

5-HTTLPR moderates the effect of relational peer victimization on depressive symptoms in adolescent girls

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Background: Relational peer victimization is associated with internalizing symptoms. Compared to boys, girls are more likely to be both relationally victimized by peers and distressed by the victimization. While previous studies have reported that a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) moderates the effect of stressful life events on depressive symptoms, the present study is the first to evaluate the interaction of this polymorphism with relational peer victimization to predict level of depressive symptoms in young girls. **Methods:** Participants were 78 girls ages 10 to 14 who had no current or past Axis I disorder. Girls were genotyped for 5-HTTLPR; peer victimization was assessed with the Social Experiences Questionnaire, and depressive symptoms with the Children's Depression Inventory. **Results:** The 5-HTTLPR polymorphism alone did not predict level of depressive symptoms; the interaction of 5-HTTLPR and relational peer victimization, however, was a significant predictor of depressive symptoms. Follow-up analyses indicated that peer victimization significantly predicted level of depressive symptoms only for girls who were homozygous for the short allele, and not for girls homozygous for the long allele or who were heterozygous for the short and long alleles. **Conclusions:** The findings support the diathesis-stress model of depression: having two 5-HTTLPR short alleles confers vulnerability to depressive symptoms in adolescent girls when they experience relational peer victimization. These findings also suggest that relational peer victimization, at least for girls with genetic vulnerability, is a significant source of stress and should be recognized in the monitoring and prevention of bullying. **Keywords:** Peer victimization, bullying, depression, genetic polymorphisms, 5-HTTLPR.

Peer victimization, or bullying, is an all-too-common experience for many children; indeed, as many as 20 to 40% of youth report peer maltreatment of some type, and 3 to 8% report frequent victimization (Nansel et al., 2001, 2004; Solberg & Olweus, 2003). Peer victimization includes not only being the target of overt, physical aggression in which one's physical integrity is damaged or threatened, but more relational forms of maltreatment as well. Examples of the latter include being intentionally excluded from a group or activity and being the target of lies or negative comments. While more research has focused on overt, or physical, victimization than on relational maltreatment, girls are less likely than boys to be physically victimized (Crick & Grotpeter, 1996), and are more likely to be relationally victimized (Crick & Bigbee, 1998) and to be distressed by relational victimization (Crick, 1995).

Both physical and relational victimization have been related to concurrent adjustment difficulties such as depression, anxiety, loneliness, and low self-worth (Austin & Joseph, 1996; Crick & Grotpeter, 1996; Slee, 1994, 1995). The results of a meta-analytic review suggest, however, that the largest effect sizes are for the association of peer

victimization with depression (Hawker & Boulton, 2000). More recently, longitudinal studies have attempted to examine the causal nature of the relation between peer victimization and adjustment difficulties. For example, while Arseneault et al. (2006) found preexisting adjustment problems to distinguish victimized versus non-victimized children, peer victimization was also found to be related to subsequent internalizing symptoms two years later, even after controlling for previous adjustment problems. In a second study, Arseneault et al. (2008) found that, among a group of monozygotic twins, those who had been bullied between the ages of 7 and 9 had more internalizing symptoms at age 10 than did their non-bullied twin, even after controlling for preexisting internalizing symptoms. This finding suggests that the environmental factor of being bullied predicts children's internalizing problems even after controlling for twin status.

Since Caspi et al. (2003) published their seminal findings supporting a diathesis-stress formulation of depression, at least 15 studies have reported results suggesting a genetic moderation of the depressogenic effects of stressful life events, such that carriers of one or two short alleles of a functional polymorphism in the promoter region of

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the serotonin transporter gene (5-HTTLPR) are more likely than are homozygous long-allele carriers to develop depression or depressive symptoms in response to negative life events (see Uher & McGuffin, 2008, for a review). Initial evidence suggests that this polymorphism is associated with greater reactivity of the hypothalamic–pituitary–adrenocortical (HPA) axis to stress, potentially conferring a biological vulnerability to depression in the face of stressful events (Gotlib, Joormann, Minor, & Hallmayer, 2008).

In this body of research, the ‘stressor’ has typically been operationalized as child maltreatment or as an accumulation of stressful/negative life events. In this context, the aims of the present study are twofold: (1) to extend this body of work to a different type of stressor, relational peer victimization, a developmentally salient stressor for adolescent girls at an age at which there is a sharp increase in the onset of depression (Kessler et al., 2003); and (2) to extend our knowledge of the mechanisms through which peer victimization affects depressive symptoms. While researchers have used twin-study designs to examine genetic and environmental influences on peer victimization (e.g., Ball et al., 2008) and the relation between peer victimization and internalizing symptomatology (Arseneault et al., 2008), the present study is the first to evaluate the interaction of a specific genetic polymorphism with relational peer victimization to predict level of depressive symptoms. We hypothesized that, in a sample of psychiatrically healthy young adolescent girls, those who had two 5-HTTLPR short alleles would report higher levels of depressive symptoms in the face of relational peer victimization than would their homozygous long-allele counterparts; we expected that girls carrying heterozygous short/long alleles would fall in between these two groups in their levels of depressive symptoms.

Methods

Sample

Participants were 78 girls ages 10 to 14 who participated in the first wave of a longitudinal study examining risk factors for major depressive disorder (MDD). Participants were recruited via their mothers through advertisements posted within the local community (cf. Gotlib et al., 2008). An initial brief telephone screening interview with the mothers was used to eliminate mothers and daughters who would not be eligible to participate in this study. Those mothers and daughters who passed the telephone screen came to the laboratory, where the daughters were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) in order to confirm their eligibility. For daughters to be eligible, both informants needed to report an absence of current or

past Axis I psychopathology. Furthermore, because of the context of the larger study, their mothers had to either have no current or past Axis I disorder (low-risk group) or a history of recurrent depressive episodes during the daughters’ lifetime but no current diagnosis of MDD (high-risk group).¹

Measures

Depressive symptoms were assessed with the short version of the Children’s Depression Inventory, a widely used 10-item self-report measure of depressive symptomatology in children between the ages of 8 and 17 (CDI-S; Kovacs, 1985). Participants indicated which of a series of descriptions best described how they have been feeling recently. Internal consistency for the CDI-S in this sample was $\alpha = .72$. Relational peer victimization was assessed with the 7-item self-report relational victimization subscale of the Social Experiences Questionnaire (SEQ; Crick & Grotpeter, 1996). Using a 5-point Likert-type scale ranging from ‘never’ to ‘all the time,’ participants indicated the frequency of being relationally victimized by one’s peers. Example items include ‘How often does a classmate tell rumors or lies about you to try to make other students not like you anymore?’ and ‘How often do other students leave you out of things or exclude you on purpose during free time or during an activity?’ Internal consistency of this measure in this sample was $\alpha = .82$. Relational victimization was used as a continuous variable in hierarchical regression models, and as a categorical variable for group comparisons. We used Crick and Bigbee’s (1998) criteria to categorize relational victimization. Specifically, girls were categorized as ‘victimized’ if their scores on the relational victimization subscale of the SEQ were greater than one standard deviation above the mean; all other girls were categorized as ‘non-victimized.’

Genotyping. Genetic material was collected through saliva using the Oragene kit for collection, preservation, transportation and purification (DNA Genotek, Ottawa, Ontario, Canada). DNA extracted by this method is of high quality and allows for a high success rate of genotyping (Rylander-Rudqvist, Hakansson, Tybring, & Wolk, 2006). Oligonucleotide primers flanking the 5-HTT-linked polymorphic region (Heils et al., 1996) and corresponding to the nucleotide positions –1416 to –1397 of the 5-HTT gene 5’-flanking regulatory regions were used to generate 484-bp or 528-bp fragments. The polymerase chain reaction products were electrophoresed through 5% polyacrylamide gel (Acrylamide/bis-Acrylamide ratio 19:1) at 60 V for 60 min. This genotyping yielded three groups of girls: girls with two short alleles (s/s), girls with one short and one long allele (s/l), and girls who were homozygous for the long allele (l/l). The allelic frequencies for 5-HTTLPR were in Hardy–Weinberg Equilibrium, $\chi^2(2,78) = .2$; $p = .90$.

¹ Daughters’ risk-group status based on mother’s diagnosis was related to depressive symptoms, but did not interact with peer victimization or genotype in predicting symptoms and, thus, was not considered further in the analyses.

Table 1 Sample characteristics by peer victimization group and genotype group

	<i>N</i>	Age in years (SD)	% Caucasian	% post-menarche	CDI (SD)
Genotype					
<i>l/l</i>	21	12.6 (1.4)	85.7	52.4	2.0 (2.2)
<i>s/l</i>	37	12.1 (1.6)	73.0	43.2	1.7 (1.9)
<i>s/s</i>	20	12.2 (1.4)	55.0	57.9	2.3 (2.7)
Relational peer victimization					
Non-victimized	62	12.3 (1.4)	71.0	52.5	1.6 (1.8)
Victimized	16	12.0 (1.7)	75.0	37.5	3.1 (3.1)*
TOTAL	78	12.2 (1.5)	71.8	49.4	1.9 (2.2)

Note. *l/l* = homozygous for long allele; *s/l* = heterozygous for short and long allele; *s/s* = homozygous for short allele. * $p < 0.02$.

Procedures

Following telephone screening, mother–daughter pairs were invited to the laboratory where they completed the K-SADS-PL and the questionnaires, and provided saliva samples for genotyping. Mothers provided informed consent for their own participation as well as their daughters' participation, and daughters provided assent to participate. Mother–daughter pairs were paid \$25 per hour for their participation in this study. The study was approved by the Stanford University Internal Review Board.

Results

Neither the 5-HTTLPR genotype groups nor the relational peer victimization groups differed with respect to age, race, or pubertal status (see Table 1). The mean CDI-S score for the total sample was 1.9 ($SD = 2.2$), far below the suggested cut-off of 10 for possible depression (Kovacs, 1985). While three genotype groups did not differ on CDI-S scores, the victimized group did report higher scores than did the non-victimized group, $t(76) = 2.5$, $p < .02$. The mean relational peer victimization score for the full sample was 12.1 ($SD = 4.2$).

To test whether the 5-HTTLPR polymorphism moderates the relation between relational peer victimization and depressive symptoms in young adolescent girls, we conducted a hierarchical linear regression using centered variables. In the first step of the equation, we included the two individual predictor variables: relational peer victimization and genotype group. In the second step, we entered the interaction term of these two variables. Neither relational peer victimization ($\beta = .20$, $p = .08$) nor genotype group ($\beta = -.03$, $p = .82$) individually predicted level of depressive symptoms when the interaction term was included; the interaction of relational peer victimization and genotype group, however, significantly predicted depressive symptoms ($\beta = .32$, $p < .01$; $F_{\text{change}}(1,74) = 8.5$, $R^2\Delta = .10$, $p < .01$). Follow-up analyses (regression analyses conducted separately for each genotype group) indicated that relational peer victimization significantly predicted depressive symptomatology for girls who were homozygous for the short allele, ($\beta = .47$, $p < .04$), but not for *s/l* girls ($\beta = .32$, $p = .06$)

or for girls who were homozygous for the long allele ($\beta = .19$, $p = .41$). Figure 1 presents CDI-S scores by genotype group and relational peer victimization group. Whereas *s/l* carriers and homozygous *l/l* girls did not differ in levels of depressive symptomatology as a function of relational peer victimization status, girls who were homozygous for the short allele and who were in the victimized group had significantly higher CDI-S scores than did their *s/s* counterparts who were in the non-victimized group, $t(18) = 3.8$, $p < .01$.²

Discussion

The main finding of this study supports the diathesis-stress model of depression: having two short alleles in the promoter region of serotonin transporter gene confers vulnerability to depressive symptoms in

² Recently, functional variants in the *l* allele, designated as l_A and l_G , have been found to confer different levels of transporter expression: the l_G and *s* alleles appear to have comparable levels of serotonin transporter expression, and both have lower levels than that of the l_A allele (Neumeister et al., 2006; Wendland, Martin, Kruse, Lesch, & Murphy, 2006). We chose to conduct our analysis classifying participants into three genetic groups based on their *s* and *l* alleles, irrespective of the l_A and l_G subtypes: (i.e., *l/l*, *s/l*, and *s/s*), because few studies to date have investigated subtypes of *l*, and this analysis therefore permits comparisons to a larger body of published work. Nevertheless, we also classified participants into the three groups that are more tightly coupled to 5-HTT expression levels: 1) individuals who are heterozygous for the long allele that confers the greatest 5-HT transporter expression (high-expressing: l_A/l_A); 2) individuals who have one copy of either the *s* allele or the reduced long allele and one copy of the l_A allele (l_A/s or l_A/l_G); and 3) individuals who have two copies of the *s* allele or one *s* and one reduced-expression long allele (low-expressing: *s/s* or s/l_G) or two low expression long alleles (l_G/l_G). The l_G allele has been reported to behave comparably to the low-expressing *s* allele (Hu et al., 2005). The results of the analyses using these groupings are comparable to those we report for the *s* and *l* allele grouping without subtyping, such that there is a significant interaction of genotype and relational peer victimization on CDI-S scores ($\beta = .75$, $p = .03$; $F_{\text{change}}(1,71) = 4.9$, $R^2\Delta = .06$, $p = .04$). Follow-up analyses are also similar, but slightly weaker, indicating that relational peer victimization predicted depressive symptomatology only for girls with two reduced expressing alleles (*s/s*, s/l_G or l_G/l_G) ($\beta = .39$, $p = .06$).

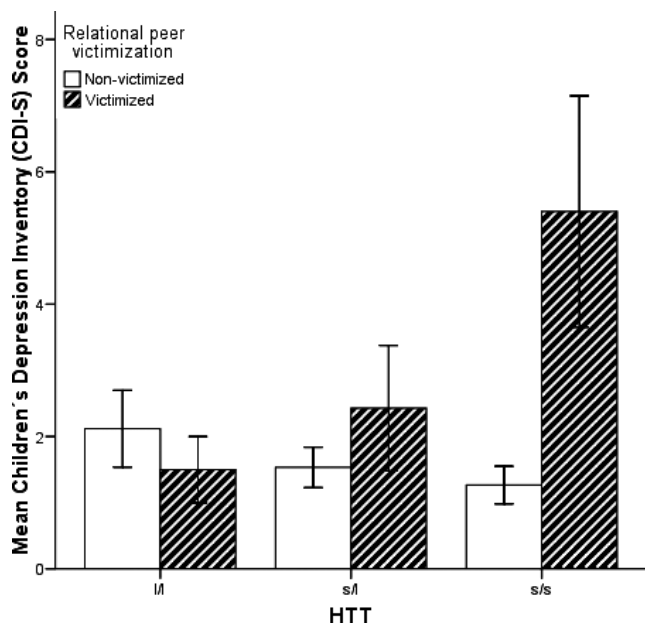


Figure 1 Depressive symptoms by genotype and relational peer victimization group. *Note.* *l/l* = homozygous for long allele; *s/l* = heterozygous for short and long allele; *s/s* = homozygous for short allele; $*t = 3.8$, $p < .01$

adolescent girls when they experience relational peer victimization. This finding may be due to the short allele playing a role in HPA-axis dysregulation, as suggested by Gotlib et al. (2008), who found that *s/s* girls produced higher and more prolonged levels of cortisol in response to a laboratory stressor than did girls with a long allele. In turn, hypercortisolemia has been posited to be involved in the development of depression through hippocampal neuronal loss (Sapolski, 2000). There is also some evidence that life stress is correlated positively with resting amygdala activation and rumination in short-allele carriers and negatively in long-allele carriers, suggesting not only that the short allele confers a vulnerability for depression when individuals encounter life stress, but also that the long allele has a protective effect, in which life stress leads to resilience (Canli et al., 2006).

Analyses for heterozygous girls, while showing a tendency towards greater vulnerability for depressive symptoms in the face of victimization, did not reach significance. The *s/l* girls had CDI-S scores between those of the two homozygous groups, and it is possible that the weaker significant findings for this group are due to statistical power. In this context, however, it is important to note that previous studies examining the interaction of 5-HTTLPR and stress in predicting depression have reported mixed results for this heterozygous group. Whereas some investigators have reported a dominant effect of the short allele such that heterozygous individuals are similar to persons homozygous for the short allele (e.g., Aguilera et al., 2009), other studies have found heterozygous individuals to fall between the two

homozygous groups (e.g., Caspi et al., 2003), and still other investigations have reported a recessive *s* effect, in which heterozygous individuals are similar to those who are homozygous for the long allele (e.g., Kendler, Kuhn, Vittum, Prescott, & Riley, 2005).

It is important to note three limitations of this study. First, we used a single informant to assess relational peer victimization. Interestingly, in a meta-analytic review of cross-section studies relating peer victimization to psychosocial maladjustment, Hawker and Boulton (2000) found larger effect sizes for studies using a single informant. It is possible that part of the association between victimization and maladjustment is due to shared method variance. More specifically, given that depressed individuals have been found to exhibit more negative attributions and to be characterized by better recall of negative than of positive information (e.g., Matt, Vazquez, & Campbell, 1992), it is possible that our findings are due to negative cognitive biases. If this were the case, however, negative attributions and better recall of negative than of positive information should characterize only girls homozygous for the short allele. In this context, it is noteworthy that Fox, Ridgewell, and Ashwin (2009) recently found attentional biases towards positive affective material and away from negative affective material in individuals homozygous for the long allele, but no attentional biases in either *s/s* or *s/l* carriers. It is also important to note that none of the girls in this study was currently in, or had previously experienced, a major depressive episode, and that genotype was not independently related to depressive symptoms. Thus, it appears that negative cognitive biases are unlikely to account for our results, and that a gene-by-environment interaction remains a plausible explanation. A second, related, limitation is that there is not an external validation of peer victimization. In this context, however, Crick and Bigbee (1998) found that girls' self-reported relational victimization was correlated significantly with peer-reported relational victimization, providing evidence for the validity of self-reported relational victimization. A final limitation concerns the sample size in this study. Although we obtained statistically reliable findings, gene-environment interactions are complex. Given the relatively small number of girls who reported high levels of victimization, it will be important in future research to replicate these results in larger samples and to examine more systematically the important question of whether this pattern of findings is influenced by ethnicity.

Despite these limitations, the present findings make an important contribution to the field. This study replicates previous findings that variations in 5-HTTLPR moderate reactions to stressful experiences, and extends those findings to the stressful experience of relational peer victimization in young adolescent girls. These results also highlight how powerful peer relationships are for young adolescent

girls and add to the peer victimization literature, increasing our understanding of the mechanisms involved in the development of depressive symptoms. Because adolescent girls report higher levels of depressive symptomatology (Ge, Lorenz, Conger, Elder, & Simons, 1994) and relational peer victimization than do boys (Crick & Bigbee, 1998), and because studies of the interaction of 5-HTTLPR and environmental variables have thus far yielded inconsistent results for adolescent boys (Uher & McGuffin, 2008), it is possible that different findings would be obtained in a sample of boys. It will be important for future research to examine this possibility more systematically.

Many studies of gene-environment interactions include severe life events as stressors, such as death or serious illness of a family member, having been robbed or assaulted, problems with the law or the police (e.g., Cervilla et al., 2007; Eley et al., 2004; Kendler et al., 2005), and child maltreatment or abuse (e.g., Aguilera et al., 2009; Caspi et al., 2003; Kaufman et al., 2006). The present findings suggest that relational peer victimization is a significant source of stress, at least for young adolescent girls at genetic risk for depression, thereby bridging the literature on negative or stressful life events and peer victimization, which has generally been considered to be a less severe form of stress, particularly when compared with overt or physical victimization. Crick and Grotpeter (1996) found that although relational and physical peer victimization were intercorrelated in a sample of girls and boys ($r = .57$), the majority of victimized children (64%) experienced only one type of victimization. It appears, therefore, that while relational and physical victimization can co-occur, they are generally distinct forms of maltreatment.

The literatures examining stressful life events and childhood adversity focus largely on stressors in the family domain (e.g., child maltreatment, parental pathology, poverty, divorce, death of a family member, birth of siblings); it is rare that peer-related stressors are included among items assessing negative life events. This is particularly unfortunate during the late childhood and early adolescent period, when peer relations take on greater importance and influence in development.

The present findings suggest that relational peer victimization is a significant source of stress for early adolescent girls and should not be ignored, minimized, or overshadowed by more overt forms of peer victimization. Relational victimization is associated with depressive symptoms in genetically vulnerable girls and, thus, might beneficially be assessed as part of the monitoring and prevention of bullying.

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Key points

- Relational peer victimization has been shown to be common, particularly distressing to girls, and associated with depression.
- Studies have reported that a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) moderates the effect of stressful life events on depressive symptoms.
- The present study is the first to evaluate the interaction of this polymorphism with relational peer victimization to predict level of depressive symptoms in young adolescent girls.
- The results support the diathesis-stress model of depression: having two short alleles confers vulnerability to depressive symptoms when girls experience relational peer victimization.
- Relational victimization is associated with depressive symptoms in genetically vulnerable girls and, thus, might beneficially be assessed as part of the monitoring and prevention of bullying.

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