

Interaction of Child Maltreatment and 5-HTT Polymorphisms: Suicidal Ideation among Children from low-SES Backgrounds

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Objective To investigate whether genotypic variation of the serotonin transporter gene-linked promoter region (5-HTTLPR) moderates the effect of maltreatment on suicidal ideation in school-aged children.

Methods Eight hundred and fifty low-income children (478 maltreated; 372 non-maltreated) provided DNA samples and self-reported depressive and suicidal symptoms. Genotypes of 5-HTTLPR (s/s or s/l vs. l/l) were determined by fragment analyses. **Results** Higher suicidal ideation was found among maltreated than non-maltreated children; the groups did not differ in 5-HTTLPR genotype frequencies. Children with one to two maltreatment subtypes and s/s or s/l genotypes had higher suicidal ideation than those with the l/l genotype; suicidal ideation did not differ in non-maltreated children or children with three to four maltreatment subtypes based on 5-HTTLPR variation. The results were applicable to emotionally maltreated/neglected and to physically/sexually abused children. Gene–environment interaction was not found for depressive symptoms.

Conclusion The protective effect of the 5-HTTLPR l/l genotype on suicidal ideation was limited to maltreated children experiencing fewer subtypes.

Key words suicidal ideation; child maltreatment; 5-HTTLPR; gene–environment interaction.

Child maltreatment is a pathogenic relational experience that represents one of the most adverse and stressful challenges that confront children (Cicchetti & Toth, 2005; National Research Council, 1993). As such, it initiates a probabilistic path of epigenesis for abused and neglected children that is marked by an increased likelihood of failure and disruption in the successful resolution of salient developmental issues across the life course (Cicchetti & Valentino, 2006; Trickett & McBride-Chang, 1995), thereby creating a profile of relatively enduring vulnerability placing maltreated children at high-risk for the emergence of maladaptation and psychopathology (Cicchetti & Toth, 2005; Koenen, Moffitt, Poulton, Martin, & Caspi 2007; Macmillan, Fleming, Streiner, Lin, Boyle, et al., 2001; Manly, Kim, Rogosch, & Cicchetti, 2001; Widom, DuMont, & Czaja, 2007).

A number of investigations have demonstrated that individuals who have been maltreated possess a significantly greater risk of experiencing suicidal behaviors (i.e., suicidal ideation; suicide attempts; completed suicide) than comparable samples of non-maltreated individuals

from the same social class background (Brodsky & Stanley, 2008; Currier & Mann, 2008; Dube, Anda, Felitti, Chapman, Williamson, et al., 2001; Molnar, Berkman, & Buka, 2001). With few exceptions, almost all of these studies have focused on the relationship between physical abuse, sexual abuse, and suicidal behaviors in adolescents and adults (Brodsky & Stanley, 2008; Thompson, Briggs, English, Dubowitz, Lee, et al., 2005). In these investigations, adolescent and adult participants have typically provided retrospective reports of their maltreatment experiences (Brodsky & Stanley, 2008). These studies have demonstrated that the experience of sexual and physical abuse is a significant risk factors for suicidal behaviors in adolescents and adults.

The relation between childhood maltreatment and suicidal behavior is of particular concern given the burden of mental illness associated with suicide. A decade ago, the then Surgeon General David Satcher highlighted suicide as a significant public health concern requiring the implementation of a national plan focusing on awareness, intervention, and methodology (1999).

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In the United States alone, over 33,000 individuals of all ages commit suicide annually (Centers for Disease Control and Prevention, 2009), resulting in an estimated \$11.8 billion in income loss (Goldsmith, Pellmar, Kleinman, & Bunney, 2002). Thus, the emotional as well as economic toll associated with suicides cannot be underestimated.

Early stresses, either physiological or emotional, may condition young neural networks to produce cascading effects through subsequent development, possibly constraining the maltreated child's flexibility to adapt to challenging situations with new strategies rather than with old conceptual and behavioral prototypes (Cicchetti & Tucker, 1994). Thus, early psychological trauma, such as that experienced by maltreated children, may eventuate not only in emotional sensitization, but also in pathological sensitization of neurophysiologic reactivity (Cicchetti & Tucker, 1994; Pollak, Cicchetti, & Klorman, 1998). Such early developmental abnormalities may lead to the development of aberrant neural circuitry (DeBellis, 2001) and often compound themselves into relatively enduring forms of psychopathology (Cicchetti & Cannon, 1999; Nowakowski & Hayes, 1999). Deviations in serotonergic activity result in altered neural information processing and the destabilization of affect, cognition, and behavior, systems that in the normal course of development are coupled under the neuromodulatory function of serotonin (5-HT) (Cicchetti & Tucker, 1994).

Besides elucidating the impact that child maltreatment exerts on biological and psychological developmental processes, the examination of gene-environment ($G \times E$) interactions can enhance our understanding of the biological and psychological mechanisms in underlying maladaptation and psychopathology in abused and neglected children. Although genetic factors are not completely expressed at birth, they play a prominent role at every phase of development. For example, the age of onset of mental disorders is most likely a function of timed biological events (e.g., pruning of the Central Nervous System, endocrine surges, etc.), genetic liability, and the quality of the resolution of stage-salient issues of development (Cicchetti & Walker, 2003; Sroufe, 1997).

The relationship between the experience of physical and sexual abuse and suicide behaviors is not direct. Whereas a number of biological, psychological, sociological, and socioeconomic factors have been shown to contribute to the complex etiology of suicide behaviors, there is convincing empirical evidence that genetic liability is also a strong contributor (Bondy, Buettner, & Zill, 2006). Behavior genetic family, twin, and adoption studies suggest the existence of a genetic diathesis for suicide

behaviors (Brent & Mann, 2005; Currier & Mann, 2008). In addition, environmental factors such as precipitating stressful and traumatic events too are associated with suicide behaviors (Bondy, et al., 2006; Brent & Mann, 2005). Identifying the relevant genetic elements contributing to the development of suicide behaviors, as well as the involvement of $G \times E$ interactions, are extremely important to advance the understanding of the complex pathways to suicidal behaviors.

The candidate genes used in the molecular genetic association studies conducted to date have been selected based on the evidence gleaned from investigations on the neurobiological factors implicated in suicides (Bondy et al., 2006; Brent & Mann, 2005). Given their importance in brain development and their pivotal role in individual differences in mood and behavioral regulations, association studies of suicide behaviors have focused on candidate genes from the serotonergic system (Brezo, Klempan, & Turecki, 2008). Among the genes responsible for serotonergic turnover and transmission, the serotonin transporter gene (5-HTT) has received the most research attention in investigations of the molecular genetics of suicide (Currier & Mann, 2008). The 5-HTT gene has a polymorphism in the linked promoter region (5-HTTLPR) in the 5'-regulatory region due to a 44 base pair deletion which eventuates in either the S- (short) or L- (long) allele (Lesch, Bengel, Heils, & Sabol, 1996). The presence of the S-allele is associated with reduced transcriptional activity of serotonin and lower level of the gene expression (Lesch et al., 1996; Lesch & Heils, 2000). The diversity in behavioral outcomes associated with 5-HTTLPR suggests the likely plausibility of its genetic influence being moderated by environmental pathogens (Moffitt, Caspi, & Rutter, 2006).

Few molecular genetic association investigations have been conducted examining $G \times E$ interactions and suicide behaviors. Caspi and colleagues (2003) discovered that adults having at least one short allele (s/s or s/l) of the serotonin transporter gene in the linked promoter region (5-HTTLPR) who had experienced a history of child maltreatment were more likely to develop increased depression than were adults who possessed the two long alleles (l/l) and who had been maltreated. Although Caspi et al. (2003) also found a $G \times E$ among negative life events, the presence of one or both s alleles of 5-HTTLPR, and suicide behaviors (i.e., suicidal ideation and suicide attempts), they did not directly examine the $G \times E$ among child maltreatment, presence of one or both short alleles, and suicide behaviors.

Relatedly, Gibb, McGeary, Beevers, and Miller (2006) discovered that a functional polymorphism in the

serotonin transporter gene in the linked promoter region (5-HTTLPR) moderated the impact of childhood physical and sexual, but not emotional, abuse on the lifetime histories of suicide attempts in a small group of adult psychiatric inpatients. In addition, Roy, Hu, Janal, and Goldman (2007) found that childhood trauma interacted with the low-expressing 5-HTTLPR genotypes to increase the risk of suicide behaviors in a group of male African American substance-dependent patients.

There has been a paucity of studies that have investigated suicide in preadolescent maltreated children. In the most comprehensive study conducted to date, Thompson and colleagues (2005) examined 1,051 8-year-old children who either had been identified as maltreated by Child Protective Services Departments or were considered to be at risk for maltreatment. The investigators found that nearly 10 percent of the sample of children reported suicidal ideation. Physical abuse severity, severity of maltreatment, and the presence of multiple subtypes of maltreatment were strong predictors of suicidal ideation. Moreover, children who were exposed to community and domestic violence were also at increased risk of suicidal ideation. Compared with the children who were at risk, the authors found that the children with maltreatment experiences were more likely to report suicidal ideation. Thus, the findings of this study reveal that thoughts of suicide are not an uncommon occurrence among young maltreated children and those at risk for maltreatment.

This investigation addresses important public health concerns—specifically, early suicidal behavior as a risk factor for later mental health problems in high risk, vulnerable children. Accordingly, we chose to examine $G \times E$ interaction and suicidal ideation in preadolescent maltreated and non-maltreated children. To our knowledge, this is the first investigation examining the interaction between genetic elements (i.e., 5-HTTLPR genotypes) and child maltreatment on suicidal ideation in school-aged children.

Hypotheses and research questions

1. We hypothesize that maltreated children will evince higher rates of suicidal ideation than non-maltreated children.
2. We do not expect differences in the distribution of 5-HTTLPR genotypes for maltreated and non-maltreated children, suggesting a lack of $G \times E$ correlation as an explanation for maltreatment group differences.
3. We expect to observe a $G \times E$ interaction between maltreatment status and 5-HTTLPR genotypes, such that maltreated children with an s allele (s/s or s/l) will have higher levels of suicidal ideation than those without an s allele (l/l). Non-maltreated children will not differ in suicidal ideation based on 5-HTTLPR genotypes.
4. We will investigate the influence of the number of subtypes of maltreatment the children experienced in order to determine whether the expected $G \times E$ effects are observed in children with one to two subtypes of maltreatment versus three to four subtypes of maltreatment. Differences between children experiencing physical and/or sexual abuse versus physical neglect/emotional maltreatment will also be examined.
5. We will determine if child depressive symptomatology excluding suicidal ideation, is influenced by the interaction of number of maltreatment subtypes and 5-HTTLPR genotypes.

Methods

Participants

The participants in this investigation included 850 children aged 6–13 years (M age = 9.19, SD = 1.70) who attended a summer camp research program designed for school-aged low-income children. The camp included recreational activities but was not designed to be a therapeutic intervention. The sample included both maltreated children (n = 478) and non-maltreated children (n = 372). Among the participants, 54.2% were boys. The maltreated and non-maltreated children were comparable in terms of racial/ethnic diversity and family characteristics: 60.6% of the sample was African American, 21.4% was white, 15.5% was Hispanic, and 2.5% was from other racial/ethnic groups. The families of the children were low income, with 95.5% of the families having a history of receiving public assistance. The average family income, including public financial support, was \$20,622 (SD = 12,101).

Participant Recruitment

Parents of all maltreated and non-maltreated children provided informed consent for their child's participation, besides conveying their consent for scrutinizing Department of Human Services' (DHS) records pertaining to the family. Children in the maltreated group were 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, their names were released to the project team for recruitment. Families were free to choose whether to

participate. Comprehensive searches of DHS records were completed and maltreatment information was coded utilizing operational criteria specified in the Maltreatment Classification System (MCS: Barnett, Manly, & Cicchetti, 1993), as discussed below.

Consistent with national demographic characteristics of maltreating families in the most recent National Incidence Study (NIS-3: Sedlack & Broadhurst, 1996), the maltreated children were predominantly from low socio-economic status families. Consequently, demographically comparable non-maltreated children were recruited from families receiving Temporary Assistance for Needy Families (TANF). A DHS recruitment liaison contacted eligible non-maltreated 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 non-maltreatment 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 was accessed. Only children from families without any history of documented abuse and/or neglect were retained in the non-maltreatment group. In addition, families who had received preventive services through DHS due to concerns over risk for maltreatment were excluded from the non-maltreated comparison group to reduce the potential for unidentified maltreatment existing within this group.

Parameters of Maltreatment Experiences

The Maltreatment Classification System (MCS: Barnett et al., 1993) is a reliable and valid method for classifying maltreatment (English, Upadhyaya, Litrownik, Marshall, Runyan, et al., 2005). The MCS 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 (weighted κ 's with the criterion ranging from .86 to .98). Reliabilities for the presence/absence of maltreatment subtypes (κ 's ranging .90 to 1.00) also were established.

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, and broken bones). Injuries range from minor and temporary to permanently disfiguring. Finally, sexual abuse involves attempted or actual sexual contact between the child and a family member or person caring for the child for purposes of that person's sexual satisfaction or financial benefits or both. 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 had histories of abuse and/or neglect occurring in their families according to DHS records. Among the maltreated children, 88.1% had incidents of maltreatment perpetrated directly against them, whereas the remaining children were from families where siblings had been maltreated. Among the directly maltreated children, 80.6% had experienced neglect, 66.4% had experienced emotional maltreatment, 38.1% had experienced physical abuse, and 12.8% had experienced sexual abuse. As is typical in maltreated populations (Manly, 2005), the majority of children had experienced multiple subtypes of maltreatment. Specifically, 65.7% of the maltreated children had experienced two or more maltreatment subtypes; on average, the maltreated children had experienced 1.98 ($SD = .88$) subtypes of maltreatment. Given the substantial overlap among maltreatment subtypes and the high rates of emotional maltreatment and neglect relative to physical and sexual abuse, we categorized all children subjected to physically or sexually abused into an abused group, whereas the remaining children were classified in an emotional maltreatment/neglect only group. Additionally, to differentiate

children with varying degrees of diversity of maltreatment experiences, we designated two groups of maltreated children—those experiencing one or two versus three or four subtypes of maltreatment. Important to note is that all children who had three to four subtypes of maltreatment had experienced physical and/or sexual abuse.

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 had a history of being 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. Each day of camp lasted for 7 hr, providing 35 hr of interaction between children and counselors. Besides the recreational activities, after providing assent, children participated in various research assessments (see Cicchetti & Manly, 1990, for detailed descriptions of camp procedures) and provided buccal cell samples for genetic analysis. Clinical consultation and intervention occurred if any concerns over danger to self or others emerged during research sessions.

Measures

The primary measure of self-report suicidal ideation in the current investigation was drawn from the Children's Depression Inventory (CDI; Kovacs, 1992). The CDI is a widely used self-report questionnaire to assess depressive symptomatology in school-aged 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 2 weeks. In the current investigation, one critical item involving suicidal ideation was of particular interest. The three options for this item (and respective scores) include: 'I do not think about killing myself' (0); 'I think about killing myself but would not do it' (1); and 'I want to kill myself' (2).

DNA Collection, Extraction, and Genotyping

Using an established protocol, trained research assistants obtained DNA samples from participants by collecting buccal cells with the Epicenter Catch-All Collection Swabs. Subsequently, using the conventional method, DNA was extracted with the Epicenter BuccalAmp DNA Extraction Kit, in order to prepare DNA for PCR amplification. Genotyping was conducted following previously published protocols. For 5-HTTLPR, the procedures of Gelernter, Kranzler, and Cubells (1997) were used.

Representative genotypes were identified and sequenced with a Beckman-Coulter CEQ8000 semi-automated fluorescent sequencing system, utilizing the Fragment Analysis Application and associated software.

Results

Preliminary Analyses

All data analyses were performed using SPSS for Windows, Version 14 (SPSS Inc., Chicago, 2007). First, we determined that the rate of any suicidal ideation was comparable for boys versus girls (23.4% vs. 26.0%); however, the rate was significantly higher in maltreated children (27.5%) than in non-maltreated children (21.2%), $\chi^2(1, N=850)=4.56, p=.03$, consistent with hypothesis 1. We next examined differences between maltreated and non-maltreated children on frequency distributions of the 5-HTTLPR genotype. Chi-square analyses revealed that for 5-HTTLPR, the distributions of the s/s, s/l, and l/l variants did not differ between the maltreated and non-maltreated children, $\chi^2(2, N=850)=1.67, ns$. For the maltreated versus non-maltreated groups, respectively, the percentages were as follows: s/s: 11.5% versus 9.4%; s/l: 40.0% versus 38.2%; and l/l: 48.5% versus 52.4%. These findings indicated that maltreatment status was not differentially associated with polymorphic variation in the 5-HTTLPR gene, in accordance with hypothesis 2. Given power concerns associated with the small cell sizes in the distribution of the homozygote ss genotype in the present sample ($n=55$ in maltreated and $n=35$ in non-maltreated), participants with the s/s and s/l genotypes were combined and compared to children with the l/l genotype in all study analyses. Follow-up chi-square analyses of the distributions of the s/s or s/l and the l/l variants among the maltreated versus non-maltreated children were not significant, $\chi^2(1, N=850)=1.26, ns$. We next examined whether the 5-HTTLPR genotypes were directly related to self-reported suicidal ideation. For 5-HTTLPR, low versus high transcriptional activity was not associated with suicidal ideation scores, $t(848)=1.60, ns$.

Maltreatment, 5-HTTLPR, and Suicidal Ideation

In order to examine the interaction between environmental risk (maltreatment vs. non-maltreatment) and genotype in predicting suicidal ideation, we used analysis of covariance models (ANCOVA). To control for possible confounds, both gender and race (African American vs. other) were included as covariates in all model analyses. Since the majority of participants were African American, we utilized this dichotomy in an effort to provide some control over

potential population stratification (Cardon & Palmer, 2003).

In our first $G \times E$ analysis, we examined the effect of maltreatment group on suicidal ideation within 5-HTTLPR genotypes. Findings revealed a significant effect of maltreatment on suicidal ideation, $F(1,843) = 4.20$, $p < .05$, such that maltreated children reported more thoughts about suicide compared to non-maltreated children. However, both the main effect of Genotype, $F(1,843) = 1.86$, $p = .17$, and the Genotype \times Maltreatment interaction, $F(2,843) = 1.35$, $p = .25$, were not significant. Subsequently, in order to address research question 4, maltreatment was examined in finer detail through categorization of the number of subtypes of maltreatment experienced by a child, by summing the number of individual subtypes of maltreatment (neglect, emotional maltreatment, physical and sexual abuses) each child had experienced. Therefore, maltreatment was scaled into three groups based on the number of maltreatment subtypes experienced: (1) children who were not maltreated; (2) children who experienced one or two forms of maltreatment (3) and children who experienced three or four forms of maltreatment.

This maltreatment designation was submitted to the same ANCOVA analysis and findings revealed that while there was a non-significant main effect of genotype, $F(1,791) = 1.57$, $p = .21$, there was a significant main effect of maltreatment on suicidal ideation, $F(2,791) = 5.85$, $p < .05$, such that children with three to four subtypes reported significantly higher suicidal ideation compared to non-maltreated children and children with one to two subtypes. However, this main effect was qualified in the presence of a significant 5-HTTLPR by maltreatment interaction, $F(2,791) = 3.33$, $p < .05$. The interaction effect is depicted in Table I and Figure 1. To follow-up the interaction, we completed a series of one-way ANOVAs within both the s/s or s/l and the l/l genotype groups. Within the s/s or s/l group, a significant effect of maltreatment group was found, $F(2,395) = 3.08$, $p < .05$. Planned contrasts revealed that children in the one to two subtypes and three to four subtypes maltreatment groups were not different from one another in self-reported suicidal ideation, $t(217) = 0.52$, ns; however, both groups had higher levels of suicidal ideation when compared to non-maltreated children, $t(335) = 2.17$ and $t(237) = 2.18$, p 's $< .05$, respectively. Within the l/l group, a significant effect of maltreatment was found, $F(2,395) = 5.98$, $p < .05$. Follow-up contrasts in this group revealed a different pattern of findings. Specifically, children who experienced three to four subtypes of maltreatment evidenced higher

Table I. Comparison of Maltreatment Groups on the Rate of ss/sl Polymorphisms and Suicidal Ideation Scores

	Nonmaltreated	Maltreated One to two subtypes	Maltreated Three to four subtypes
<i>5-HTTLPR gene</i>			
ss/sl genotypes	47.6%	51.9%	50.4%
Suicidal Ideation Score	M (SD)	M (SD)	M (SD)
ss/sl genotypes	0.21 (0.41)	0.32 (0.47)	0.36 (0.48)
ll genotype	0.21 (0.41)	0.16 (0.37)	0.39 (0.49)
Total	0.21 (0.41)	0.24 (0.43)	0.37 (0.49)

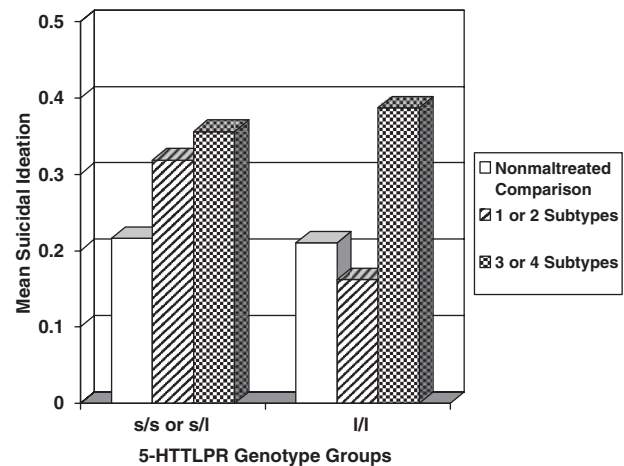


Figure 1. $G \times E$ interaction for number of subtype groups and 5-HTTLPR genotypes.

suicidal ideation when compared to both the children with one to two subtypes of maltreatment, $t(200) = 3.50$, $p < .05$, and non-maltreated children, $t(247) = 2.71$, $p < .05$. In addition, the children who experienced one to two subtypes of maltreatment were not different from non-maltreated children in suicidal ideation, $t(341) = 1.12$, ns.

To definitively pinpoint the locus of the $G \times E$ interaction, we also examined whether suicidal ideation differed within maltreatment groups according to the 5-HTTLPR genotypes. To accomplish this, we first examined whether suicidal ideation among non-maltreated children differed by gene status. Results of the univariate ANCOVA revealed a nonsignificant effect of genotype on suicidal ideation for the non-maltreated children, $F(1,371) = 0.95$, $p = .76$. Analyses of the one to two maltreatment subtype group revealed a different pattern of findings, such that a significant effect of gene variation on suicidal ideation was present, $F(1,306) = 8.22$, $p < .05$, with the children with s/s or s/l genotypes reporting significantly higher suicidal ideation compared to

children with the l/l variant, suggesting a $G \times E$ interaction within this group such that the l/l genotype conferred a protective effect in this group. Finally, in the maltreated group experiencing three to four subtypes, a nonsignificant gene effect was found, $F(1,112) = .029$, $p = .86$, indicating no differences in suicidal ideation for the different genotypes among children experiencing three to four subtypes.

Finally, given existing literature documenting associations between physical abuse and sexual abuse and suicidal behaviors, we further examined whether these specific forms of maltreatment were driving the $G \times E$ interaction within the one to two maltreatment subtype group. To accomplish this, we collated children who had experienced physical abuse or sexual abuse into one group and compared them with children who had experienced physical neglect or emotional maltreatment besides non-maltreated comparisons (see Figure 2). As expected, a significant $G \times E$ interaction among these three groups was found, $F(2,680) = 3.54$, $p < .05$. Follow-up with univariate analyses within genotype revealed a significant effect of maltreatment within the ss/sl genotypes, $F(2,338) = 3.91$, $p < .05$. Post-hoc probes revealed that children who had experienced sexual or physical abuse had significantly higher rates of suicidal ideation when compared to non-maltreated children, $t = 2.63$, $p < .05$, but were not different from children who had experienced physical neglect or emotional maltreatment, $t = 1.83$, $p > .05$. Thus, this finding suggests that the $G \times E$ effect within s/s or s/l genotype within the one to two maltreatment subtype group was similar across maltreatment

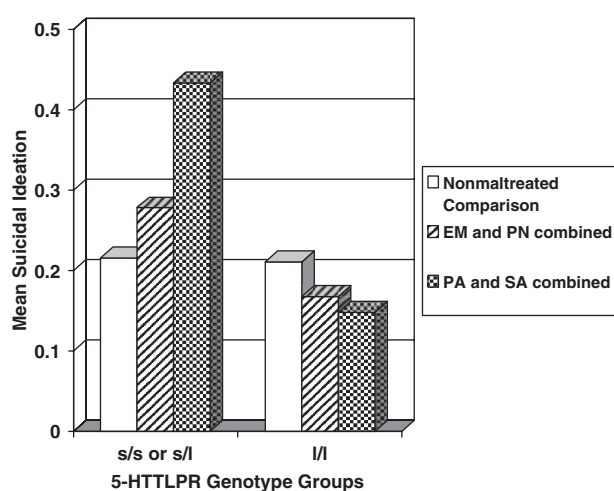


Figure 2. $G \times E$ interaction for subtype groups and 5-HTTLPR genotypes among non-maltreated children and maltreated children with one to two subtypes.
 Note: EM: emotional maltreatment; PN: physical neglect; PA: physical abuse; SA: sexual abuse.

subtypes. However, while not significantly different from one another, it is interesting to note that children experiencing physical or sexual abuse reported higher rates of suicidal ideation compared to children experiencing physical neglect or emotional maltreatment.

This is further highlighted when comparisons are made examining suicidal ideation within maltreatment subtype across the two 5-HTTLPR genotypes. Results of univariate ANCOVAs revealed a nonsignificant effect of genotype on suicidal ideation for the non-maltreated children, $F(1,396) = 0.01$, $p = .98$. Analyses of the children experiencing emotional maltreatment/physical neglect revealed a different pattern of findings, such that a significant effect of gene variation on suicidal ideation was present, $F(1,235) = 4.92$, $p < .05$, with the children with s/s or s/l genotypes reporting significantly higher suicidal ideation compared to children with the l/l variant. Finally, in the group experiencing physical and/or sexual abuse, a significant gene effect was found, $F(1,74) = 8.10$, $p < .05$, suggesting significantly higher suicidal ideation among those with the s/s or s/l genotype compared to those with the l/l genotype.

Maltreatment, 5-HTTLPR, and Depressive Symptomatology

Our final analysis addressing research question 5 explored whether these findings were the result of generalized depressive symptoms in the sample. To accomplish this, we examined the interaction between environmental risk (maltreatment vs. non-maltreatment) and genotype in predicting depressive symptoms as recorded on the CDI, with the suicide item removed. Thus, depression scores without the suicidal ideation item were submitted to the same ANCOVA analysis and findings revealed that while there was a non-significant main effect of genotype, $F(1,791) = 0.37$, $p = .54$, there was a significant main effect of maltreatment on depressive symptoms, $F(2,791) = 3.34$, $p < .05$, such that children with three to four subtypes reported significantly higher depressive symptoms compared to non-maltreated children and children with one to two subtypes. However, the 5-HTTLPR by Maltreatment interaction was not significant, $F(2,791) = 0.04$, $p = .96$, indicating that a genotype \times environment interaction for depressive symptoms was not present in this sample.¹

¹Results did not differ when CDI scores including the suicidal ideation item were used in these analyses: main effect for 5-HTTLPR: $F(1, 791) = .19$, $p = .67$; main effect for subtype groups: $F(2, 791) = 3.58$, $p = .03$; interaction effect: $F(2, 791) = .05$, $p = .95$.

Discussion

Consistent with prior research (Kendall-Tackett, Williams, & Finkelhor, 1993; Thompson et al., 2005; Toth, Manly, & Cicchetti, 1992; Widom et al., 2007), we found that maltreated children had higher levels of depressive symptomatology, and, in particular, a greater likelihood of suicidal ideation than did non-maltreated children from a comparable low-socioeconomic (SES) background. We investigated whether 5-HTTLPR genotypes would moderate the association between child maltreatment and suicidal ideation. The lack of differences in the distributions of the 5-HTTLPR polymorphisms across the maltreatment groups suggests that children with specific genetic variants were not differentially susceptible to being maltreated.

This finding that maltreatment status was not differentially associated with polymorphic variation in the 5-HTTLPR gene is consistent with our hypothesis that the existence of an evocative $G \times E$ correlation could not explain the group differences in depressive symptoms and suicidal ideation found between maltreated and non-maltreated children.

We also determined that the extensiveness of children's maltreatment, as indicated by the number of maltreatment subtypes experienced (i.e., one to two vs. three to four), was an important consideration. Specifically, we found evidence for a $G \times E$ interaction between the number of subtypes of maltreatment and 5-HTTLPR genotypes; however, the results were more complex. The interaction effect that we detected was restricted to children with one to two subtypes of maltreatment. For these maltreated children, those with the l/l polymorphic variant of 5-HTTLPR did not exhibit an increased risk for suicidal ideation. In contrast, maltreated children with the s/s or s/l genotype evinced elevated rates of suicidal ideation. We also discovered that among children with the s/s or s/l genotype and one to two subtypes of maltreatment, both children who had experienced emotional maltreatment and/or physical neglect and those who had experienced physical abuse and/or sexual abuse were more likely to report thoughts about suicide than were children with any combination of one to two maltreatment subtypes who possessed the l/l genotype. Thus, the subtype of maltreatment experienced was not differentially related to suicidal ideation.

The findings of this investigation suggest that the relation between maltreatment and suicidal ideation is modified by genotype. That is, the l/l genotype of 5-HTTLPR appears to confer a protective effect among maltreated children, while not being influential among non-maltreated

children. However, there are limits to this protective function. For more extensively maltreated children (i.e., those with three to four subtypes), children expressed higher levels of suicidal ideation, irrespective of genotypic variation. Thus, the pathogenic relational environment of children who experienced extensive maltreatment appears to have predominated over genotypic variation in the risk for, or protection against, suicidal ideation.

Although the $G \times E$ effects in the present investigation were operative for suicidal ideation, they were not obtained for depressive symptomatology more broadly. The absence of a $G \times E$ interaction between child maltreatment and the presence of one or more of the low transcriptional activity s alleles of 5-HTTLPR on depressive symptomatology is not consistent with results reported by Kaufman et al. (2004) in their investigation of school-aged maltreated children whose mean age was 10 years. Differences in sampling and methodology between the investigations must be considered. First, all maltreated children in the Kaufman et al. (2004) study had been removed from their homes, whereas children in the current investigation were residing with their biological families. Second, the sample size in the Kaufman investigation included only 57 maltreated and 44 non-maltreated children, resulting in relatively small numbers of children in each of the allele frequency groups. The inclusion of siblings and half-siblings in the Kaufman investigation further complicates the interpretation of the findings. Kaufman acknowledged the limitation associated with sample size and recommended independent replication. We also endorse the need for future investigations to further examine this emerging area of research.

The present investigation is the first study to examine $G \times E$ for suicide ideation among school-aged maltreated and non-maltreated children. Suicide is very rare in childhood; however, the fact that suicidal ideation is not uncommon, is related to maltreatment status, and is modified by genotypic variation, is extremely informative. These findings underscore the importance of preventive efforts. Children who have been extensively maltreated are at high risk for suicidal ideation, irrespective of genetic variation. The extensive assault on the self from experiencing diverse forms of maltreatment (Cicchetti, 1991) is associated with higher suicidal ideation in these youths. Likewise, children with less pervasive maltreatment (i.e., those experiencing one to two subtypes), and who possess one or more of the low transcriptional activity s/s or s/l polymorphic variants of 5-HTTLPR, also are at increased risk for thinking about suicide. Accordingly, the aforementioned groups of maltreated children would all benefit from interventions designed to improve self-worth,

self-determination, impulse control, problem solving, and executive functions. Notably, any combination of maltreated children with one to two subtypes with the s/s or s/l genotype are at risk for increased suicidal ideation. As such, despite the primary emphasis on the role of physical and sexual abuse for the emergence of suicidal behaviors, our results demonstrate that children who experience emotional maltreatment and physical neglect also are at increased risk for suicidal behaviors. Because children who have been subjected to emotional maltreatment or physical neglect historically have been afforded far less attention by the child welfare system than have those who have experienced physical abuse or sexual abuse, our findings highlight the importance of addressing the presence of suicidal ideation in these children, as well.

Moreover, given the low base rate of suicide during the school-age years, mental health practitioners may not directly ask maltreated children about suicidal ideation. The failure to do so may result in missed opportunities for intervening preventively to reduce actual suicidal behaviors as these children enter adolescence and transition into adulthood. This work also possesses implications for pediatric and child welfare providers. Since these professionals are often the gatekeepers for detecting child maltreatment and making referrals for services, our results highlight the importance of ascertaining whether suicidal ideation is present in children who have experienced maltreatment. Too often, only children who exhibit aggressive or impulsive behaviors are referred for mental health services. Unless pediatricians and child welfare professionals inquire directly about whether a child has ever thought about self-harm, the provision of necessary preventive services is unlikely. Although professionals may fear that asking a child about suicide will give the child ideas that otherwise may not have been present, such is not the case, and failing to make inquiries poses significant risk to the child's welfare.

Despite the importance of this investigation, it has a few limitations. First, only a single item was utilized to assess suicidal ideation. This item has face validity in terms of capturing suicidal ideation, but it does not reflect suicidal behavior. Although a more in-depth assessment of suicide thoughts would have been preferable, the strong psychometrics of the Children's Depression Inventory (Kovacs, 1992) and the face validity of the suicide question somewhat mitigate this limitation. Second, since all maltreated children in the current sample were officially identified as maltreated by authorities, our results cannot be generalized to the population of maltreated children who have not been reported to authorities. Notably,

however, it is possible that unidentified maltreated youngsters might be at even greater risk of suicidal ideation in view of the absence of any intervention. The latter point also highlights the criticality of comprehensively assessing suicidal ideation in all children who present for mental health services because undetected maltreatment and increased risk for suicide may be present.

In conclusion, suicidal ideation is associated with depression; however, there are likely to be aspects of suicidal behaviors that are unique. Impulsivity, emotion dysregulation, personality characteristics, neurobiological processes, and stress dysregulation (e.g., hypocortisolism) are likely to be among the features that distinguish suicide behaviors from depression in maltreated children. Importantly, maltreatment experiences themselves promote less adaptive functioning across these domains, and the degree of impairment may be influenced by genetic variation. In the future, multi-level, prospective, longitudinal studies of the developmental sequelae of child maltreatment should be conducted that incorporate measures of stage-salient issues, neurobiological functioning, and neuroendocrine regulation, along with assessments of suicidal ideation that are initiated during the early school-age period. Additional genes, such as the glucocorticoid receptor gene, also should be considered. Such investigations would be in a strong position to contribute important knowledge to the precursors of suicidal ideation in maltreated children. Likewise, it will be essential to follow the longitudinal developmental course of suicidal ideation as maltreated children progress into adolescence and adulthood. Through the conduct of this work, important insight will be shed on whether suicidal ideation in childhood portends an increased risk for suicidal behaviors later in development.

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References

- Barnett, D., Manly, J. T., & Cicchetti, D. (1993). Defining child maltreatment: the interface between policy and research. In D. Cicchetti, & S. L. Toth (Eds.),

- Child abuse, child development, and social policy* (pp. 7–74). Norwood, NJ: Ablex.
- Bondy, B., Buettner, A., & Zill, P. (2006). Genetics of suicide. *Molecular Psychiatry*, 11, 336–351.
- Brent, D. A., & Mann, J. J. (2005). Family genetic studies, suicide, and suicidal behavior. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 133, 13–24.
- Brezo, J., Klempman, T., & Turecki, G. (2008). The genetics of suicide: A critical review of molecular studies. *Psychiatric Clinics of North America*, 31, 179–203.
- Brodsky, B. S., & Stanley, B. (2008). Adverse childhood experiences and suicidal behavior. *Psychiatric Clinics of North America*, 31, 223–235.
- Cardon, L. R., & Palmer, L. J. (2003). Population stratification and spurious allelic association. *Lancet*, 361, 598–604.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H. L., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386–389.
- Centers for Disease Control and Prevention, National Center for Injury Prevention and Control (2009). *Suicide: Facts at a Glance*. From <http://www.cdc.gov/ViolencePrevention/pdf/Suicide-DataSheet-a.pdf> (30 August 2009 date last accessed).
- Cicchetti, D. (1991). Fractures in the crystal: Developmental psychopathology and the emergence of the self. *Developmental Review*, 11, 271–287.
- Cicchetti, D., & Cannon, T. D. (1999). Neurodevelopmental processes in the ontogenesis and epigenesis of psychopathology. *Development and Psychopathology*, 11, 375–393.
- Cicchetti, D., & Manly, J. T. (1990). A personal perspective on conducting research with maltreating families: Problems and solutions. In G. Brody, & I. Sigel (Eds.), *Methods of family research: Families at risk* (Vol. 2, pp. 87–133). Hillsdale, NJ: Child Abuse and Neglect.
- Cicchetti, D., & Toth, S. L. (2005). Child maltreatment. *Annual Review of Clinical Psychology*, 1, 409–438.
- Cicchetti, D., Toth, S. L., & Manly, J. T. (2003). *Maternal Maltreatment Interview*. Unpublished manuscript. NY: Rochester.
- Cicchetti, D., & Tucker, D. (1994). Development and self-regulatory structures of the mind. *Development and Psychopathology*, 6, 533–549.
- Cicchetti, D., & Valentino, K. (2006). An ecological transactional perspective on child maltreatment: failure of the average expectable environment and its influence upon child development. In D. Cicchetti, & D. J. Cohen (Eds.), *Developmental Psychopathology* (Vol. 3, 2nd ed., pp. 129–201). New York: Wiley.
- Cicchetti, D., & Walker, E. F. (Eds.). (2003). *Neurodevelopmental Mechanisms in Psychopathology*. New York: Cambridge University Press.
- Currier, D., & Mann, J. J. (2008). Stress, genes, and the biology of suicidal behavior. *Psychiatric Clinics of North America*, 31, 247–269.
- DeBellis, M. D. (2001). Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. *Development and Psychopathology*, 13, 539–564.
- Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the adverse childhood experiences study. *Journal of the American Medical Association*, 286, 3089–3096.
- English, D. J., Upadhyaya, M. P., Litrownik, A. J., Marshall, J. M., Runyan, D. K., Graham, J. C., et al. (2005). Maltreatment's wake: The relationship of maltreatment dimensions to child outcomes. *Child Abuse and Neglect*, 29, 597–619.
- Gibb, B. E., McGeary, J. E., Beevers, C. G., & Miller, I. W. (2006). Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients. *Suicide and Life-threatening Behavior*, 36, 687–693.
- Goldsmith, S.K., Pellmar, T.C., Kleinman, A.M., & Bunney, W.E. (Eds.). (2002). *Reducing suicide: A national imperative*. Washington, DC: National Academies Press.
- Kaufman, J., Yang, B., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J., et al. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 17316–17321.
- Kendall-Tackett, K. A., Williams, L. M., & Finkelhor, D. (1993). Impact of sexual abuse on children: A review and synthesis of recent empirical studies. *Psychological Bulletin*, 113, 164–180.
- Koenen, K. C., Moffitt, T. E., Poulton, R., Martin, J., & Caspi, A. (2007). Early childhood factors associated with the development of post-traumatic stress disorder: Results from a longitudinal birth cohort. *Psychological Medicine*, 37, 181–192.

- Kovacs, M. (1992). *Children's Depression Inventory Manual*. N. Tonawanda, NY: Multi-health Systems.
- Lesch, K. P., Bengel, D., Heils, A., & Sabol, S. Z. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274, 1527–1531.
- Lesch, K. P., & Heils, A. (2000). Serotonergic gene transcriptional control regions: Targets for antidepressant drug development? *International Journal of Neuropsychopharmacology*, 3, 67–79.
- Macmillan, H. L., Fleming, J. E., Streiner, D. L., Lin, E., Boyle, M. H., Jamieson, E., et al. (2001). Childhood abuse and lifetime psychopathology in a community sample. *American Journal of Psychiatry*, 158, 1878–1883.
- Manly, J. T. (2005). Advances in research definitions of child maltreatment. *Child Abuse & Neglect*, 29, 425–439.
- Manly, J. T., Kim, J. E., Rogosch, F. A., & Cicchetti, D. (2001). Dimensions of child maltreatment and children's adjustment: Contributions of developmental timing and subtype. *Development and Psychopathology*, 13, 759–782.
- Moffitt, T. E., Caspi, A., & Rutter, M. (2006). Measured gene–environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspectives on Psychological Science*, 1, 5–27.
- Molnar, B. E., Berkman, L. F., & Buka, S. L. (2001). Psychopathology, childhood sexual abuse and other childhood adversities: Relative links to subsequent suicidal behavior in the US. *Psychological Medicine*, 31, 965–977.
- National Research Council (1993). *Understanding child abuse and neglect*. Washington, DC: National Academy of Sciences.
- Nowakowski, R. S., & Hayes, N. L. (1999). CNS development: An overview. *Development and Psychopathology*, 11, 395–418.
- Pollak, S. D., Cicchetti, D., & Klorman, R. (1998). Stress, memory, and emotion: Developmental considerations from the study of child maltreatment. *Development and Psychopathology*, 10, 811–828.
- Roy, A., Hu, X., Janal, M. N., & Goldman, D. (2007). Interaction between childhood trauma and serotonin transporter gene variation in suicide. *Neuropsychopharmacology*, 32, 2046–2052.
- Sedlak, A., & Broadhurst, D. (1996). *The third national incidence study of child abuse and neglect: NIS 3*. Washington, DC: U.S. Department of Health and Human Services.
- Sroufe, L. A. (1997). Psychopathology as an outcome of development. *Development and Psychopathology*, 9, 251–268.
- Toth, S. L., Manly, J. T., & Cicchetti, D. (1992). Child maltreatment and vulnerability to depression. *Development and Psychopathology*, 4, 97–112.
- Thompson, R., Briggs, E., English, D. J., Dubowitz, H., Lee, L. C., Brody, K., et al. (2005). Suicidal Ideation among 8-year-olds who are maltreated and at risk: Findings from the LONGSCAN studies. *Child Maltreatment*, 10, 26–36.
- Trickett, P. K., & McBride-Chang, C. (1995). The developmental impact of different types of child abuse and neglect. *Developmental Review*, 15, 311–337.
- U.S. Public Health Service (1999). *The surgeon general's call to action to prevent suicide*. Rockville, MD: U.S. Department of Health and Human Services.
- Widom, C. S., DuMont, K., & Czaja, S. J. (2007). A prospective investigation of major depressive disorder and co-morbidity in abused and neglected grown up children (grown up). *Archives of General Psychiatry*, 64, 49–56.