Take Your Mind Off It: Coping Style, 5-HTTLPR Genotype, and Children’s Internalizing and Externalizing Problems

Jessie I. Cline, PhD, University of Pennsylvania
Jay Belsky, PhD, University of California, Davis
Zhi Li, MS, University of California, Davis
Edward Melhuish, PhD, University of London and Oxford University
Laura Lysenko, PhD, King’s College London
Tara McFarquhar, MS, University College London and the Anna Freud Centre
Suzanne Stevens, PhD, University of Auckland
Sara R. Jaffee, PhD, University of Pennsylvania

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Sara Jaffee
3720 Walnut Street
Philadelphia, PA 19104
Phone: +1 215.756.4566
srjaffee@psych.upenn.edu
Abstract

Individuals with the short ‘S’ variant of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) are more susceptible than individuals homozygous for the long ‘L’ allele to the effects of stressful life events on risk for internalizing and externalizing problems. We tested whether individual differences in coping style explained this increased risk for problem behavior among youth who were at both genetic and environmental risk. Participants included 279 children, ages 8-11, from the Children’s Experiences and Development Study. Caregivers and teachers reported on children’s internalizing and externalizing symptoms, and caregivers and children on children’s exposure to harsh parenting and parental warmth in middle childhood, and traumatic events. Children reported how frequently they used various coping strategies. Results revealed that S/S homozygotes had higher levels of internalizing problems compared with L allele carriers and that S allele carriers had higher levels of externalizing problems compared with L/L homozygotes under conditions of high cumulative risk. Moreover, among children who were homozygous for the S allele, those who had more cumulative risk indicators less frequently used distraction coping strategies, which partly explained why they had higher levels of internalizing problems. Coping strategies did not significantly mediate GxE effects on externalizing symptoms.

Keywords: serotonin transporter, internalizing, externalizing, coping
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*Take Your Mind Off It: Coping Style, 5-HTTLPR Genotype, and Children’s Internalizing and Externalizing Problems*

When faced with stressful situations, individuals react differently depending on many factors, including their genetic make-up. For example, individuals who carry one or two copies of the short ‘S’ variant of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) are more susceptible than individuals who are homozygous for the long ‘L’ allele to the effects of stressful life events on risk for internalizing problems, particularly when stressful events comprise hostile or abusive relationships with family members or peers (Aslund et al., 2009; Caspi et al., 2003; Cicchetti, Rogosch, & Sturge-Apple, 2007; Karg, Burmeister, Shedden, & Sen, 2011; Taylor et al., 2006, but see Munafo, Durrant, Lewis, & Flint, 2009 and Risch et al., 2009 for negative findings). Adults who report having experienced family violence or hostility in childhood (Taylor et al., 2006), maltreatment (Caspi et al., 2003; Cicchetti et al., 2007; Kaufman et al., 2004), and youth who report having been bullied (Sugden et al., 2010) are at elevated risk for symptoms of depression, but only if they carry one or two copies of the S allele. In contrast, individuals who are homozygous for the L allele usually have low levels of depression regardless of their exposure to stressful life events.

5-HTTLPR is a 43 base pair insertion/deletion polymorphism (Heils et al., 1996; Lesch et al., 1996). The serotonin transporter (5-HTT) plays a vital role in the regulation of serotonin (5HT) reuptake (Lesch et al., 1996; Neumeister et al., 2002; Verona, Joiner, Johnson, & Bender, 2006), and dysregulated 5-HT functioning is associated with both depression as well as aggression (Caspi et al., 2002; Maes & Meltzer, 1995; Moeller et al., 1998; Verona et al., 2006). Homozygosity for the L allele is associated with increased transcriptional efficiency in human lymphoblast cells, whereas the S allele is associated with diminished 5-HTT gene transcription.
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(Greenberg et al., 1999; Heils et al., 1996). Compared to the L-variant, the S-allele is less active, which leads to reduced 5-HT expression or function as well as reduced 5-HT binding sites and uptake (Greenberg et al., 1999).

There is growing evidence (reviewed below), that the S allele is involved in the physiological response to psychosocial stress and to cognitive appraisals of stressors, suggesting that S allele carriers may cope differently than youth who are homozygous for the L allele when confronted with potential threats or chronic stressors. This physiological and psychological profile may on the one hand hinder youth from practicing coping strategies that are usually associated with greater psychological well-being, such as actively engaging with and acting on sources of stress, while on the other hand promoting the use of coping strategies that are usually associated with poorer psychological functioning, such as avoiding or withdrawing from stressors (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001). Thus, the goal of research reported herein is twofold: to test whether 5-HTTLPR genotype moderates the effect of stressful relationships and experiences (measured as caregiver-child relationships characterized by hostility, lack of warmth and exposure to traumatic events) on children’s internalizing and externalizing problems and to evaluate whether individual differences in coping style explain the anticipated elevated risk of problem behaviors among S allele carriers faced with high levels of environmental risk.

Why Do Stressful Life Events Increase Risk for Depression Among S Allele Carriers?

Although the interaction between 5-HTTLPR genotype and stressful life events is reasonably robust across studies (but see Munafo et al., 2009 and Risch et al., 2009 for an alternative perspective), research has only begun to identify possible explanations for why S
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allele carriers are particularly susceptible to the adverse effects of stressful life events. Meta-analyses have shown that S/S homozygotes mount a significantly greater cortisol response to acute stressors than L-allele carriers (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2013) and that S allele carriers show enhanced amygdala reactivity to negatively-valenced stimuli compared with individuals who are homozygous for the L allele (Munafò, Brown, & Hariri, 2008). A handful of investigations have shown that elevated cortisol reactivity to acute stressors and amygdala reactivity to negative emotional stimuli in S allele carriers is most pronounced among those who have experienced numerous stressful life events (Alexander et al., 2009; Alexander et al., 2012; Williams et al., 2009, but see Canli et al., 2006 and Mueller et al., 2011 for alternative interaction patterns), thus demonstrating that potential endophenotypes for depression (and aggression) are also predicted by genotype X environment (GXE) interactions. Moreover, functional connectivity between the amygdala and hypothalamus is enhanced in healthy adult men who are homozygous for the S allele and who have experienced high levels of stressful life events. This suggests that elevated HPA axis reactivity to psychosocial stress and limbic system reactivity to threatening stimuli reflect a coordinated biological response in individuals who are homozygous for the S allele and who have experienced multiple stressful life events (Alexander et al., 2012). Finally, the 5-HTTLPR genotype has been shown to moderate the effect of stressful life events on fear conditioning. Thus, individuals who are homozygous for the S allele and who have experienced multiple stressful life events show greater reactivity in some (but not all) regions of the fear network of the brain to conditioned versus unconditioned fear stimuli compared with individuals who have experienced low levels of stressful life events or who are homozygous for the L allele (Klucken et al., 2013). Considering that heightened physiological reactivity and fear conditioning are hypothesized to underlie depression and
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anxiety, these findings potentially reflect brain mechanisms by which the S allele confers risk for depression and anxiety in the context of stressful life events, although this hypothesis has not been tested directly.

Along with the imaging genetic studies, there is evidence that the S allele is associated with cognitive vulnerabilities to depression, particularly under stressful conditions (Gibb, Beevers, & McGeary, 2013). For example, compared with individuals who are homozygous for the L allele, healthy adults who carry the S allele take longer to disengage attention from facial expressions of emotions (Beevers, Wells, Ellis, & McGeary, 2009) and to appraise recent stressful life events as being more negative (Conway et al., 2012a), with negative appraisals correlated with elevations in depressive symptoms (Conway et al., 2012a). Another study found that healthy children who carried the S allele had enhanced memory for negative (versus positive) self-descriptive traits (Hayden et al., 2013), thus exhibiting a potential cognitive vulnerability for depression. None of these studies formally tested the hypothesis that cognitive vulnerabilities to depression associated with the 5-HTTLPR genotype account for the elevated risk for depression among S allele carriers who experience stressful life events. Thus, mediating psychological processes remain largely unexplored, a lacuna addressed directly in this report.

The Role of Coping

To the extent that S allele carriers are more physiologically reactive to stressful situations and have a tendency to perceive situations as more stressful, they may engage in less effective coping strategies when faced with stressful life events than individuals who are homozygous for the L allele (Compas, 2006; Taylor & Stanton, 2007). According to Compas et al. (2001) coping is defined as “…conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances” (p.
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Several dimensions of coping have been identified in adults, including problem-focused versus emotion-focused coping (Lazarus & Folkman, 1984), primary control versus secondary control coping (Weisz, McCabe, & Dennig, 1994), and engagement versus disengagement coping (Ebata & Moos, 1991; Tobin, Holroyd, Reynolds, & Wigal, 1989). These different dimensions distinguish between efforts to change the nature of the stressor (e.g., by taking some action to solve the problem as would be observed in problem-focused, primary control, or engagement coping strategies) versus efforts to change how one feels about or responds to the stress (e.g., by reframing one’s circumstances, denying the existence of the stressor, or distracting oneself as would be observed in emotion-focused, secondary control, or disengagement coping strategies). These dimensions have been criticized for being overly-broad (e.g., emotion-focused coping comprises highly disparate strategies some of which may be more adaptive than others) and for failing to capture adequately the dimensions of children’s coping (Ayers, Sandler, West, & Roosa, 1996; Compas et al., 2001).

In contrast to studies of adults, research on children reveals three to four dimensions that differ slightly in terms of how coping strategies are grouped together. One framework distinguishes primary control (e.g., problem solving, emotional expression), secondary control (e.g., distraction, cognitive restructuring), and disengagement strategies (e.g., denial, avoidance) (Connor-Smith, Compas, Wadsworth, Harding Thomsen, & Saltzman, 2000). A second framework distinguishes active coping (e.g., direct problem solving, cognitive restructuring), avoidance (e.g., denial, staying away from the source of the problem), distraction (e.g., physical release of emotions or distracting actions), and support-seeking strategies (e.g., emotion- or problem-focused social support) (Ayers et al., 1996; Sandler, Tein, & West, 1994). Ayers et al. (1996) found that among a sample of fourth through sixth grade children, the four-dimension
framework provided a better fit to the data than did a two-dimension framework (i.e., problem-versus emotion-focused and passive versus active); for this reason, we rely on the four-dimension framework in the current work.

In general, the more frequent use of active coping, support-seeking, distraction, or primary and secondary control strategies is associated with fewer internalizing and externalizing symptoms (Connor-Smith et al., 2000; Fear et al., 2009; Gonzales, Tein, Sandler, & Friedman, 2001; Jaser et al., 2005; Jaser et al., 2008; Nicolotti, El-Sheikh, & Whitson 2003; Weisz, Francis, & Bearman, 2010). In contrast, the more frequent use of avoidance or disengagement coping strategies is associated with more symptoms of internalizing and externalizing problems (Forns, Balluerka, Gomez-Benito, Kirchner, & Amador, 2010; Nicolotti et al., 2003; Sandler et al., 1994; Wadsworth, Raviv, Santiago, & Etter, 2011). Intriguingly, however, recent research suggests that avoidance coping may be adaptive for inner-city youth (Gonzales et al., 2001; Grant et al., 2000; Sanchez et al., 2013).

Coping Genetics

Might coping and genotype be related, even perhaps helping to explain the untoward consequences of carrying one or two short alleles when subject to stress? A few investigations have shown that coping or perceptions of coping are associated with the 5-HTTLPR genotype; for example, among adults who were asked to recall recent situations in which they had felt strong emotions of fear, sadness, or joy, those who carried the S allele reported that they had felt less able to cope with situations that evoked strong feelings of sadness or fear than did individuals who were homozygous for the L allele (Szily, Bowen, Unoka, Simon, & Kéri 2008). In another study, healthy young adults who were homozygous for the S allele less frequently
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endorsed the use of cognitive reappraisals to deal with negative emotions or events (e.g., “When I want to feel less negative emotion, I change what I’m thinking about” or “I look for the positive side of the matter”) than L allele carriers. In turn, their less frequent use of cognitive reappraisal strategies explained why individuals who carried two copies of the S allele had increased symptoms of social anxiety (Miu, Vulturar, Chis, Ungureanu, & Gross, 2013). Finally, in a sample of 156 healthy adults, Wilhelm et al. (2007) reported that S allele carriers utilized fewer problem-solving coping strategies in response to a stressor. Thus, it is possible that the interaction between exposure to stressful life events and 5-HTTLPR may affect internalizing and externalizing symptoms through its influence on coping strategies. To repeat, that is a core hypothesis we test in the research reported herein, predicting that this will be the case.

Beyond Internalizing Problems

The majority of research on the 5-HTTLPR genotype and stressful life events has focused on outcomes like depression and anxiety. However, serotonin is involved in regulating both depression and aggressive behavior (Lucki, 1998) and internalizing and externalizing problems tend to co-occur at relatively high rates in children (Angold, Costello, & Erkanli, 1999; Marmorstein, 2007; Russo & Beidel, 1994).

Some work indicates that individuals who exhibit externalizing symptoms, including conduct problems, aggression and violence, are more likely to carry the S allele than individuals with lower levels of externalizing problems (Gerra et al., 2005; Haberstick, Smolen, & Hewitt, 2006; Lyons-Ruth et al., 2007; Retz et al., 2004; Verona & Patrick, 2000; Zalsman et al., 2001). However, this association has not been found consistently; in samples of younger children, the
association between 5-HTTLPR genotype and aggressive behavior tends to be non-significant (Beitchman et al., 2006; Davidge et al., 2004).

In addition to a shared genetic vulnerability, both internalizing and externalizing disorders have common environmental risk factors such as exposure to harsh, rejecting and dangerous environments (Margolin & Gordis, 2000), which could help to explain their co-occurrence in middle childhood. Inconsistencies among genetic studies of children’s externalizing problems may reflect the fact that genetic associations are only observed under conditions of high environmental risk or that the direction of genetic associations may change at low versus high levels of environmental risk (Belsky & Pluess, 2009; 2013; Belsky, Bakermans-Kranenburg & van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kraneneburg & van IJzendoorn, 2011). The few studies that have tested interactions between 5-HTTLPR and measures of environmental risk on externalizing symptoms indicate that individuals with the 5-HTTLPR S allele have more symptoms of externalizing problems than L/L carriers if they have experienced high levels of environmental risk (Conway et al., 2012b; Reif et al., 2007; Retz et al., 2008; Simons et al., 2011; Verona et al., 2006). Thus, we hypothesized that the association between cumulative environmental risk and externalizing problems would be more pronounced, the more S alleles a child had. Moreover, because poor coping strategies are associated with externalizing as well as internalizing problems, we hypothesized that coping would explain why stressful relationships and experiences were associated with elevations in externalizing problems among S/S and potentially among S/L allele carriers.

Diathesis Stress or Differential Susceptibility?
Recent thinking about GXE interaction from a differential-susceptibility perspective calls attention to the fact that opposite genetic effects may be observed under benign or supportive conditions versus high risk environments (Belsky, Joinissaint, et al., 2009; Belsky & Pluess, 2009, 2013). Indeed, a recent meta-analysis of relevant research reveals that to be the case in Caucasian children and adolescents (van IJzendoorn, Belsky & Bakermans-Kranenburg, 2012). Thus, we further expect that S carriers, especially perhaps homozygotes, will manifest both the most problems under conditions of adversity, but least when contextual conditions are benign. To test this hypothesis, we employed a new model-fitting approach that directly evaluates alternative models of GXE interactions, in this case diathesis stress vs. differential susceptibility (Widaman et al., 2012; Belsky, Pluess & Widaman, 2013).

The Current Study

In summary, the current study tested whether the 5-HTTLPR genotype moderates the effect of a cumulative risk index of stressful relationships and experiences on children’s risk for internalizing and externalizing problems. Moreover, we tested whether children’s coping styles (including active, support-seeking, distraction, and avoidance strategies) were associated with children’s internalizing and externalizing problems and whether children’s coping strategies explained observed genotype X environment effects. The current study is only the second of which we are aware to evaluate a mediated moderation model of 5-HTTLPR genotype X environment effects in order to elucidate how 5-HTTLPR functions at the psychological level. The other investigation that made a similar effort (Davies & Cicchetti, 2014) found that children’s angry reactivity partially mediated the effects of maternal unresponsiveness on increases in externalizing symptoms, but revealed, intriguingly, that children who were homozygous for the long rather than short allele were most susceptible to maternal
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unresponsiveness. The fact that the children in that study were mostly African-American and that
the aforementioned meta-analysis by van IJzendoorn et al. (2012) documented differential-
susceptibility-related GXE effects involving 5-HTTLPR only in the case of Caucasian children
would seem to support the prediction that it will be S-allele carriers who will prove most
susceptible to environmental effects and in a for better-and-for-worse manner consistent with
differential-susceptibility thinking (Belsky et al., 2007; Belsky & Pluess, 2009, 2013; Ellis et al.,
2011).

Method

Sample

The sample included 400 children (49% female, 51% male) who participated in the
Children’s Experiences and Development Study (CEDS), which was conducted from 2009
through 2011 in England. CEDS children were born between 1999 and 2001 and were originally
assessed as part of a separate study of over 6,000 families when they were 3 years old (Belsky et
al., 2006). Children ranged in age from 8 to 11 years ($M = 9.99$, $SD = .74$). Details of the CEDS
sampling frame are described in Jaffee et al. (2015). The 400 families who were successfully
recruited to CEDS were similar to the 729 families who were eligible to participate, but who
refused or could not be located in terms of parental education, perceived financial hardship,
ethnicity, child problem behaviors at age 3, and parenting at age 3. However, families who
participated were more likely to be employed, to own their own homes, and to speak only
English at home (Jaffee et al., 2015).

In 20% of CEDS households, the highest educational qualification attained was an O-
level degree or equivalent (the degree required to complete school at 16 years), in 24% of
families it was an A-level degree or equivalent (advanced secondary school degree), and in 37% of families it was an advanced vocational degree, undergraduate degree, or higher qualification. In 19% of families, caregivers did not complete secondary schooling. Mean pre-tax household income ($M = 8.89, SD = 4.44$) corresponded to £18,000 - £19,000 (approximately $29,000 to $30,500), which is below the mean income of £26,500.

To avoid confounding by population stratification in the gene × environment interaction analyses reported below, the analysis sample was restricted to 279 children (70% of the CEDS sample) who were of White British or other White race/ethnicity. In the full sample including all ethnic/racial groups, 7% were Black British, 16% were Asian (including Pakistani, Indian, and Bangladeshi), and 7% were other ethnicities. The analysis sample of White children was 46% female ($n = 129$) and 54% male ($n = 150$) who were 9.97 years, on average ($SD = .73$). We compared Caucasian participants to the other racial/ethnic groups on several demographic and clinical variables. Caucasian youth did not significantly differ from non-Caucasian participants in terms of child age, child sex, household standard occupational classification, household education level, or externalizing, or internalizing problems. However, Caucasians reported significantly greater household income compared to non-Caucasian participants, $t(385) = 4.06$, $p < .001$.

CEDS Protocol

Week-long training sessions were held before research workers were sent into the field. Visits were conducted in the family’s home and lasted for approximately 4 hours. Visits were usually scheduled for weekday afternoons and involved an interview with the child and with the child’s main caregiver (the mother in 98% of families). Research workers obtained signed
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consent from caregivers and signed and/or verbal assent from children before beginning the interview. Store vouchers were paid to caregivers (£35) and children (£10) for their participation. Ninety-seven percent of caregivers provided contact details for their child’s teacher and 70% of teachers who were contacted completed questionnaires about the child’s behavior. Teachers were given a £10 store voucher for their participation. The study was approved by the King’s College London Research Ethics Committee.

Measures

Cumulative risk. A cumulative risk index was created to capture children’s exposure to harsh parenting in middle childhood, low parental warmth in middle childhood, and lifetime traumatic events. Harsh parenting in middle childhood was measured by two items from the corporal punishment subscale (“you smack your child when s/he does something wrong,” “you slap your child when s/he does something wrong”) and one item from the other discipline subscale (“you yell or scream at your child when s/he does something wrong”) of the Alabama Parenting Questionnaire (Shelton, Frick, & Wooton, 1996) plus an additional item from a measure of parental hostility that was developed for use in the Iowa Youth and Families Project (“you criticize your child’s ideas”) (Conger, Wallace, Sun, McLoyd, & Brody, 2002). Parental warmth in middle childhood was measured with 9 items developed for use in the Iowa Youth and Families Project (e.g., “you act lovingly and affectionately towards NAME,” “you listen carefully to NAME’s point of view”) (Conger et al., 2002). Caregivers were asked if they engaged in these harsh and warm behaviors (1 ‘no, never’ to 3 ‘yes, often) and scores were summed to create harsh and warm parenting scale scores. Cronbach’s alpha for the parental warmth measure was $\alpha=.72$. Internal consistency reliability for the harsh parenting measure was low ($\alpha=.52$), although the harsh parenting items are better represented as causal indicators rather
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than effects indicators of harsh parenting; thus Cronbach’s alpha may not be a relevant metric (Bollen & Lenox, 1991). To create dichotomous indicators for use in the cumulative risk score, high levels of harsh and low levels of warm parenting were defined at the top and bottom tertiles, respectively, of their distributions.

Traumatic events were assessed with the Traumatic Events Screening Inventory (Ribbe, 1996) in which caregivers and children reported if the child ever experienced any of 13 traumatic events. Because agreement between caregiver and child reports was modest (kappas ranged from 0 for low base rate events like “child was kidnapped” to .51 for “family member was in trouble with the police or in prison”), events were coded as having happened if both the child and caregiver reported the event. To maintain approximate consistency with the other cumulative risk indicators for which high risk reflected the top (or bottom) tertile of the distribution, we identified children who had experienced 2 or more traumatic events in their lifetime (35%) for use in the cumulative risk score.

To create the cumulative risk score, we summed the indicators for harsh parenting in middle childhood, low parental warmth in middle childhood, and lifetime traumatic events. Thirty-six percent of youth were not characterized by any of the risk indicators, 36% had one risk indicator, and 28% had more than one risk indicator (Table 1). We describe this as cumulative risk, because all three indicators are robust risk factors for children’s internalizing and externalizing problems. We note that youth in our analysis sample experienced relatively fewer cumulative risks than non-Caucasian youth, \( r(395) = -2.50, p < .05 \).

To assess the validity of the cumulative risk variable, we tested whether cumulative risk status predicted children’s use of medical, educational, or counseling services, and specifically, their use of emotional and behavioral health services (psychiatrists, psychotherapists, behavioral
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therapists, family therapists, school counselors). We also tested whether the cumulative risk variable was associated with clinically significant levels of internalizing and externalizing problems. We identified children with clinically significant internalizing and externalizing problems as those who exceeded the CASI-defined clinical cut-point for conduct disorder or oppositional defiant disorder (externalizing) and generalized anxiety disorder or dysthymia (internalizing) according to caregivers or teachers.

Results of logistic regression analyses showed that the odds of using any services were 2.05 times greater (95% CI = 1.09 to 3.84) and the odds of using emotional and behavioral health services specifically were 3.35 times greater (95% CI = 1.33 to 8.47) for children who had two or more risk factors compared with children who had no risk factors. Compared to children with no risk factors, those with only one cumulative risk factor did not have a greater odds of using any services (OR = 1.19, 95% CI = .65 to 2.18) or emotional and behavioral health services specifically (OR = 1.66, 95% CI = .64 to 4.32).

Results of logistic regression analyses also showed that the odds of having clinically-significant externalizing (OR = 8.64, 95% CI = 3.56 to 20.97) and internalizing problems (OR = 4.90, 95% CI = 1.56 to 15.34) were significantly greater for children with two or more risk factors compared with children who had no risk factors. There was a trend-level association between having one versus zero risk factors and children's clinically-significant externalizing problems (OR = 2.38, 95% CI = .95 to 5.97), but this association was not significant for children's internalizing problems (OR = 1.85, 95% CI = .55 to 6.21). Thus, children with two or more risk factors were more likely to have clinically significant levels of internalizing and externalizing problems and were significantly more likely to use emotional and behavioral health
services as well as medical and educational services compared with children who had none of the cumulative risk factors.

5-HTTLPR. The promoter activity of the 5-HTT gene, located on 17q11.2, is modified by sequence elements within the 5’ regulatory region, designated the serotonin transporter gene-linked polymorphic region (5-HTTLPR). There is a 20-23 base pair repeat motif within this region within which two alleles are typically identified: a 14-repeat short (‘S’) allele vs. a 16-repeat long (‘L’) allele.

DNA was extracted from buccal swabs as described by Freeman, Curtis, Huckett, Mill, and Craig (2003) for the 91% of the White British and other White participants within the sample. 5-HTTLPR was genotyped using standard PCR protocols using a PTC-225 thermocycler. The forward primer had the sequence 5’- TCGAGGCTGAGCGTCTAGAGGGACTGAGCT-3’ and the reverse primer had the sequence 5’- CTTGTTGGGGATTCTCCCGCTGGCGT-3’. Cycling conditions included an initial 10-minute denaturing step at 95°C, followed by 30 cycles at 65°C for one minute each, and a final extension phase at 72°C for 5 minutes. Reactions were performed on 2µl DNA, 10x NH4 buffer, 25mM MgCl2, 5 pmols of primer, 1 unit of Taq polymerase, and made up to 10µl total volume with H2O. PCR fragments were resolved on a 2% Ethidium Bromide stained agarose gel by electrophoresis for 1.5 hours at 220 Volts. Visualization under UV allowed for identification of genotypes (Table 1). The three groups were in Hardy-Weinberg equilibrium, $\chi^2(2) = .01$, $p = .56$. Twenty-five children refused to provide DNA and one sample was lost.

Internalizing problems were measured with the Child and Adolescent Symptom Inventory-4 (CASI-4R; Gadow & Sprafkin, 2005). Caregivers and teachers reported how often children engaged in behaviors reflecting symptoms of generalized anxiety disorder (6 items for
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caregivers and 5 items for teachers) and symptoms of dysthymia (8 items for caregivers; 6 items
for teachers). Responses ranged from 0 “never” to 3 “very often”. Children were coded as having
met criteria for a symptom if they did it “often” or “very often” or if they did it “sometimes” in
the case of low base rate behaviors. Symptoms were summed within informant. Generalized
anxiety and dysthymia symptom sum scores were correlated within informant (caregivers: \( r = .60, p < .001 \); teachers: \( r = .64, p < .001 \)). These scores were standardized and averaged to create
caregiver- (\( \alpha = .71 \)) and teacher-reported (\( \alpha = .79 \)) internalizing scores, respectively. The
correlation between caregiver and teacher internalizing scores was \( r = .37, p < .001 \), and these
scores were standardized and averaged to form the combined informant internalizing score used
in our analyses. Means and standard deviations are provided in Table 1.

*Externalizing problems* were measured with the CASI-4R (Gadow & Sprafkin, 2005).
Caregivers and teachers reported how often children engaged in behaviors reflecting symptoms
of conduct disorder (15 items for caregivers, 8 for teachers) and symptoms of oppositional
defiant disorder (8 items for both caregivers and teachers). Responses ranged from 0 “never” to 3
“very often”. Children were coded as having met criteria for a symptom if they did it “often” or
“very often” or if they did it “sometimes” in the case of low base rate behaviors (e.g., “starts
fires”). Symptoms were summed within informant. Conduct and oppositional defiant symptom
sum scores were correlated within informant (caregivers: \( r = .60, p < .001 \); teachers: \( r = .76, p < .001 \)). These scores were standardized and averaged to create caregiver-
(\( \alpha = .87 \)) and teacher-reported (\( \alpha = .92 \)) externalizing scores, respectively. The correlation between caregiver and
teacher externalizing scores was \( r = .42, p < .001 \), and these scores were standardized and
averaged to form the combined informant externalizing score used in our analyses. Means and
standard deviations are provided in Table 1.
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*Coping strategies* were measured with a modified version of the Children’s Coping Strategies Checklist – Revision 1 (CCSC-R1: Program for Prevention Research, 1999; Ayers et al., 1996). Children were asked to think about how often they used various coping strategies to solve their problems, or make themselves feel better, during the past month (0 “never” to 3 “most of the time”). The CCSC-R1 comprises four higher-order scales (active, distraction, avoidance, and support seeking strategies), each of which consists of two to six lower-order scales (13 in total) comprising 4 to 5 items each. To reduce the time burden on participants, we administered a shortened version of the CCSR-R1 that included 2 items from each of the 13 subscales, with items selected for face validity. This included 4 items reflecting distraction coping, 4 items reflecting support seeking, 12 items reflecting active coping, and 6 items reflecting avoidant coping.

Given evidence that the four higher-order factors of the CCSC-R1 are highly correlated (Ayers et al., 1996), we subjected the 26 items to an exploratory factor analysis with direct oblimin rotation. All items (except 2 which were excluded) loaded on their original scales and the internal consistency reliability of most of the original scales was adequate, although Cronbach’s alpha was low for the avoidance coping measure (α=.56). Within each coping scale, items were summed (see Table 1 for means and standard deviations). Cronbach’s alpha for distraction coping was α=.70 (after deleting one item “you read a book or magazine” which reduced the magnitude of Cronbach’s alpha to α=.67). For support seeking the Cronbach’s alpha was α=.64, and for active coping the Cronbach’s alpha was α=.75. As shown in Table 2, correlations among the coping subscales ranged from r = .18 to r = .42, all p < .001.

Statistical Analysis
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First, bivariate correlations were conducted among study variables (see Table 2). Second, we attempted to replicate previous findings in the literature (and facilitate the work of future meta-analysts) by conducting ordinary least squares (OLS) regression analyses to test whether 5-HTTLPR moderated the effect of cumulative environmental risk on children’s problem behaviors. An additive mode of transmission was assumed for genetic data (0, 1, 2 S alleles). Thereafter, hypothesis-testing analyses were undertaken. The Widaman et al. (2012) model-testing approach which we describe and implement below is designed to evaluate, on an a-priori basis, competing models of person-X-environment interaction. In contrast to traditional OLS approaches which evaluate whether an omnibus interaction—taking no particular form—is statistically significant, the model-testing approach can determine whether the anticipated moderating effect of 5-HTTLPR on contextual risk in predicting problem behavior proves more consistent with diathesis-stress or differential-susceptibility thinking.¹

In order to illuminate—and competitively evaluate—the form of the hypothesized genetic moderational process under investigation, we employed SAS 9.3 PROC NLIN and NLMIXED to fit all models. The re-parameterized model adapted from Widaman et al. (2012) follows the form:

$$Y = A_0 + B_1 (X_1 - C) + B_4 ((X_1 - C) \cdot D_2) + B_5 ((X_1 - C) \cdot D_3) + E$$  \hspace{1cm} \text{(Equation 1)}$$

Within Equation 1, Y represents the combined-informant internalizing or externalizing score, adjusted for sex; $X_4$ demarcates cumulative risk; $D_2$ and $D_3$ are the dummy variables with unit values for individuals in 5-HTTLPR allelic group 2 and 3, respectively (i.e., Group 2: S/L

¹The model testing approach developed by Widaman et al. (2012) is designed to be an alternative to traditional OLS approaches. Opinions vary -- even within our research group -- as to whether there are conditions under which traditional OLS and model-fitting approaches should be used in tandem; one perspective is that the inclusion of OLS regression coefficients is solely to facilitate the work of future meta-analysts whereas another perspective is that model-fitting and traditional OLS approaches can be mutually informative, particularly when the goal is to replicate reported interaction effects.
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heterozygotes; Group 3: S/S homozygotes); and C is the crossover point of the three allelic
groups. Note that the current inquiry only evaluates three allelic groups using the same crossover
point.

Equivalent to Equation 1, the following reflects the equation for each allelic group:

\[
Y = \begin{cases} 
\text{Group 1(long/long):} & Y = A_0 + B_1(X_1 - C) + E \\
\text{Group 2(short/long):} & Y = A_0 + B_2(X_1 - C) + E \\
\text{Group 3(short/short):} & Y = A_0 + B_3(X_1 - C) + E 
\end{cases} \tag{Equation 2}
\]

where \( B_2 = B_1 + B_4 \), and \( B_3 = B_1 + B_5 \) (\( B_4, B_5 \) are in Equation 1). \( B_1, B_2 \) and \( B_3 \) stand for the
slope for each allelic group, and \( A_0 \) is the intercept for each group. All other symbols are defined
above.

The model in equation 1 is the weak differential-susceptibility model (Model 1w) in
which the crossover point falls within the range of environmental measurement and all allelic
groups prove susceptible to environmental influence to some degree, though some more strongly
than others. In contrast, the strong differential-susceptibility model (Model 1s) stipulates that the
association between environmental predictor and outcome is non-significant for the least (or less)
malleable group(s), thereby fixing \( B_1 \) (or \( B_1 \) and \( B_2 \)) to be zero, and significant for the most (or
more) malleable group(s). Weak and strong diathesis-stress models (Models 2w and 2s) differ in
similar ways from each other, though for both the crossover point is fixed at the positive end
(i.e., low risk end) of the environmental parameter.

Each model supplies Akaike and Bayesian information criteria (AIC and BIC,
respectively). Lower values of AIC and BIC indicate better fit to the data. Both AIC and BIC
contain penalties for model complexity, so adding unnecessary parameters will lead to a rise in
the index, thereby indicating poorer fit to the data. We evaluated relative model fit using the
AIC and BIC in connection with statistical significance of model parameters. Additional
statistical details can be found in Widaman et al. (2012) and Belsky et al. (2013). Recommendations for comparing differential susceptibility versus diathesis stress models have also been made by Roisman et al. (2012).

**Results**

**OLS Regression Results**

We conducted OLS regression analyses in which we regressed internalizing and externalizing problems (separately) on the cumulative risk score, 5-**HTTLPR** genotype (0, 1, or 2 S alleles), and the cumulative risk x genotype cross-product. Prior to analysis, all variables were examined for fit between their distributions and the assumptions of OLS regression analysis including normality, linearity, and homoscedasticity of residuals.

**Internalizing Symptoms**

After controlling for child sex, the interactive effect of 5-**HTTLPR** genotype and cumulative risk on combined caregiver and teacher-reported internalizing problems was significant (b = .19, SE = .10, p < .05). The interaction term accounted for 2% of the variance, with the full model accounting for 6% of the variance in combined caregiver and teacher reported internalizing problems.

**Externalizing Symptoms**

The interaction between 5-**HTTLPR** genotype and cumulative risk was significant for combined caregiver and teacher reported externalizing problems (b = .25, SE = .09, p < .01), with the interaction accounting for 3% of the variation and the full model accounting for 20% of the variation in caregiver-reported externalizing problems.

**Form of the Interactions**
Based on the preliminary analyses, we added gender as another parameter in the equation. \( Y = \)

\[
\begin{align*}
\text{Group 1 (long/long)}: & \quad Y = A_0 + B_1(X_1 - C) + B_4 \times \text{Gender} + E \\
\text{Group 2 (short/long)}: & \quad Y = A_0 + B_2(X_1 - C) + B_4 \times \text{Gender} + E \quad \text{(Equation 3)} \\
\text{Group 3 (short/short)}: & \quad Y = A_0 + B_3(X_1 - C) + B_4 \times \text{Gender} + E
\end{align*}
\]

Then we fit a set of re-parameterized models (Equation 3). Summary model results, including each estimated parameter and AIC and BIC for each model, are displayed in Tables 3 and 4. We next fixed the corresponding parameters to be zero\(^2\) as previously described in order to compare the four alternative models (Model 1s/1w, 2s/2w).

**Internalizing Problems.** Results proved consistent with the *strong diathesis-stress* model for internalizing problems (Figure 1). This was because (a) all four alternative models fit the data well (see R-squared values in Table 3) and equally so (see F test results for comparing models in Table 3); (b) Model 2s (i.e., strong diathesis-stress) had the smallest BIC and the second smallest AIC values; (c) in the freely estimated model (Model 1w), the crossover point (see values of C and CI in Table 3) fell partly outside the possible range of the environmental predictor, thus proving inconsistent with differential susceptibility; and (d) estimated slopes and 95% confidence intervals in Model 1w were significantly different from zero for the 5-HTTLPR s/s homozygotes but not for the l-allele carriers (i.e., s/l and l/l). Furthermore, constraining the two slopes to be zero did not result in a significant decrease in R-square.

**Externalizing Problems.** Results proved consistent with the *weak diathesis stress* model for externalizing problems (Figure 2). This was because: (a) although all four alternative models

---

\(^2\) The current analyses involved three allelic groups, whether the strong models (i.e., Model 1s/2s) constrain slope(s) for one or two allelic groups depends on whether the slope estimates differ significantly from zero in the freely estimated model (i.e., Model 1w).
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(Model 1w/s, 2w/s) fit the data (see R-squared values in Table 4), the weak diathesis stress model (i.e., Model 2w) accounted for the most variance, an amount comparable to the full Model 1w (See F test results in Table 4); (b) AIC and BIC values for Model 2w were the smallest; (c) in the freely estimated Model 1w (i.e., weak differential susceptibility model), the 95% confidence interval for the crossover point fell partly outside the possible range of the measured environmental predictor (see values C and CI in Table 4), thus proving inconsistent with differential susceptibility; (d) in Model 1w, estimated slopes for all allelic groups were different from zero; (e) and even though the confidence interval for the estimated slope of 5-HTTLPR l/l homozygotes (i.e., $\beta_1$) in Model 1w fell slight below zero, constraining it to zero in the more parsimonious Model 2w did not significantly decrease $R^2$ relative to Model 1w.

Mediated Moderation
To test the hypothesis that individual differences in coping strategies explained why the relationship between cumulative risk and internalizing and externalizing problems varied as a function of genotype, we used PROCESS (Model 8; Hayes, 2013), which estimates indirect effects using a bootstrapping procedure. Bias-corrected bootstrap confidence intervals based on 5,000 bootstrap samples were used to test indirect effects. Coping strategies were evaluated as potential mediators by entering them simultaneously into the model, which allowed for testing whether these strategies collectively mediated observed associations as well as whether individual strategies uniquely mediated the associations, above and beyond the inter-correlations with the other strategies.

Internalizing Problems. Results of the mediated moderation model are presented in Figure 3. Mediated moderation analyses indicated that avoidance, support seeking, and active coping strategies did not significantly mediate the interaction between 5-HTTLPR genotype and cumulative risk on internalizing problems. However, distraction coping was a significant
mediator. Bootstrapping results yielded a total indirect effect of distraction coping \((b = .02, SE = .02)\) with a 95% confidence interval that did not contain zero (.0016, .0855). We further examined the indirect effects for each of the three genotype groups by testing for mediation in the simple slopes. These results demonstrated that the indirect effect of cumulative risk on combined caregiver and teacher reported internalizing problems through distraction coping was only significant for children who were homozygous for the S allele \((b = .04, SE = .03; 95\% CI: .0073, .1249)\), and that 16% of the effect of cumulative risk on combined caregiver and teacher reported internalizing symptoms could be explained by distraction coping. Among children who were homozygous for the S allele, the more cumulative risk indicators they had, the less frequently they used distraction coping which in turn was associated with higher levels of internalizing problems. The indirect effects via the mediator were not significant for children who were heterozygous \((b = .01, SE = .01; 95\% CI: -.0066, .04444)\) or children who were homozygous for the L allele \((b = -.02, SE = .02; 95\% CI: -.0818, .0078)\).

*Externalizing problems.* Although youth who more frequently used avoidance coping strategies had fewer externalizing problems (Table 2), none of the coping strategies significantly mediated the interactive effect of 5-HTTLPR genotype and cumulative risk on externalizing problems.

*Discussion*

In a sample of 8- to 11-year-olds, we found that those who were exposed to more stressful relationships and experiences (including harsh parenting, lack of parental warmth, and lifetime traumatic events, most of which concerned family and neighborhood conflict) had more symptoms of internalizing and externalizing problems. Contrary to predictions, our findings were not reflective of differential susceptibility and were more supportive of diathesis-stress, such that
genetic effects on internalizing and externalizing problems were more pronounced under conditions of high vs. low environmental risk. Thus, our study adds to a growing number of studies showing that \textit{5-HTTLPR} genotype moderates the effect of stressful life events and stressful experiences – particularly those involving harsh or abusive parenting and victimization – on internalizing as well as externalizing problems (Conway et al., 2012b; Karg et al., 2011; Reif et al., 2007; Retz et al., 2008; Simons et al., 2011; Uher & McGuffin, 2010; Verona et al., 2006). It must be acknowledged, however, that like most other \textit{5-HTTLPR}-related GXE studies, ours included only Caucasian children, as there is suggestive evidence that this GXE process may operate differently in the case of children of other races/ethnicities (van IJzendoorn et al., 2012; Davies & Cicchetti, 2014).

We also found that individual differences in coping style partly explained why youth who were homozygous for the S allele and who were exposed to high levels of cumulative risk had high levels of internalizing problems relative to other genotype groups. In the sample overall, children who more often reported using distraction strategies like playing a video game or playing sports or doing a hobby to cope with their problems had fewer symptoms of internalizing problems than children who reported using distraction coping strategies less frequently. Tests of a mediated moderation model revealed that children who had more indicators of cumulative risk used distraction coping strategies less frequently than children who had fewer indicators of cumulative risk, but only in the group of children who carried two copies of the S allele. In contrast, among youth who carried the L allele, the cumulative risk index was unrelated to how often they used distraction coping strategies. Although youth who more frequently used avoidance coping strategies had fewer externalizing problems than youth who less frequently used avoidance coping strategies, individual differences in avoidance coping did not explain why
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S/S and S/L carriers had relatively high levels of externalizing problems under conditions of increasing environmental risk.

*Implications for Research and Theory*

To date, a relatively small number of studies have identified potential mechanisms by which risk for internalizing problems is increased among (Caucasian) S allele carriers who experience stressful life events. As reviewed earlier, these include imaging genetic studies showing that S/S homozygotes mount a significantly greater cortisol response to acute stressors than L-allele carriers (Miller et al., 2013) and that the association between *5-HTTLPR* genotype and amygdala reactivity is most pronounced in individuals who have been exposed to high levels of stressful life events (Alexander et al., 2009; Alexander et al., 2012; Williams et al., 2009). These also include studies showing that the S allele is associated with cognitive vulnerabilities to depression, particularly under stressful conditions (Gibb et al., 2013) and suggestive evidence that S allele carriers cope differently with problems than do individuals who are homozygous for the L allele (Miu et al., 2013; Szily et al., 2008; Wilhelm et al., 2007). Consistent with this body of research, we found that (Caucasian) youth who carried two copies of the S allele differed from L allele carriers in how they coped with problems, particularly in the context of hostile and cold relationships with caregivers and exposure to traumatic events, mainly in their homes and neighborhoods.

Our finding that distraction coping strategies were associated with reductions in internalizing problems is consistent with (a) experimental evidence showing that inducing depressed people to focus on benign or positive thoughts reduces their dysphoria and improves their ability to generate effective solutions to problems and (b) some correlational data indicating that the more people manage to distract themselves from their problems, the less depressed they
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feel (Compas et al., 2001; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). One possible explanation of such results is that instead of distracting themselves from potentially chronic and uncontrollable problems, youth who were homozygous for the S allele ruminated about those problems. Youth who were less capable of suitably distracting themselves from problems within their families or neighborhoods might have engaged in perseverative negative thinking that made it more difficult to think constructively or take action to solve problems or to enlist social support, thus increasing their chances of becoming depressed or anxious (Mor & Winquist, 2002; Nolen-Hoeksema et al., 2008). Another possibility is that youth who carried two copies of the S allele were simply not getting exercise-related benefits associated with distraction coping. Two of the distraction coping strategies referred to playing sports and doing exercise and there is evidence that exercise itself may relieve symptoms of internalizing problems, possibly by stimulating the release of endorphins (Craft & Landers, 1998; Rimer et al., 2012).

Interestingly, we did not find that coping styles mediated the 5-HTTLPR genotype X environment effect on externalizing problems. Given the common co-occurrence of internalizing and externalizing symptoms in this developmental period (Angold et al., 1999; Caron & Rutter, 1991; Drabick, 2009; Klein & Riso, 1993), we expected that similar coping constructs would account for both outcomes. While S allele carriers who were exposed to stressful experiences and relationships were at increased risk for internalizing and externalizing problems, our findings suggest that the mechanism by which this gene x environment interaction exerts its effect may differ for internalizing versus externalizing problems. In the case of externalizing problems, it may be that heightened physiological reactivity associated with S allele genotype, coupled with executive function deficits that weaken inhibitory control (Morgan & Lilienfeld, 2000), increases the likelihood that youth will respond with reactive aggression to perceived threats.
Although we measured four coping strategies, only two – distraction and avoidance – were associated with children’s internalizing and externalizing problems, respectively, particularly when youth were homozygous for the S allele. Distraction and avoidance may be particularly effective coping strategies when stressors are perceived as uncontrollable, as may have been the case for youth in our sample who were exposed to yelling, shouting, and violence in their homes and neighborhoods as well as relationships with caregivers that were relatively harsh and lacking in affection.

Although distraction coping has frequently been associated with reduced risk of internalizing and externalizing problems, avoidance coping shows mixed associations. Consistent with the possibility that avoidance coping may be beneficial in the context of uncontrollable stressors, several studies of socioeconomically disadvantaged, inner-city youth faced with high rates of family and neighborhood poverty and violence indicate that avoidance coping is associated with reductions in externalizing problems and other outcomes, at least for some groups (Gonzalez et al., 2001; Grant et al., 2000; Sanchez et al., 2013). Like the youth in these studies, CEDS youth were predominantly from socioeconomically disadvantaged neighborhoods with relatively high rates of family and community violence. In this context, engaging with the stressor may provoke aggressive interactions and thus be associated with increases in children’s externalizing problems, whereas avoidance behaviors like trying to stay away from things that make you upset or trying to avoid people who make you feel bad may decrease the chances that children will engage in externalizing behavior.

Although we did not find that active and support-seeking coping strategies were associated with children’s internalizing and externalizing problems, it is possible that these strategies will be used to greater benefit as the children get older. For example, children’s
effective use of active coping strategies may rely on a level of cognitive maturity and abstraction that our participants lacked. Similarly, as children age they may have a broader social circle on which to rely for advice and support, making support-seeking strategies more effective in reducing the risk for internalizing and externalizing problems. Such a developmental transition, in which children learn to engage with their emotions may be necessary to prevent distraction coping strategies from morphing into more harmful avoidance behaviors (Nolen-Hoeksema et al., 2008).

Limitations

Although the study had a number of strengths, including assessments of children’s internalizing and externalizing problems by multiple informants, it was also characterized by various weaknesses. First, although internal consistency reliability for the active and distraction coping subscales was adequate (≥ .70), it was lower for the support-seeking and avoidance coping subscales. Thus, measurement error might have attenuated observed associations between coping style and other predictor or outcome variables in our models. Second, although the effect of the interaction between 5-HTTLPR genotype and cumulative environmental risk on children’s internalizing problems was significantly mediated by distraction coping strategies, the mediated effect was small, suggesting that other factors also explain why S/S homozygotes are at elevated risk for internalizing problems in the context of stressful relationships and experiences.

Finally, cumulative risk measures have been criticized for making arbitrary designations of risk status (e.g., the “risk” end of a continuously-distributed variable can be identified anywhere from above the median to the top 10%), for presuming additive (versus interactive) effects of risk variables, for weighting all risks equally (despite potential differences in risk severity), and for comprising combinations of more proximal versus more distal risk factors.
representing conceptually distinct domains of risk (e.g., socioeconomic stressors versus parental psychopathology) (Evans, Li, & Whipple, 2013). Nevertheless, cumulative risk measures reflect the reality that physical and psychosocial risk factors frequently co-occur (Evans, 2004); they are parsimonious; and they are more highly predictive of poor developmental outcomes than measures of single exposures (Evans et al., 2013). Although our cumulative risk measure comprised indicators of caregiver-child relations and children’s exposure to traumatic events, these generally reflected caregiver-child, family, and neighborhood relationships that were high in hostility and low in warmth given that children in our sample most frequently reported traumatic events involving family and neighborhood discord. Our measure of cumulative risk also showed predictive validity in that youth who had experienced 2 or more of the risk indicators were more likely to have received services (including emotional and behavioral health services) and to have clinically significant levels of internalizing and externalizing problems.

**Future Directions for Translating Research on the Influential Child into Preventive Interventions**

Children in our sample benefited from the use of avoidance and distraction strategies (particularly S/S carriers in the case of distraction strategies). Given the potential for these strategies to become maladaptive if children fail to eventually engage with their emotions, distractions that provide opportunities for children to form socially-supportive relationships may be especially beneficial in the short- and long-term. Playing sports on a team or joining a club might be a good distraction and have the added benefit of surrounding children and adolescents with peers and adults who could encourage them to share their feelings and help them address whatever problems they may be experiencing. Sports teams and clubs may also provide youth with structured alternatives to engaging in more risky behaviors. In contrast, more solitary distractions like reading books, watching movies, or playing video games may not benefit youth
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in the long term if they do not ultimately provide opportunities to engage with emotions or to actively problem-solve. We note that such opportunities could present themselves if, for example, youth gained insight into their own circumstances by seeing them mirrored in the lives of fictional and non-fictional figures.

Youth who are homozygous for the S allele and who appear to be highly physiologically and emotionally reactive in the face of stress may benefit the most by being trained to do something they enjoy that takes their minds off their problems when they feel overwhelmed. If research on child effects has taught us anything, however, it is that this hypothesis must be evaluated so as to rule out the possibility of reverse causation. That is, children who are naturally capable of distracting themselves may be the same children who are least likely to experience internalizing or externalizing problems. A randomized control trial would demonstrate whether exercises or activities that facilitate distraction coping strategies reduce children’s internalizing or externalizing problems independent of whatever characteristics children bring to the activity.
Table 1

Means and (Standard Deviations) or Percentages and (n’s) for Study Variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or % (n)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 risks</td>
<td>36% (101)</td>
<td></td>
</tr>
<tr>
<td>1 risk</td>
<td>36% (99)</td>
<td></td>
</tr>
<tr>
<td>2 or 3 risks</td>
<td>28% (78)</td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L</td>
<td>31% (79)</td>
<td></td>
</tr>
<tr>
<td>S/L</td>
<td>49% (124)</td>
<td></td>
</tr>
<tr>
<td>S/S</td>
<td>20% (50)</td>
<td></td>
</tr>
<tr>
<td>Internalizing Behavior</td>
<td>-.00 (.86)</td>
<td>-.68 – 5.17</td>
</tr>
<tr>
<td>Externalizing Behavior</td>
<td>-.01 (.87)</td>
<td>-.61 – 4.29</td>
</tr>
<tr>
<td>Avoidance Coping</td>
<td>13.99 (2.90)</td>
<td>5.00 – 20.00</td>
</tr>
<tr>
<td>Distraction Coping</td>
<td>8.39 (2.64)</td>
<td>3.00 – 12.00</td>
</tr>
<tr>
<td>Active Coping</td>
<td>24.07 (5.49)</td>
<td>13.00 – 38.00</td>
</tr>
<tr>
<td>Support-seeking Coping</td>
<td>9.71 (2.85)</td>
<td>4.00 – 16.00</td>
</tr>
</tbody>
</table>

Note: Genotypic data was available for 253 of the 279 children. There were 25 cases in which children refused to give DNA, and one sample was lost.
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**Table 2**

*Bivariate Correlations among Study Variables*

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female Sex</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Cum. Risk</td>
<td>-.10</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 5-HTTLPR</td>
<td>-.02</td>
<td>.08</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. EXT</td>
<td>-.14*</td>
<td>.36**</td>
<td>.18**</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. INT</td>
<td>-.05</td>
<td>.22**</td>
<td>.14*</td>
<td>.53**</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Avoidance Coping</td>
<td>-.03</td>
<td>-.03</td>
<td>-.04</td>
<td>-.16**</td>
<td>-.09</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Distraction Coping</td>
<td>-.21**</td>
<td>-.04</td>
<td>.07</td>
<td>-.03</td>
<td>-.16**</td>
<td>.20**</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Active Coping</td>
<td>.01</td>
<td>-.15*</td>
<td>-.05</td>
<td>-.09</td>
<td>-.09</td>
<td>.36**</td>
<td>.39**</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>9. Support Coping</td>
<td>.09</td>
<td>-.05</td>
<td>-.01</td>
<td>-.08</td>
<td>-.04</td>
<td>.23**</td>
<td>.18**</td>
<td>.42**</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: **p < .01, *p < .05; Female Sex = 1; Cum. Risk = cumulative risk; EXT = externalizing; INT = internalizing**
Table 3

*Alternative Regression Analyses for Internalizing Behavior (N= 252)*

<table>
<thead>
<tr>
<th></th>
<th>Differential susceptibility</th>
<th></th>
<th>Diathesis stress</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weak Model 1w</td>
<td>Strong Model 1s</td>
<td>Weak Model 2w</td>
<td>Strong Model 2s</td>
</tr>
<tr>
<td></td>
<td>Estimate (SE) 95% CI</td>
<td>Estimate (SE) 95% CI</td>
<td>Estimate (SE) 95% CI</td>
<td>Estimate (SE) 95% CI</td>
</tr>
<tr>
<td>$A_0$</td>
<td>-0.06(0.20)</td>
<td>0.03(0.17)</td>
<td>-0.08(0.18)</td>
<td>0.02(0.17)</td>
</tr>
<tr>
<td></td>
<td>[-0.45, 0.34]</td>
<td>[-0.30, 0.36]</td>
<td>[-0.43, 0.27]</td>
<td>[-0.31, 0.34]</td>
</tr>
<tr>
<td>$C$</td>
<td>0.16(0.57)</td>
<td>0.35(0.41)</td>
<td>0.00(-) a</td>
<td>0.00(-) a</td>
</tr>
<tr>
<td></td>
<td>[-0.96, 1.29]</td>
<td>[-0.46, 1.15]</td>
<td>[-]</td>
<td>[-]</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.03(0.12)</td>
<td>0.00(-) a</td>
<td>0.05(0.10)</td>
<td>0.00(-) a</td>
</tr>
<tr>
<td></td>
<td>[-0.20, 0.26]</td>
<td>[-]</td>
<td>[-0.15,0.24]</td>
<td>[-]</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.16(0.08)</td>
<td>0.00(-) a</td>
<td>0.16(0.08)</td>
<td>0.00(-) a</td>
</tr>
<tr>
<td></td>
<td>[-0.002, 0.32]</td>
<td>[-]</td>
<td>[0.003, 0.31]</td>
<td>[-]</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>0.41(0.14)</td>
<td>0.41(0.15)</td>
<td>0.39(0.10)</td>
<td>0.33(0.09)</td>
</tr>
<tr>
<td></td>
<td>[0.14, 0.68]</td>
<td>[0.12, 0.70]</td>
<td>[0.19, 0.59]</td>
<td>[0.15, 0.52]</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.0658</td>
<td>0.0519</td>
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<td>3.46</td>
<td>4.52</td>
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<td>0.004</td>
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<td>$F$ vs. 1w</td>
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<td>1.83</td>
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<tr>
<td>$p$</td>
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<tr>
<td>$F$ vs. 1s</td>
<td>1.83</td>
<td>-</td>
<td>-</td>
<td>0.49</td>
</tr>
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<td>-</td>
<td>1, 248</td>
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<tr>
<td>$p$</td>
<td>0.16</td>
<td>-</td>
<td>-</td>
<td>0.48</td>
</tr>
<tr>
<td>$F$ vs. 2s</td>
<td>1.38</td>
<td>0.49</td>
<td>2.05</td>
<td>-</td>
</tr>
<tr>
<td>$df$</td>
<td>3, 246</td>
<td>1, 248</td>
<td>2, 247</td>
<td>-</td>
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<tr>
<td>$p$</td>
<td>0.25</td>
<td>0.48</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>AIC</td>
<td>628.0</td>
<td>627.7</td>
<td>626.0</td>
<td>626.2</td>
</tr>
<tr>
<td>BIC</td>
<td>652.7</td>
<td>645.3</td>
<td>647.2</td>
<td>640.3</td>
</tr>
</tbody>
</table>
Note. AIC, Akaike information criterion; BIC: Bayesian information criterion. $F$ vs. $1w$ stands for an $F$ test of the differences in $R^2$ for a given model versus Model 1w. a Parameter fixed at the reported value; Standard error(SE) and 95% Confidence interval(CI) are not applicable and are listed as (-)/[-]. b The original model included another estimated parameter for child gender(as a covariate), the parameter estimates(i.e., $\beta_4$) are not reported in the table, but the degree of freedom counted for this parameter.
Table 4 Alternative Regression Analyses for Externalizing Behavior (N = 252)

Note. AIC, Akaike information criterion; BIC: Bayesian information criterion. $F$ vs. 1w stands for an $F$ test of the differences in $R^2$ for a given differential susceptibility.

<table>
<thead>
<tr>
<th></th>
<th>Weak Model 1w</th>
<th>Strong Model 1s</th>
<th>Differential susceptibility</th>
<th>Weak Model 2w</th>
<th>Strong Model 2s</th>
<th>Diathesis stress</th>
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<tbody>
<tr>
<td></td>
<td>Estimate (SE)</td>
<td>95% CI</td>
<td>Estimate (SE) 95% CI</td>
<td>Estimate (SE) 95% CI</td>
<td>Estimate (SE) 95% CI</td>
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<tr>
<td>$A_0$</td>
<td>0.08(0.20)</td>
<td>[-0.31, 0.48]</td>
<td>0.19(0.16)</td>
<td>[-0.12, 0.51]</td>
<td>-0.01(0.16)</td>
<td>0.12(0.16)</td>
</tr>
<tr>
<td>$C$</td>
<td>0.27(0.35)</td>
<td>[-0.42, 0.95]</td>
<td>0.44(0.22)</td>
<td>[0.01, 0.87]</td>
<td>0.00(-) $^a$</td>
<td>0.00(-) $^a$</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.20(0.10)</td>
<td>[-0.01, 0.40]</td>
<td>0.00(-) $^a$</td>
<td>[-]</td>
<td>0.22(0.09)</td>
<td>0.00(-) $^a$</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.29(0.08)</td>
<td>[0.14, 0.44]</td>
<td>0.27(0.08)</td>
<td>[0.11, 0.42]</td>
<td>0.30(0.07)</td>
<td>0.24(0.07)</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>0.71(0.13)</td>
<td>[0.46, 0.97]</td>
<td>0.73(0.13)</td>
<td>[0.48, 0.99]</td>
<td>0.65(0.09)</td>
<td>0.59(0.09)</td>
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<tr>
<td>$F$ vs. 1w</td>
<td>-</td>
<td>3.36</td>
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<td>1, 246</td>
<td>1, 246</td>
<td>2, 246</td>
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<td>3.36</td>
<td>-</td>
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<tr>
<td>$df$</td>
<td>1, 246</td>
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<tr>
<td>$p$</td>
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<tr>
<td>$F$ vs. 2s</td>
<td>3.19</td>
<td>2.99</td>
<td>5.96</td>
<td>-</td>
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<tr>
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<td>2, 246</td>
<td>1, 247</td>
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<td>585.3</td>
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<tr>
<td>BIC</td>
<td>607.6</td>
<td>607.6</td>
<td>602.5</td>
<td>603.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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model versus Model 1w.  

 Parameter fixed at the reported value; Standard error (SE) and 95% Confidence interval (CI) are not applicable and are listed as (-)/[-].  

 b The original model included another estimated parameter for child gender (as a covariate), the parameter estimates (i.e., $\beta_4$) are not reported in the table, but the degree of freedom counted for this parameter.
Figure Captions

Figure 1. Interaction between exposure to cumulative risk and 5-HTTLPR genotype predicting internalizing behavior. (Cumulative risk: “0” = 0 risk, “1” = 1 risk, “2”= 2 or 3 risks. “Adjusted Internalizing Behavior” represented the dependent variable after adjusting for child gender.)

Figure 2. Interaction between exposure to cumulative risk and 5-HTTLPR genotype predicting externalizing behavior. (Cumulative risk: “0” = 0 risk, “1” = 1 risk, “2”= 2 or 3 risks. “Adjusted Externalizing Behavior” represented the dependent variable after adjusting for child gender.)

Figure 3. Mediated moderation model for internalizing and externalizing symptoms.
Figure 1. Interaction between exposure to cumulative risk and 5-HTTLPR genotype predicting internalizing behavior. (Cumulative risk: “0” = 0 risk, “1” = 1 risk, “2” = 2 or 3 risks. “Adjusted Internalizing Behavior” represented the dependent variable after adjusting for child gender.)
Figure 2. Interaction between exposure to cumulative risk and $5$-HTTLPR genotype predicting externalizing behavior. (Cumulative risk: “0” = 0 risk, “1” = 1 risk, “2”= 2 or 3 risks. “Adjusted Externalizing Behavior” represented the dependent variable after adjusting for child gender.)
Figure 3. Mediated moderation model for internalizing symptoms.
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doi: [http://dx.doi.org/10.1016/0193-3973(91)90029-4](http://dx.doi.org/10.1016/0193-3973(91)90029-4)


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doi:[http://dx.doi.org/10.1016/j.janxdis.2006.06.004](http://dx.doi.org/10.1016/j.janxdis.2006.06.004)


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