ in their genetic presentation.

Method

Participants

The participants in this investigation included 595 children aged six to twelve ($M_{age} = 9.81$, $SD = 2.06$) who attended a summer camp research program designed for school-aged low-income children. Some children attended the camp for multiple years, and the data from their first year of attendance were used in the current study. The sample included both maltreated children ($n = 313$) and nonmaltreated children ($n = 282$). Among the participants, 53.4 % were boys. The maltreated and nonmaltreated children were comparable in terms of racial/ethnic diversity and family demographic characteristics. The Add Health system for coding race and ethnicity was used (<http://www.cpc.unc.edu/projects/addhealth/data/code/race>) (DeYoung, Cicchetti, Rogosch, Gray, Eastman, & Grigorenko, 2011). 62.0% of the sample was African American, 19.0% was white, 17.0% was Hispanic, and 2.0% was from other racial/ethnic groups. The families of the children were low income, with 95.1% of the families having a history of receiving welfare benefits. Single mothers headed 62.9% of the families.

Recruitment and Classification Procedures

Parents of all maltreated and nonmaltreated children provided informed consent for their child's participation, as well as consent for examination of any Department of Human Services (DHS) records pertaining to the family. Children in the maltreated group had been identified by the county DHS as having experienced child abuse and/or neglect, and the sample was representative of the children in families receiving services from the DHS. A recruitment liaison from DHS contacted eligible maltreating families, explained the study, and if parents were interested, then their names were released to the project team for recruitment. Families were free to choose whether or not to participate. Comprehensive searches of DHS records were completed, and maltreatment information was coded utilizing operational criteria from maltreatment nosology specified in the *Maltreatment Classification System* (MCS; Barnett, Manly, & Cicchetti, 1993), as discussed below.

Consistent with national demographic characteristics of maltreating families (National Incidence Study – NIS-4; Sedlak et al., 2010), the maltreated children were predominantly from low socioeconomic status families. Consequently, demographically comparable nonmaltreated children were recruited from families receiving Temporary Assistance for Needy Families (TANF). A DHS recruitment liaison contacted eligible nonmaltreating families, described the project, and if interested, parents signed a release for their names to be given to the project for recruitment. DHS record searches were completed for these families to verify the absence of any record of child maltreatment. Trained research assistants also interviewed mothers of children recruited for the nonmaltreatment group to confirm a lack of DHS involvement and prior maltreatment experiences utilizing the *Maternal Maltreatment Classification Interview* (Cicchetti, Toth, & Manly, 2003). Subsequently, record searches were conducted in the year following camp attendance to verify that all available information had been accessed. Only children from families without any history of documented abuse or neglect were retained in the nonmaltreatment group. In addition, families who had received preventive services through DHS due to concerns over risk for maltreatment were excluded from the sample to reduce the potential for unidentified maltreatment existing within this group.

The MCS is a reliable and valid method for classifying maltreatment (Bolger, Patterson, & Kupersmidt, 1998; English et al., 2005; Manly, 2005) that utilizes DHS records detailing investigations and findings involving maltreatment in identified families over time. Rather than relying on official designations and case dispositions, the MCS codes all available information from DHS records, making independent determinations of maltreatment experiences. Based on operational criteria, the MCS designates all of the subtypes of maltreatment children have experienced (i.e., neglect, emotional maltreatment, physical abuse, sexual abuse). Coding of the DHS records was conducted by trained research assistants, doctoral students, and clinical psychologists. Coders were required to meet acceptable reliability with criterion standards before coding actual records for the study. Coders demonstrated acceptable reliability with the criterion (weighted κ 's with the criterion ranging from .86 to .98. Reliabilities (κ 's) for the presence vs. absence of maltreatment subtypes ranged from .90 to 1.00.

In terms of the subtypes of maltreatment, *neglect* involves failure to provide for the child's basic physical needs for adequate food, clothing, shelter, and medical treatment. In addition to inadequate attention to physical needs, forms of this subtype include lack of supervision, moral-legal neglect, and education neglect. *Emotional maltreatment* involves extreme thwarting of children's basic emotional needs for psychological safety and security, acceptance and self-esteem, and age-appropriate autonomy. Examples of emotional maltreatment of increasing severity include belittling and ridiculing the child, extreme negativity and hostility, exposure to severe marital violence, abandoning the child, and

suicidal or homicidal threats. *Physical abuse* involves the non-accidental infliction of physical injury on the child (e.g., bruises, welts, burns, choking, broken bones). Injuries range from minor and temporary to permanently disfiguring. Finally, *sexual abuse* involves attempted or actual sexual contact between the child and caregiver for purposes of the caregiver's sexual satisfaction or financial benefit. Events range from exposure to pornography or adult sexual activity, to sexual touching and fondling, to forced intercourse with the child.

Children in the maltreatment group all had documented histories of abuse and/or neglect occurring in their families according to DHS records. However, DHS record information was not complete enough to code maltreatment subtype information for 42 (13.4%) of the maltreated children. Among the remaining maltreated children, 77.1% had experienced neglect, 67.2% had experienced emotional maltreatment, 31.0% had experienced physical abuse, and 8.9.1% had experienced sexual abuse. As is typical in maltreated populations (Bolger et al., 1998; Manly et al., 1994; 2001), the majority of children had experienced multiple subtypes of maltreatment. Specifically, 63.3% of the maltreated children had experienced two or more maltreatment subtypes. Among maltreated children, we derived two indices to characterize maltreatment subtype experiences. First, based on the number of subtypes of maltreatment children had experienced, we grouped children who had experienced one or two subtypes (80.7%) versus those who had experienced 3 or 4 subtypes (19.3%). Second, given the overlap among subtypes and the relatively lower rates of physical and sexual abuse as compared to neglect and emotional maltreatment, we identified children who had experience neglect and/or emotional maltreatment (PNEM; 63.1%) without physical or sexual abuse versus children who had experience physical and/or sexual abuse (PASA; 36.9%). The PASA group also may have experienced neglect or emotional maltreatment.

Procedure

Children attended a week-long day camp program and participated in research assessments. At the camp, children were assigned to groups of eight same-age and same-sex peers; half of the children assigned to each group were maltreated. Each group was conducted by three trained camp counselors, who were unaware of the maltreatment status of children and the hypotheses of the study. Camp lasted 7 hrs/day for five days, providing 35 hours of interaction between children and counselors. In addition to the recreational activities, after providing assent, children participated in various research assessments (see Cicchetti & Manly, 1990, for detailed descriptions of camp procedures) and provided DNA samples. Trained research assistants, who also were unaware of research hypotheses and maltreatment status, conducted individual research sessions with children, in which questionnaires and other research measures were administered. Clinical consultation and intervention occurred if any concerns over danger to self or others emerged during research sessions. At the end of the week, children in each group completed sociometric ratings of their peers. The counselors, who had been trained extensively for two weeks prior to the camp, also completed assessment measures on individual children, based on their observations and interactions with children in their respective groups.

Measures

The measures described below constitute a subset of assessments conducted during the research camp. The camp context and associated measurement battery provide a multi-informant, multi-perspective view of child adaptive functioning. Measures include child self-report, peer evaluations, counselor observations, and counselor-report assessments of individual children, as well as school record data obtained from children's school districts.

DNA collection, extraction, and genotyping

Using an established protocol, trained research assistants obtained DNA samples from participants by collecting buccal cells with the Epicentre Catch-All Collection Swabs. Subsequently, using the conventional method, DNA was extracted with the Epicentre BuccalAmp DNA Extraction Kit, in order to prepare DNA for PCR amplification. Genotyping was conducted following previously published protocols.

DNA was whole-genome amplified using the Repli-g kit (Qiagen, Catalogue No. 150043) per the kit instructions to ensure the availability of data over the long term for this valuable sample. Amplified samples were then diluted to a working concentration.

The 5-HTT gene has a polymorphism in the linked polymorphic region (5-HTTLPR) in the 5' regulatory region due to a 44-base pair deletion that eventuates in either the short (s) or long (l) allele (Lesch et al., 1996). 5-HTTLPR samples were genotyped for fragment length polymorphisms of 5-HTTLPR with Hot Star Taq PCR Mix (Qiagen, Catalog No. 203205) and previously described primers (Gelernter, Kranzler, & Cubells, 1997), followed by fragment analysis using a CEQ 8000 (Beckman-Coulter, Inc.). The call rate for 5-HTTLPR was 99.7%.

CRHR1 was genotyped using assays for SNPs rs110402, rs242924, and rs7209436 purchased from Applied Biosystems, Inc. (ABI) as C2544843 10, C2257689 10, and C1570087 10, respectively. Individual allele discriminations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Inc. (ABI), Catalog No. 4371357) with amplification in an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200.

The call rates for the three SNPs for CRHR1 were as follows: rs7209436 = 99.7%; rs1104202 = 99.8%; rs242924 = 99.8%. For four individuals, we could not confidently determine the genotype of one SNP of CRHR1. For two individuals, rs7209436 was indeterminate, whereas one individual was indeterminate for rs1104202 and one for rs242924. Because the remaining two CRHR1 SNPs for these four individuals were able to be genotyped, all participants in this study had a haplotype for each of the three CRHR1 SNPs.

Haplotypes for the three CRHR1 SNPs were determined using GeneticsBase (Warnes, 2003). Because the three SNPs were very strongly related (all $r > .92$), GeneticsBase was able to estimate haplotypes for every participant with a posterior probability higher than .98, which allowed us to assign a score of 0, 1, or 2 copies of the TAT haplotype to participants with a high degree of certainty. The TAT haplotype accounted for 32.1% of all haplotypes in the sample, with its complement, CGG, accounting for 60.1%.

The rs1800955 polymorphism is located 521 bp upstream from the first codon in the DRD4 gene. This SNP consists of either a C or a T and because of its location in the promoter region may affect transcription of the gene. The DRD4 -521 C/T polymorphism was genotyped using a Taq Man SNP assay from Applied Biosystems, Inc. Individual allele determinations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification on an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200 with JMP 8.0 (SAS, Inc.). The call rate for DRD4 -521C/T was 99.5%.

The OXTR rs53576 SNP was genotyped using a TaqMan SNP assay from Applied Biosystems, Inc. Individual allele determinations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification on an ABI 9700

thermal cycler and analyzing the endpoint fluorescence using a Tecan M200 with JMP 8.0 (SAS, Inc.).

If a genotype for any gene or SNP could not be determined after the first run, then it was repeated up to four times. If the null result persisted, then a genotype was not assigned to that individual.

All DNA samples were genotyped in duplicate for quality control. Additionally, human DNA from cell lines was purchased from Coriell Cell Repositories for all representative genotypes in duplicate and genotypes confirmed by sequencing using DTC& chemistry on an ABI 3130x1. These and a no template control were run alongside study samples representing 9% of the total data output. Any samples that were not able to be genotyped to a 95% or greater confidence level were repeated under the same conditions.

Child self-report measures

Children's Depression Inventory (CDI; Kovacs, 1982, 1992)—The CDI is a widely used self-report questionnaire to assess depressive symptomatology in school-age children. For each item, children chose from among three option statements, depicting increasing levels of depressive symptoms, in order to characterize their experiences in the past two weeks. Internal consistency for the total scale has ranged from .71 to .89, and validity has been well established (Kovacs, 1992). In the present sample, CDI scores ranged from 0 to 42 ($M = 8.93$, $SD = 7.51$).

Peer measures

Peer Nominations—After children had interacted with each other during the week of summer camp, children evaluated the characteristics of their peers in their respective camp groups using a peer nomination method on the last day of camp (cf., Coie & Dodge, 1983). Counselors conducted the sociometric assessment with individual children. For each peer in the camp group, children were given five brief behavioral descriptors characterizing different types of social behavior and asked to select one peer from the group who best fit the behavioral description, as well as select the one child who he/she liked most and liked least. The behavioral descriptors included a child who was: cooperative, a leader, shy, disruptive, and a fighter. The total number of nominations that each individual child received from peers in each category was determined, and these totals were converted to proportions of the possible nominations in each category, and these scores in each category were standardized within each year of camp.

Counselor Measures

Behavior ratings—Observations of children's social behavior were made based on the methodology of Wright (1983). Camp counselors rated the behavior of individual children on nine items tapping three aspects of interpersonal functioning, including prosocial behavior, aggressiveness, and social withdrawal. Seven-point ratings were completed each day based on 45-min observations of children in structured and unstructured camp settings (e.g., sports, lunch, art, free play, awards). Inter-rater reliabilities based on average intraclass correlations among pairs of raters across the years of assessment ranged from .68 to .80 ($M = .76$) for prosocial, .70 to .84 ($M = .77$) for aggression, and .61 to .77 ($M = .71$) for withdrawal. Individual counselor assessments for each of the three scales across measurement occasions were averaged to generate individual child scores.

Pupil Evaluation Inventory (PEI; Pekarik, Prinz, Liebert, Weintraub, & Neale, 1976)—The PEI was completed by camp counselors for children in their respective groups at the end of each camp week. The PEI consists of 35 items assessing social behavior,

yielding three homogeneous and stable factors, including likeability, aggression, and withdrawal. Similar to peer nomination procedures, counselors were asked to select no more than two children who were best characterized by each individual item. Inter-rater reliabilities based intraclass correlations across the years of camp ranged from .72 to .85 ($M = .78$) for likeability, .85 to .90 ($M = .88$) for aggression, and .72 to .84 ($M = .78$) for withdrawal.

Teacher Report Form (TRF; Achenbach, 1991)—Behavioral symptomatology was evaluated at the end of each week by counselors' completion of the TRF. The TRF is a widely used and validated instrument to assess behavioral disturbance from the perspective of teachers, and the measure was used in the present study, because camp counselors are able to observe similar behaviors to that of teachers. The TRF, containing 118 items rated for frequency, assesses two broadband dimensions of child symptomatology, externalizing and internalizing, as well as total behavior problems. In the present study, interrater reliability for the internalizing and externalizing scales based on average intraclass correlations among pairs of raters ranged from .56 to .84 ($M = .68$) for internalizing, and from .78 to .88 ($M = .83$) for externalizing. The counselors' scores for each child were averaged to obtain individual child scores for the broadband dimensions. In the current sample, T scores ranged from 36 to 72 ($M = 48.90$, $SD = 7.88$) for internalizing and 39 to 80 ($M = 52.46$, $SD = 8.79$) for externalizing.

School Record Data

School risk index—Each year, information from school districts on children's adaptation to school was obtained for the academic year prior to camp. Annual evaluations of each child were used by the school districts to determine broad indicators of deficient school functioning. The school risk index is a total of five possible risk indicators, including: a. attendance problems in the form of excessive absences or tardiness, b. poor performance on standardized achievement tests, c. suspension from school, d. failing school grades, and e. being two or more years below age level for grade placement. Meeting criteria for any of these five indicators was considered substantial risk in adapting successfully to school.

Composite of Resilient Functioning

Consistent with prior work examining resilience in maltreated and nonmaltreated children (Cicchetti & Rogosch, 1997; 2007; Cicchetti et al., 1993), a composite of resilient functioning was derived from indicators of children functioning well in domains of particular developmental importance for school-aged children. Initially, three composite indicators of social competence, combining the perspectives of peers and adults, were generated. First, a prosocial composite combined peer nomination scores for leader and cooperative with counselor behavior rating scores for prosocial behavior and counselor PEI scores for likeability. This composite was internally consistent with alphas ranging from .66 to .75 ($M = .70$). Second, a disruptive-aggressive composite was comprised of peer nominations of disruptive and fights, and counselor behavior ratings of aggressive and counselor PEI scores for aggressiveness. The internal consistencies for this composite across the years ranged from .80 to .87 ($M = .85$). Third, a withdrawn composite included peer nomination scores for shy, counselor behavior ratings for withdrawn, and counselor PEI scores for the withdrawn subscale. Alphas ranged from .68 to .78 ($M = .69$). For each of these internally consistent composites, component variables were standardized within each camp year, and the standardized variables were averaged to generate the composite scores for each child.

In addition to these three indicators of social competence, the child's self-report of depressive symptoms on the CDI, counselor assessment of internalizing and externalizing

behavior problems from the TRF, and the school risk index were other components of the resilience composite. For each of the seven indicators, criteria for the most competent functioning were established. More specifically, children were considered demonstrating competent functioning if they had scores in the top third of the distribution for the prosocial composite, scored in the lowest one third of the distribution for the aggressive composite, the withdrawn composite, the CDI score, and TRF internalizing and externalizing scores, and had no school risk indicator. Children meeting the criterion on a given dimension were given a score of 1; all other children were given a score of 0 for that dimension. Summing across the seven indicators produced a composite index of resilient functioning with a possible range of scores ranging from 0 to 7 ($M = 2.07$, $SD = 1.59$). We also established criteria for levels of resilient functioning, with scores of 0-1 classified as low resilient function, 2-4 as medium, and 5 or more as high.

Results

We first evaluated whether there was evidence for an association between maltreatment status and genetic variation in each of the candidate genes under consideration, Gene-Environment correlation (rGE). Chi-square tests were conducted for maltreatment status and the genotype distributions of each of the genes. All χ^2 tests were nonsignificant, $\chi^2(2, N = 595) = 1.36$, $p = .51$ (5-HTTLPR); $.89$, $p = .64$ (CRHR1 TAT haplotype); 1.09 , $p = .58$ (DRD4 - 521C/T), and 1.50 , $p = .47$ (OXTR). Thus, genetic variation in each of the genes was unrelated to maltreatment status and children with different genotypes were not differentially more likely to experience maltreatment. We found no evidence for an evocative rGE .

Resilient Functioning and Candidate Genes: Evidence for GxE effects

In the next series of analyses, we used ANCOVAs to examine the influence of maltreatment status and genetic variation on each of the candidate genes, and their interaction (GxE) in order to predict individual differences in resilient functioning scores. In each ANCOVA model, gender and age were included as covariates. Additionally, a categorical race/ethnicity (black, white, Hispanic, other) was included as a main effect in each of the models in order to address potential population stratification, and control for race and ethnicity effects.

5-HTTLPR—In the ANCOVA utilizing the 5-HTTLPR genotypes, the main effect for maltreatment status was significant, $F(1,593) = 21.57$, $p < .001$, partial $\eta^2 = .036$. Specifically, maltreated children had significantly lower resilient functioning scores than nonmaltreated children. In contrast, the main effect for 5-HTTLPR genotypes was nonsignificant, $F(2,593) = .097$, $p = .91$, partial $\eta^2 = .00$. However, a significant maltreatment status by 5-HTTLPR interaction was observed, $F(2,593) = 3.13$, $p = .045$, partial $\eta^2 = .011$. This interaction effect is depicted in Figure 1a. Follow-up ANCOVAs were used to probe the interaction effect within genotype groups. As shown in Figure 1a, the largest difference between maltreated and nonmaltreated children on resilient functioning was observed among children in the SS genotype group, $F(1,60) = 10.78$, $p = .002$, partial $\eta^2 = .166$; the maltreatment status difference also was significant in the LL genotype, $F(1,300) = 15.71$, $p = .001$, partial $\eta^2 = .051$, but not in the SL genotype group, $F(1,233) = 2.56$, $p = .11$, partial $\eta^2 = .011$. Thus, while maltreated children generally have lower resilient functioning scores than nonmaltreated children, the difference between maltreated and nonmaltreated children is larger among children with the SS genotype.

CRHR1 TAT haplotype—We next considered the effects of the CRHR1 TAT haplotype in the ANCOVA model, and its interaction with maltreatment status. The effect of maltreatment status was significant, $F(1,595) = 10.37$, $p = .001$, partial $\eta^2 = .017$, whereas

the effect of the CRHR1 TAT haplotype was not, $F(2,595) = 1.67, p = .19$, partial $\eta^2 = .006$. The interaction effect also did not attain significance, $F(2,595) = 2.07, p = .13$, partial $\eta^2 = .007$. However, when we inspected the interaction effect, the figure indicated a larger difference between maltreated and nonmaltreated children's resilient functioning scores for the group with 0 TAT copies, relative to those children with 1 or 2 copies.

Accordingly, we reran the ANCOVA, grouping children with 1 or 2 copies together, and contrasting them with children with 0 copies. In this analysis, maltreatment status retained a significant effect, $F(1,595) = 24.89, p < .001$, partial $\eta^2 = .041$, the effect of the CRHR1 grouped variable was not significant, $F(1,595) = .13, p = .72$, partial $\eta^2 = .00$, and a significant GxE interaction was observed, $F(2,595) = 3.90, p = .049$, partial $\eta^2 = .007$. The interaction is depicted in Figure 1b. We probed the interaction effect with separate ANCOVAs within the CRHR1 TAT haplotype groups. Whereas maltreated children in both CRHR1 groups had lower resilient functioning scores than nonmaltreated children, the difference between maltreatment status groups was larger among children with 0 copies of the TAT haplotype, $F(1,252) = 21.49, p < .001$, partial $\eta^2 = .079$, than among children with 1 or 2 copies, $F(1,343) = 4.67, p = .03$, partial $\eta^2 = .014$.

DRD4 -521C/T—A similar pattern of findings was observed when genotypes of the DRD4 -521C/T were considered. The main effect for maltreatment status was significant, $F(1,575) = 16.86, p < .001$, partial $\eta^2 = .028$, whereas the main effect for DRD4 -521C/T genotypes was not significant, $F(2,575) = 1.39, p = .25$, partial $\eta^2 = .005$. The GxE interaction also did not attain significance, $F(2,575) = 2.10, p = .12$, partial $\eta^2 = .007$. Again, however, inspection of the figure of this interaction suggested larger differences between maltreated and nonmaltreated children for those with TT genotypes, as compared to those children with CC or CT genotypes.

We examined this relation further by combining the children with a C allele (CC or CT) as compared to children with a TT genotype. In this ANCOVA, the effect of maltreatment status was significant, $F(1,575) = 24.31, p < .001$, partial $\eta^2 = .041$, whereas the main effect of the DRD4 genotype group was not, $F(1,575) = 2.78, p = .10$, partial $\eta^2 = .005$. However, the interaction effect was found to be significant, $F(1,575) = 4.02, p = .045$, partial $\eta^2 = .007$.

As shown in Figure 1c, maltreated children irrespective of genotype group had lower resilient functioning scores than nonmaltreated children; however, the strength of these maltreatment group differences was stronger for children who had the TT genotype, $F(1,204) = 16.49, p < .001$, partial $\eta^2 = .079$, as compared to children who had CC or CT genotypes, $F(1,371) = 6.75, p = .01$, partial $\eta^2 = .018$.

OXTR—The fourth candidate gene considered was the oxytocin receptor, and similar results emerged, as with the other genes. Maltreatment status had a significant main effect, $F(1,594) = 16.42, p < .001$, partial $\eta^2 = .027$, but neither the OXTR main effect, $F(2,594) = .73, p = .48$, partial $\eta^2 = .003$, nor the GxE interaction, $F(2,594) = 1.77, p = .17$, partial $\eta^2 = .006$, was significant. As previously, however, inspection of the interaction effect suggested that there were larger differences in resilience functioning scores for maltreated and nonmaltreated children with AA or AG genotypes, as compared to children with the GG genotype.

We reconducted the ANCOVA with a dichotomized OXTR variable (AA or AG versus GG). In this analysis, the maltreatment status main effect was significant, $F(1,594) = 25.31, p < .001$, partial $\eta^2 = .041$, but the dichotomized OXTR effect was not, $F(1,594) = .25, p = .62$, partial $\eta^2 = .000$. A marginally significant interaction effect was obtained, $F(1,594) =$

3.03 $p = .08$, partial $\eta^2 = .005$. This interaction effect is depicted in Figure 1d. For children with AA or AG genotypes, the magnitude of the difference between maltreated and nonmaltreated children was larger, $F(1,262) = 23.00$, $p < .001$, partial $\eta^2 = .083$, than it was for children with a GG genotype, $F(1,332) = 5.16$, $p = .024$, partial $\eta^2 = .016$.

Resilient functioning and genetic moderation effects of multiple genes

Across the four candidate genes under consideration, a similar pattern of genetic and GxE effects has been found. Whereas maltreatment status as an environmental pathogen consistently negatively influences children's resilient functioning, none of the main effects for the genes were significantly related to resilience. However, for each of the genes, we observed GxE effects in which maltreated and nonmaltreated children evinced larger differences in resilient functioning for one genotype group vs. others. We sought to determine the collective effects these genes have on resilient functioning. Accordingly, we focused on the genotype group for each gene where there was a larger effect size in differentiating maltreated and nonmaltreated children. We determined how many of these differentiating genotypes each child had. In particular, the SS genotype for 5-HTTLPR, 0 copies of the CRHR1 TAT haplotype, the TT genotype of DRD4 - 521C/T, and the AA or AG genotypes of OXTR were examined. We counted how many of these differentiating genotypes each child had, with totals ranging from 0 to 4. Only 5 children had all four of the differentiating genotypes; thus, we combined children with 3 or 4 into one group.

We used this genotype sum variable in our ANCOVA model to predict resilient functioning scores. As in our prior analyses, the main effect of maltreatment status was significant, $F(1,573) = 24.15$, $p < .001$, partial $\eta^2 = .041$, whereas the main effect for the multiple genotypes was not, $F(3,573) = .70$, $p = .55$, partial $\eta^2 = .004$. Furthermore, the GxE interaction was significant, $F(3,573) = 5.19$, $p = .002$, partial $\eta^2 = .027$.

The GxE interaction effect is shown in Figure 2. We probed this interaction by conducting ANCOVAs within the genotype sum groups. The significance of the difference between maltreated and nonmaltreated children and the partial η^2 's for the respective groups are as follows: 0 differentiating genotypes: $p = .46$, $\eta^2 = .006$; 1 differentiating genotype: $p = .006$, $\eta^2 = .032$; 2 differentiating genotypes: $p = .006$, $\eta^2 = .044$; and 3 or 4 differentiating genotypes: $p < .001$, $\eta^2 = .299$. The interaction pattern indicates an increasing larger effect size difference between maltreated and nonmaltreated children in resilience functioning scores as the number of differentiating genotypes increases, ranging from no difference for children with 0 of the differentiating genotypes to large differences for children with 3 or 4 of the differentiating genotypes.

Effects of maltreatment subtype experiences

We also considered whether the effects of variation in maltreatment experiences among maltreated children contributed to further understanding of the GxE effects, beyond maltreatment status. Specifically, we examined the number of subtypes of maltreatment the maltreated children experienced, grouping children who had experienced one or two subtypes of maltreatment vs. those who had experienced 3 or 4, and included nonmaltreated children in subsequent analyses. Additionally, we also examined variation in the subtypes of maltreatment that maltreated children had experienced; maltreated children were dichotomized into two groups depending on whether they had experienced emotional maltreatment and/or neglect without abuse versus those who had experienced physical and/or sexual abuse (without restrictions on the experience of additional emotional maltreatment or neglect); nonmaltreated children were included as a third group. We used these subtype variables in a series of ANCOVAs in place of maltreatment status. Significant GxE effects were not found using the number of subtypes and subtype group variables for 5-HTTLPR,

CRHR1, or OXTR. However, we did obtain significant GxE effects when examining DRD4 -521C/T and the total number of differentiating genotypes.

In the ANCOVA using number of subtypes of maltreatment to predict resilient functioning, the number of subtypes was found to have a significant main effect, $F(2,532) = 12.47$, $p < .001$, partial $\eta^2 = .046$, whereas the DRD4 genotype group effect was not significant, $F(1,532) = 1.46$, $p = .23$, partial $\eta^2 = .003$. Importantly, the GxE interaction attained significance, $F(2,532) = 6.55$, $p = .002$, partial $\eta^2 = .025$. (See Figure 3a). We conducted follow-up tests of the interaction effect within genotype groups. Although the effect of the number of subtypes of maltreatment was significant for children with CC or CT genotypes, $F(2,348) = 2.96$, $p = .05$, partial $\eta^2 = .017$, number of subtypes had a stronger effect size among children with the TT genotype, $F(2,184) = 13.04$, $p < .001$, partial $\eta^2 = .129$. It is of interest to note how children with 3-4 subtypes of maltreatment were indistinguishable from nonmaltreated children in resilient functioning scores when then had the CC or CT genotype, whereas these two groups were substantially differentiated in resilient functioning scores among children who had the TT genotype.

When maltreatment subtype group was used in the ANCOVA model, the main effect for subtype was significant, $F(2,534) = 15.17$, $p < .001$, partial $\eta^2 = .055$, whereas the genotype group effect was not significant, $F(2,534) = .01$, $p = .93$, partial $\eta^2 = .000$. A significant GxE interaction effect also was obtained, $F(2,534) = 4.07$, $p = .018$, partial $\eta^2 = .015$. (See Figure 3b). Follow-up ANCOVAs to explore the effects within genotype group suggested that the effects of the number of subtypes experienced was marginally significant for children who had the CC or CT genotype, $F(2,349) = 2.90$, $p = .056$, partial $\eta^2 = .017$, whereas the differences in resilient functioning were substantially stronger among children who had the TT genotype, $F(2,185) = 12.23$, $p < .001$, partial $\eta^2 = .121$. The children who had experienced physical or sexual abuse were not substantially different from other maltreated children or nonmaltreated children if they had a CC or CT genotype, whereas the variation in resilient functioning was large for these subtype groups when children had the TT genotype.

GxE effects involving the subtype variables also were obtained when we examined the sum of genotypes that differentiated resilient functioning among maltreated and nonmaltreated children. For number of maltreatment subtypes, a significant main effect was obtained, $F(2,530) = 12.34$, $p < .001$, partial $\eta^2 = .046$, whereas the main effect for number of differentiating genotypes was not significant, $F(2,530) = .20$, $p = .90$, partial $\eta^2 = .001$. Moreover, the GxE interaction was found to be significant, $F(6,530) = 3.28$, $p < .004$, partial $\eta^2 = .037$. This interaction is depicted in Figure 4a. For children with 0 differentiating genes, the ANCOVA within this group of children revealed a nonsignificant main effect for number of subtypes, $F(2,102) = .60$, $p = .55$, partial $\eta^2 = .013$. In contrast, the size of the difference in resilient functioning increased as the number of differentiating genes increased. For children with 1 and 2 differentiating genotypes, significant differences between groups emerged, $F(2,219) = 3.76$, $p = .025$, partial $\eta^2 = .034$ and $F(2,156) = 3.64$, $p = .03$, partial $\eta^2 = .047$. For children with 3-4 differentiating genotypes, the effect of the number of subtypes was sizable, $F(2,53) = 14.61$, $p < .001$, partial $\eta^2 = .394$. Thus, with no differentiating genotypes, maltreated children and nonmaltreated children showed no differences in resilient functioning scores, whereas with increasing numbers of differentiating genotypes, the differences progressively increased. Among children with 3-4 differentiating genotypes, the nonmaltreated children and children with 3-4 subtypes had widely diverging levels of resilient functioning, with nonmaltreated children evincing the highest scores and those children with 3-4 subtypes the lowest.

We also investigated whether the specific subtypes of maltreatment children had experienced influenced the GxE effects, utilizing the subtype group variable in the ANCOVA model. The results revealed a significant main effect for subtype group, $F(2,532) = 15.37, p < .001$, partial $\eta^2 = .056$, a nonsignificant number of genotypes effect, $F(2,530) = .054, p = .98$, partial $\eta^2 = .000$, as well as a significant GxE interaction, $F(6,532) = 3.35, p = .003$ partial $\eta^2 = .038$. (See Figure 4b). The same fanning out interaction pattern is revealed in the figure. For children with 0 differentiating genes, no differences in resilient functioning were observed among the subtype groups, $F(2,102) = 1.29, p = .28$, partial $\eta^2 = .027$. In contrast, the size of the difference in resilient functioning increased as the number of differentiating genes increased. For children with 1 and 2 differentiating genotypes, significant differences between groups emerged between subtype groups, $F(2,219) = 3.52, p = .03$, partial $\eta^2 = .032$ and $F(2,158) = 3.98, p = .02$, partial $\eta^2 = .050$. However, among children with 3-4 differentiating genes, group differences were large, $F(2,53) = 16.87, p < .001$, partial $\eta^2 = .428$. The children with abuse experiences had the lowest level of resilient functioning, whereas the nonmaltreated children evinced the highest resilient functioning.

Genetic variation in resilient functioning groups

Consistent with prior research, our findings have shown that maltreated children on average have lower resilient functioning scores than nonmaltreated children. We also examined the number of maltreated children and nonmaltreated children in each of the resilient functioning groups: Low (0 or 1 indicator of resilient functioning); Medium (2 to 4 indicators); and High (5 or more indicators). A chi-square analysis indicated a significant difference in the distribution of maltreated versus nonmaltreated in each of the groups, for maltreated and nonmaltreated children, respectively: Low (49.2% vs. 31.6%); Medium (44.7% vs. 57.1%); and High (6.1% vs. 11.3%), $\chi^2(2, N=595) = 20.61, p < .001$. Thus, whereas nearly half of the maltreated children had low levels of resilient strivings, a small percentage of maltreated children with high levels of resilient functioning were identified.

We next sought to determine if maltreated and nonmaltreated children with the same level of resilient functioning differed in the number of differentiating genotypes they had. Accordingly, we conducted an ANCOVA with maltreatment status and resilient group as main effects. Gender, age, and race and ethnicity were controlled as in previous analyses. The dependent variable was the number of differentiating genotypes a child had. Neither maltreatment status, $F(1,573) = .54, p = .49$, nor resilience group, $F(2,573) = 1.25, p = .29$, had a main effect on the number of differentiating genotypes. However, a significant interaction effect was observed, $F(1,573) = 4.56, p = .01$. See Figure 5. Follow-up ANCOVAs within resilience groups were conducted in order to probe the interaction. Among children with high resilient functioning, nonmaltreated children had significantly higher numbers of differentiating genotypes than maltreated children, $F(1,49) = 4.62, p = .04$, partial $\eta^2 = .099$; among medium level resilient functioning, no differences were found between maltreated and nonmaltreated children, $F(1,290) = .002, p = .96$, partial $\eta^2 = .000$, and among children in the low group of resilience, maltreated children were found to have significantly higher mean number of differentiating genotypes than nonmaltreated children, $F(1,234) = 8.03, p = .005$, partial $\eta^2 = .034$. Thus, maltreated and nonmaltreated children had the opposite pattern of numbers of differentiating genotypes depending on whether they were in the high or low resilience groups. Follow-up analyses within the maltreated and the nonmaltreated group indicated that the effect of resilience group on number of differentiating genotypes was significant within the nonmaltreated group, $F(2,269) = 6.37, p = .005$, partial $\eta^2 = .047$, but not in the maltreated group, $F(2,304) = 1.17, p = .31$, partial $\eta^2 = .008$, indicating the more prominent role of gene variation on resilient functioning among the nonmaltreated children.

Discussion

This study was the first empirical investigation of the interaction of molecular genetic variants and child maltreatment on the development of resilient functioning. Despite the number of risks they encounter both within and outside the family context (Cicchetti & Valentino, 2006), maltreated children nonetheless strive to be resilient. We found that maltreated children evinced lower resilient functioning than nonmaltreated children. Moreover, fewer maltreated children were in the high resilient group, whereas more maltreated children were in the low resilient group. These results are consistent with findings from extant studies on the neurobiological, hormonal, and psychosocial determinants of resilient functioning conducted in our laboratory (Cicchetti, 2010).

In our research, we have strived to ascertain the processes that impel some maltreated children to function resiliently despite the experience of significant adversity in their lives. Psychosocial processes were the first focus of our work. We discovered that individual personality characteristics, in particular ego resiliency and moderate ego overcontrol, self-system processes, and relationship factors, were differentially predictive of resilient functioning in maltreated children and nonmaltreated children (cf. Cicchetti & Rogosch, 1997). Multilevel predictors, including research on hemispheric EEG activation asymmetry, emotion regulation, stress hormones, and personality characteristics have been investigated subsequently and have been demonstrated to be related to resilient functioning (Cicchetti & Rogosch, 2007; Curtis & Cicchetti, 2007). In order to examine the processes underlying the development of resilience at additional levels of analysis, we embarked on research aimed at discovering whether there were gene variants of specified genes, in interaction with the experience of child maltreatment, that were associated with higher levels of resilient functioning in maltreated and nonmaltreated children. We chose four genes that have been found to be related to behaviors associated with resilient functioning.

Maltreatment consistently exerted a strong, adverse main effect on resilient functioning; however, none of the gene variants of respective genes were shown to have a main effect on resilience. In contrast, GxE interaction effects were obtained and a similar pattern emerged for all four genes – a particular genotype variant was found to differentiate between the level of resilient functioning of maltreated and nonmaltreated children more strongly.

Opposite of the typical gene-environment interaction (GxE) studies on psychopathology, our results generally revealed that genetic variation has a negligible effect for the maltreated group in predicting resilient functioning. In contrast, genotype was shown to contribute to higher resilient functioning in nonmaltreated children when they possess a particular genotype, at least relative to the maltreated children with the same genotype.

In the case of 5-HTTLPR, nonmaltreated children with the SS genotypic variant were significantly more likely to have higher resilient functioning, whereas maltreated children who possessed the same genetic variant had lower resilient functioning. These findings are consistent with a differential susceptibility to environmental influences interpretation (Belsky et al., 2011; Belsky & Pluess, 2009; Ellis et al., 2011). For children who possess the same SS genotypic variant of 5-HTTLPR, in the context of a more normal childrearing environment, nonmaltreated children achieve higher resilient functioning, whereas maltreated children, in the context of an adverse childrearing environment, show lower resilient functioning.

For CRHR1, nonmaltreated children, especially those with 0 copies of the TAT haplotype, had higher levels of resilient functioning relative to maltreated children with the same number of copies of the TAT haplotype. Once again, these findings are in keeping with a differential susceptibility to the environment perspective (Belsky & Pluess, 2009; Ellis et al.,

2011); maltreated and nonmaltreated children have the same genetic variant (i.e., 0 copies of the TAT haplotype), yet the nonmaltreated children show higher levels of resilient functioning, whereas the maltreated children (living in a more stressful context) evince lower levels of resilient functioning.

Analyses of the DRD4 -521C/T single nucleotide polymorphism (SNP), revealed that nonmaltreated children and, in particular, those with the TT genotype, were more likely to exhibit higher resilient functioning scores than were maltreated children with this same genotype. The maltreated children manifested lower levels of resilient functioning. As with our previous analyses, the findings with DRD4 -521C/T provide support for the differential susceptibility to environmental influences perspective (Belsky & Pluess, 2009; Ellis et al., 2011).

In further analyses we examined the relation between number of maltreatment subtypes and DRD4 -521C/T genotype to resilient strivings. Maltreated children who had experienced 3 or 4 subtypes fared dramatically worse with the TT genotype, whereas nonmaltreated children with this genotype fared the best. Maltreated children with 3 – 4 subtypes with the CC or CT genotypes were indistinguishable in level of resilient functioning from nonmaltreated children with these genotypes. Despite the very large detrimental effect that extensive maltreatment exerts on resilient functioning independent of genotype, these results provide an example of where the 3 – 4 maltreatment subtype group exhibits the same level of resilient functioning as do nonmaltreated comparisons with the same CC or CT genotypes.

Finally, with OXTR, not being maltreated was related to higher resilient functioning scores; in contrast, maltreatment was strongly related to lower levels of resilient functioning. In particular, nonmaltreated children who had either the AA or AG genotypes of OXTR displayed greater levels of resilient functioning than maltreated children with these same genotypes. Consistent with the findings obtained with the three previous candidate genes, the results provide strong support for the differential susceptibility to environmental influences framework (Belsky & Pluess, 2009; Ellis et al., 2011).

The analysis aggregating the number of genotypes that most strongly differentiated the maltreated and nonmaltreated children revealed that the nonmaltreated comparison children evinced much higher levels of resilient functioning than the maltreated children among the group of children who had three or four of the differentiating genotypes. In contrast, among the group of children who did not have any of the differentiating genotypes, maltreated and nonmaltreated children were not different in their resilient functioning scores. By examining the collective influence of the gene variants, a more robust picture of potential differences in how the four candidate genes relate to resilient functioning differentially for maltreated and nonmaltreated children was attained (see Belsky and Beaver, 2011; Sonuga-Barke et al., 2009).

We obtained the same pattern of results when we examined the relation of the number of maltreatment subtypes and specific maltreatment subtype groups. For children with 3 – 4 differentiating genotypes, nonmaltreated children exhibited much higher resilient functioning scores than children with 3 – 4 maltreatment subtypes. For children with 0 differentiating genotypes, nonmaltreated children and children with 3 – 4 maltreatment subtypes did not differ in their levels of resilient functioning.

Additionally, for children with 3 – 4 differentiating genotypes, nonmaltreated children evinced much higher resilient functioning scores than children with PA and/or SA. In contrast, for children with 0 differentiating genotypes, there were no differences in the resilient functioning scores of nonmaltreated children and children with PA and/or SA.

Thus, children who have experienced many forms of maltreatment and those who have been abused are comparable to nonmaltreated children in resilient functioning when the children share one pattern of genotypic variation, whereas maltreated and nonmaltreated children vary widely in resilient functioning when they share a different pattern of genotypic variation.

Utilizing a more person-oriented analysis, we were able to obtain a clearer picture of the differences between nonmaltreated and maltreated children. We considered not mean levels of the resilient functioning scores, but instead focused on groups of children who demonstrated low, medium, and high levels of resilience. This person-oriented approach allowed us to examine genetic differences between maltreated and nonmaltreated children who showed the same levels of resilient strivings. In this analysis, we examined the number of differentiating genotypes on average that were observed in maltreated and nonmaltreated children in each resilience group. Maltreated children with high resilience had a significantly *lower* number of these differentiating gene variants compared to nonmaltreated children with high resilience. Whereas there were no differences between maltreated and nonmaltreated children with medium levels of resilience in the number of differentiating gene variants, when children with low levels of resilient strivings were examined, the maltreated children with low resilience had a *higher* number of the differentiating genes than the nonmaltreated children with low resilience.

Thus, the genetic variant profiles of maltreated and nonmaltreated children with high resilience are different; the genetic profile of resilient adaptation differs for maltreated and nonmaltreated children. Conversely, among children with very low resilience, the genetic profile of maltreated and nonmaltreated children also differs, but in the opposite direction.

It is noteworthy that we identified different gene variants as differentially important through contrasting maltreated and nonmaltreated children and their strivings for resilience. The variation among the genotypes and their relation to functioning differences would not be apparent without the consideration of experience. The genes did not have a singular role, outside of experiential context. The contrast between groups of maltreated and nonmaltreated children was important for understanding development in normal and atypical rearing environments.

Our findings suggest that the genes included in this investigation appear to be minimally related to resilient functioning in maltreated children. Maltreatment consistently had a statistically significant main effect on resilient functioning with each of the genes examined. Accordingly, it appears that the powerful maltreatment main effects may have overpowered any potential contribution of genetics to resilient functioning. Genetic variation had more of an impact on resilient functioning among the nonmaltreated children.

We must acknowledge that other biological systems are negatively impacted by abuse and neglect (Cicchetti & Toth, 2005; Cicchetti & Valentino, 2006). Differences in brain structure and function (DeBellis, 2001, 2005), stress neurobiology (Cicchetti, Rogosch, Gunnar, & Toth, 2010), and inflammatory processes (Miller, Chen, & Parker, 2011), among other biological systems, are not innate features of children, but rather are consequences of maltreatment. Maltreatment experiences also may influence genetic processes, including epigenetic processes involving the extent to which DNA methylation has occurred and the degree to which genes are expressed; however, these effects are not examined when focusing exclusively on GxE interaction. Moreover, genotypic variation for genes other than those utilized in this investigation may be related to higher resilient functioning in maltreated children. Thus, broader approaches to genetic influences associated with

resilience in maltreated children must occur. Ongoing research in our laboratory is focusing on these critical genetic processes in studies of maltreated and nonmaltreated children.

Finally, psychosocial predictors also should be included in future multilevel longitudinal investigations of genetic influences on resilient functioning in maltreated and nonmaltreated children. For example, prior research has revealed that the personality characteristic moderate ego overcontrol was a strong predictor of resilient functioning in maltreated but not in nonmaltreated children (Cicchetti & Rogosch, 1997). These results show an interesting parallel to genetic findings reported herein. Specifically, some genetic variants were related to resilient functioning in nonmaltreated but not in maltreated children, and thus the same genetic influences may not operate in the same manner for children who have had different experiences.

Given the consistent detrimental impact of maltreatment on resilient functioning and the larger number of maltreated children who exhibit low levels of resilience, the importance of prevention and intervention to ameliorate the effects of maltreatment must be underscored. The results do not suggest that there are some maltreated children who are unaffected by maltreatment based on their genetic heritage, and thus gene variation is unlikely to be useful to identify maltreated children who may be more in need of intervention. At this time, a focus on promoting adaptive psychological processes, such as ego resiliency and moderate ego overcontrol, may advance resilient strivings in maltreated children.

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a.

b.

c.

d.

Figure 1.

- Interaction of 5-HTTLPR and maltreatment status in predicting resilient functioning scores.
- Interaction of CRHR1 TAT haplotype and maltreatment status in predicting resilient functioning scores.
- Interaction of DRD4 -521C/T and maltreatment status in predicting resilient functioning scores.
- Interaction of OXTR and maltreatment status in predicting resilient functioning scores.

Figure 2. Interaction of the number of differentiating genotypes and maltreatment status in predicting resilient functioning scores.

a.

b.

Figure 3.

- a. Interaction of DRD4 -521C/T and number of maltreatment subtypes in predicting resilient functioning scores.
- b. Interaction of DRD4 -521C/T and maltreatment subtype groups in predicting resilient functioning scores.

a.

b.

Figure 4.

- Interaction of the number of differentiating genotypes and number of maltreatment subtypes in predicting resilient functioning scores.
- Interaction of the number of differentiating genotypes and maltreatment subtype groups in predicting resilient functioning scores.

Figure 5. Number of differentiating genotypes for maltreated and nonmaltreated children at different levels of resilient functioning.