Childhood Emotional and Sexual Maltreatment Moderate the Relation of the Serotonin Transporter Gene to Stress Generation

Kate L. Harkness
Queen’s University

R. Michael Bagby
University of Toronto

Jeremy G. Stewart, Cherie L. Larocque, and Raegan Mazurka
Queen’s University

John S. Strauss and Arun Ravindran
University of Toronto

Neil A. Rector
Sunnybrook Health Sciences Centre

Katherine E. Wynne-Edwards
University of Calgary

James L. Kennedy
University of Toronto

Emerging evidence suggests that the tendency to generate stressful life events may be, at least in part, genetically determined. However, the role of the early environment in shaping responses to later stressors is crucial to fully specifying biogenetic models of stress generation. The current study examined the moderating role of childhood emotional, physical, and sexual maltreatment on the relation of the serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism of the serotonin transporter gene to proximal independent, dependent, and dependent-interpersonal life events. This question was tested in a cross-sectional community sample of 297 adolescents and young adults. Childhood maltreatment history and proximal life events were assessed with state-of-the-art interviews that provide independent and standardized ratings of the environmental context. Consistent with the stress generation hypothesis, individuals with the risk s-allele of the serotonin transporter gene reported significantly higher rates of dependent and dependent-interpersonal life events than those homozygous for the l-allele, but only in the context of a history of maternal emotional maltreatment or sexual maltreatment. Neither serotonin transporter gene polymorphisms or childhood maltreatment, or their interaction, were associated with reports of independent life events. The current results demonstrate the importance of considering specificity in the early environmental context when examining the relation of genetic factors to the generation of proximal stress.

Keywords: serotonin transporter gene, child maltreatment, stress generation, depression, stressful life events

A large amount of research has accumulated over the past 25 years suggesting that individuals with certain vulnerability characteristics generate stress in their lives (Hammen, 1991; Hammen, 2006). For example, both cross-sectional and prospective longitudinal studies have documented that, in comparison with those who are not depressed, individuals with a history of depression report significantly higher rates of life events that are at least partly dependent on their own behavior, especially in the interpersonal
domain (e.g., conflict in or dissolution of relationships). In contrast, these two groups do not differ in rates of independent, or “fateful,” life events (e.g., grandmother dies of a stroke, tornado ruins home) (see Hammen, 2006; Liu & Alloy, 2010 for reviews). Importantly, even in the absence of depression, trait characteristics, such as high neuroticism (Brown & Rosellini, 2011; Kercher, Rapee, & Schniering, 2009; Uliaszek et al., 2012) and trait rumination (Hankin, Stone, & Wright, 2010; McLaughlin & Nolen-Hoecksema, 2012) are significantly associated with the generation of stress. Furthermore, a history of early environmental adversity, such as childhood maltreatment, heightens the generation of later dependent and dependent-interpersonal life events, and may moderate the effect of dispositional characteristics on the generation of stress (Hankin, 2005; Hankin, Lumley, & Truss, 2008; Liu, Choi, Boland, Mastin, & Alloy, 2013; Uhrlass & Gibb, 2007).

Evidence indicating a stable disposition to generate stress suggests that the tendency to generate dependent events in the environment may be, at least in part, genetically determined (Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983). For example, in Kendler and colleagues’ pioneering twin studies, they found that even in the absence of proband depression, having a cotwin affected with depression significantly raised the proband’s risk of experiencing several different classes of life events (Kendler & Karkowski-Shuman, 1997). Importantly, approximately one third of the association between stress and depression could be accounted for by genetic factors that increased risk for both stress exposure and depression onset (Kendler, Karkowski & Prescott, 1999). To explain these findings, Kendler and his colleagues suggested “genes have feet” that lead individuals to select themselves into particular environmental contexts.

More recent molecular genetic work has supported the conclusions from Kendler and colleagues’ landmark studies. This research has focused specifically on polymorphisms in the serotonin transporter gene (SLC6A4), with a particular emphasis on the serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism. The 5-HTTLPR is a 43-base pair insertion or deletion containing two allelic variants—short (s), with 14 repeat units, and long (l) with 16 repeat units. The s-allele of the 5-HTTLPR results in decreased transcriptional efficiency, and consequently, reduced serotonin transporter (5-HT) expression and 5-HT reuptake, than the l-allele (Greenberg et al., 1999). The neural circuitry mediated by this polymorphism has been well laid-out and involves an amygdala-anterior cingulate-prefrontal cortical circuit that has been associated with sustained cognitive-emotional processing of emotionally relevant stimuli (Casp, Hariri, Holmes, Uher, & Moffitt, 2010; Hariri et al., 2005), or rumination (Antypa & Van der Does, 2010; Pezawas et al., 2005; Siegle, Steinhauser, Thase, Stenger, & Carter, 2002), as well as dispositional stress reactivity, or neuroticism (Hariri et al., 2005; Karg, Burmeister, Shedden, & Sen, 2011; Lesch et al., 1996). As noted above, many cross-sectional and prospective studies have shown that dispositional factors such as rumination and neuroticism significantly predict the generation of stress, particularly in the interpersonal domain (Brown & Rosellini, 2011; Flynn, Kecmanovic, & Alloy, 2010; Hamilton et al., 2014; Hankin et al., 2010; Kercher et al., 2009; Shapero, Hankin, & Barrocas, 2013 Uliaszek et al., 2012). Therefore, the 5-HTTLPR polymorphism is particularly relevant to testing hypotheses related to stress generation.

A role of the 5-HTTLPR polymorphism of the SLC6A4 in stress generation was recently found in a longitudinal study of 381 adolescents. In the context of elevated levels of depression symptoms at age 15, s-allele carriers had significantly higher levels of dependent and dependent-interpersonal stress at age 20 than those homozygous for the l-allele. In contrast, no moderation relation was found for independent stress (Starr, Hammen, Brennen, & Najman, 2012). This stress generation effect for s-allele carriers was further moderated in the same sample by perceptions of relational security, an intrapsychic construct reflecting cognitions about one’s place in interpersonal relationships (Starr, Hammen, Brennen, & Najman, 2013). The results from this sample are important and, along with Kendler’s early work, suggest that the tendency to generate stress may be an endophenotype that may subsequently raise individuals’ risk for depression and other psychopathologies.

The development of a phenotype results from the transactional relation of an individual’s genotype and their environment over development (Monaghan, 2008). As such, the role of the early environment in shaping responses to later stressors is crucial to more fully articulating and specifying biogenetic models of stress generation. Childhood maltreatment is one of the strongest early environmental risk factors for lifetime psychiatric illness, with significant odds ratios ranging from 2 to over 12 (MacMillan et al., 2001). Childhood emotional, physical, and sexual maltreatment, in particular, have been found to mediate the effects of other childhood adversities on depression onset (Bifulco, Brown, & Harris, 1987), and are associated with significantly more severe manifestations of depression in those who develop the disorder (Harkness & Monroe, 2002; Harkness, Bagby, & Kennedy, 2012; Nanni, Uher, & Danese, 2012).

An important pathological mechanism that may translate childhood maltreatment into psychopathology is stress generation. Indeed, there is now a consistent literature documenting that a history of childhood maltreatment heightens the generation of later dependent and dependent-interpersonal life events (Hankin, 2005; Hankness et al., 2008; Liu, Choi, Boland, Mastin, & Alloy, 2013; Uhrlass & Gibb, 2007). Furthermore, there is strong and consistent meta-analytic evidence that childhood maltreatment significantly moderates the relation of the 5-HTTLPR polymorphism of the SLC6A4 to depression (i.e., $p = .00007$ in Karg et al., 2011; Uher & McGuffin, 2010). However, the role of childhood maltreatment in moderating a genetic diathesis to the pathological mechanism of stress generation has yet to receive empirical investigation. We suggest that, even independent of current psychopathology, the risk s-allele of the serotonin transporter gene, in the context of childhood maltreatment, will be associated with dependent stressful life events.

A further promising area of inquiry that stands to substantially advance research on the childhood maltreatment moderation of genetic effects on stress generation is a specification of the environmental context at a fine-grained level. Broad general constructs such as “childhood adversity” or “stress” encapsulate widely varying environmental contexts that may have widely differing pathological consequences. Specifying the environments most relevant to interactions with genetic diatheses will enable the identification of individuals at greatest risk for the pathological effects of these interactions. Within the childhood maltreatment literature, emotional, physical, and sexual maltreatment are all associated with...
strong effect sizes in the prediction of later psychopathology onset in epidemiological studies (see Harkness & Lumley, 2007). However, the pathological processes that result from each of these experiences may differ. In particular, research on stress generation has uniformly reported that experiences of childhood emotional maltreatment or neglect, but not physical or sexual maltreatment, significantly predict the generation of proximal dependent and dependent-interpersonal life events (Hankin, 2005; Liu et al., 2013; Uhrlass & Gibb, 2007). In addition, while no evidence has been found for a relation of childhood sexual maltreatment to stress generation broadly, there is substantial evidence that a history of sexual maltreatment in childhood raises the risk for subsequent stressors in the interpersonal domain, including intimate partner physical and sexual violence (e.g., Rich, Gidycz, Warkentin, Loh, & Weiland, 2005). Despite these compelling findings, there is no evidence regarding the moderating role of specific types of maltreatment on the genetic association to proximal stress generation.

The goal of the current study was to examine the moderating role of childhood emotional, physical, and sexual maltreatment on the relation of the 5-HTTLPR polymorphism of the serotonin transporter gene to independent, dependent, and dependent-interpersonal life events reported in the past three months. We examined this question in a community sample of 297 adolescents and young adults whose maltreatment and life event histories were assessed with rigorous contextual life event interviews that provided standardized anchored ratings of stressor presence, severity, and independence. Because determinations of stress occurrence and severity are contextually defined in this study, we avoid conflation of reports of maltreatment and life events with the phenotype under study. This approach yields much greater reliability and validity than self-report checklist assessments of stress (see Monroe, 2008). For example, in the wider literature, studies of 5-HTTLPR by environment effects in depression have been very mixed and have suffered many failures to replicate (see Munafò, 5-HTTLPR by environment effects in depression have been very mixed and have suffered many failures to replicate (see Munafò, 2009; Risch et al., 2009). However, meta-analytic reports that have stratified these studies by method of stress assessment have demonstrated a dramatic advantage of studies using contextual-based and interview approaches to assessing stress ($p = .0014 - .000029$) versus studies using self-report checklists ($p = .093$) (Karg et al., 2011; see also Caspi et al., 2010; Monroe & Reid, 2008; Uhler & McGuffin, 2010).

We hypothesized that s-allele carriers would report a significantly higher threat level of proximal dependent and dependent-interpersonal stressful life events than I/I homozygotes, but only if they also reported a history of emotional maltreatment or sexual maltreatment, but not physical maltreatment. Consistent with the hypothesis that individuals with a genetic diathesis and maltreatment are generating stress, we did not predict that this relation would hold for independent events.

Method

Participants

Ethical approval for this study was obtained by the Research Ethics Boards at the Centre for Addiction and Mental Health, University of Toronto, and at Queen’s University. All participants provided written informed consent or assent, and a parent or guardian provided written consent for participants under age 18. The current study included 297 adolescents and young adults ranging in age from 12–31 (mean age = 19.72; 231 women) recruited from two cities as part of a larger study on gene-environment interaction. Ninety-nine participants were recruited from newspaper advertisements and clinician referrals in the Greater Toronto Area and were assessed at either the Centre for Addiction and Mental Health in Toronto ($n = 85$) or Sunnybrook Health Sciences Centre ($n = 14$). The remaining 198 participants were recruited from newspaper advertisements and clinician referrals in Kingston, Ontario and were assessed in the Psychology Department at Queen’s University. Participants from the two cities did not differ significantly in terms of sex, ethnicity, depression diagnosis, or 5-HTTLPR allelic distribution (all $p > .16$). Participants recruited in Toronto were significantly older than those in Kingston ($M_s = 22.11, 18.53; SD_s = 3.77, 2.81; t(295) = 9.21, p < .001$). Therefore, site was included as a covariate in all of the primary analyses.

The larger study from which the current participants were drawn was a case-control design. Inclusion criteria for the depressed group were Diagnostic and Statistical Manual for Mental Disorders (DSM–IV; American Psychiatric Association, 1994) criteria for a current episode of nonpsychotic, nonchronic (i.e., episode duration less than two years) major depressive disorder (MDD). Exclusion criteria were a current or past diagnosis of bipolar disorder, psychotic disorder, substance dependence, or a concurrent medical illness judged to be contributing to the depression. Participants in the nondepressed group could not have any current or lifetime psychiatric diagnosis and they were matched to the depressed group on sex, age, and ethnicity. All participants in the study had a minimum seventh grade education and fluency in reading English.

A total of 1,587 individuals across the two sites made an initial contact for the study. Of these, 547 could not be recontacted, or declined participation when contacted. A further 585 failed to meet criteria during an initial telephone screen, and a further 141 failed to meet inclusion criteria during an initial in-person diagnostic interview. A further 17 declined to take part in either the childhood maltreatment or life event interview, leaving a final sample for the current analyses of 297. The 17 with missing data did not differ from the remaining 297 on any demographic or clinical characteristic (all $p > .24$).

Measures

Diagnoses. Participants younger than 18 years were administered the child and adolescent version of the Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman, Birmaher, Brent, Rao, & Ryan, 1996), and those 18 years and over were administered the Structured Clinical Interview for DSM–IV Axis I Disorders (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002). The K-SADS and the SCID-IV are semistructured interviews used to determine present and past DSM–IV diagnoses. Interviews were administered by advanced graduate students in clinical psychology or licensed clinical psychologists who were trained to “gold standard” reliability status (Grove, Andreasen, McDonald-Scott, Keller, & Shapiro, 1981). Trainees participated in at least six interviews (three observing a trained interviewer, and three conducting the interview) and coded diagnoses independently of their
participants reported a history of maltreatment. For emotional maltreatment, variables were dichotomized into “presence” (1-marked, 2-moderate, or 3-some) or “absence” (4-little/none). Thirty-six percent (n = 108) of participants reported a history of maltreatment. For emotional maltreatment we examined mother’s and father’s ratings separately. For physical and sexual maltreatment numbers were not sufficient to permit examination of ratings separately by perpetrator. Percentages of participants who reported maternal emotional maltreatment, paternal emotional maltreatment, physical maltreatment, or sexual maltreatment were 26% (n = 76), 26% (n = 77), 15% (n = 45), and 11% (n = 33), respectively. These categories are not mutually exclusive and, as is typical, there was co-occurrence among the maltreatment types (e.g., McGee, Wolfe, Yuen, Wilson, & Carnochan, 1995; see Table 2).

Life Events and Difficulties Schedule (LEDS-II). The LEDS is a semistructured contextual interview and rating system that assesses recent life events in 10 domains: education, occupation, housing, finances, role changes, legal, health, romantic relationships, other relationships, and deaths (Bifulco et al., 1998; adolescent version; Frank, Matty, & Anderson, 1997). Note that the LEDS does not assess for the variables covered by the CECA. We examined events that occurred in the three months prior to the interview because this very proximal period is associated with accurate retrospective recall for even minor events (Brown & Harris, 1989).

Interviewers were advanced graduate students in clinical psychology who were trained to obtain contextual information regarding events and to not query about participants’ subjective reactions. Event vignettes were then presented to a team of 2–4 raters who used the LEDS manuals, which include rules and criteria for rating events and over 5,000 examples, to anchor and standardize the ratings. Life event severity was rated on a 4-point scale (1 = marked, 2 = moderate, 3 = some, 4 = little/none). Events were also rated as independent (e.g., father develops multiple sclerosis; laid off from job due to company bankruptcy) or dependent (e.g., boyfriend breaks up with respondent; respondent drops out of college). Furthermore, within the category of dependent events, events could be interpersonal (e.g., respondent and confidant have a fight and stop speaking) or noninterpersonal (e.g., respondent causes a car accident). Pairwise comparisons among raters for threat ranged from $\kappa = .74$ to $\kappa = .78$, and for independence and interpersonal were $\kappa = 1.00$. Consensus ratings were used in analyses.

We created total threat scores by reverse-coding the threat ratings and then summing them over the number of events in the 3-month period. This procedure for defining life events is preferable in the current context to life event frequency totals or average threat ratings because it incorporates both frequency and severity (Hammen, Henry, & Daley, 2000; Starr et al., 2012). Note, however, that our results below replicated using life event frequency totals and average threat ratings (results are available by request). Furthermore, because total event threat is a continuous variable it is preferable to examining the presence versus absence of a “severe” event, which in logistic regression models would result in very low cell sizes. We examined the following variables: (a) total independent threat ($M = 1.42, SD = 2.05$); (b) total dependent threat ($M = 2.11, SD = 2.44$); (c) total dependent-interpersonal threat ($M = .99, SD = 1.70$); and (d) total dependent-noninterpersonal threat ($M = 1.12, SD = 1.50$). The first three types of life events are the most germane to tests of stress generation, and are the events most consistently examined in the large stress generation literature (see Hammen, 2006). None of our models examining total dependent-noninterpersonal threat emerged as significant; therefore, for the sake of parsimony, re-
sults pertaining to these events are not presented below, but are available by request (see also Starr et al., 2012).

Childhood maltreatment is significantly associated with the generation of chronic difficulties (e.g., ongoing problems in relationships, at school, with health, etc.; Cicchetti & Toth, 2005); therefore, research must account for the possibility that a history of childhood maltreatment may be associated with higher rates of stressful life events not because of stress generation, but simply because these individuals have a high baseline level of chronic stress, which itself makes acute stressors more likely to occur. We examined chronic difficulties that were present in the three months prior to the interview, but could have begun any time before. They were rated for their level of threat on a 6-point scale (1-high marked; 2-low marked; 3-high moderate; 4-low moderate; 5-mild; 6-very mild). Similar to events, threat scores for chronic difficulties were reverse-coded and then summed over the total number of difficulties that were present in the 3 month time period (M = 3.45, SD = 4.35).

Procedure

After provision of written informed consent or assent, participants at both sites completed the SCID-I/P or K-SADS and the BDI-II during one assessment session. Then, to reduce participant burden, they participated in the LEDS and CECA interviews at a separate session no more than two weeks later. Participants in Toronto had three 10 cc EDTA tubes of blood drawn by a laboratory technologist at the first session. At the Kingston site, participants provided a saliva sample in Oragene OG-500 collection tubes (DNA Genotek, Ottawa, ON) at the first session. Extraction and genotyping of the DNA from all samples was performed at the Neurogenetics Laboratory at the Centre for Addiction and Mental Health in Toronto, Canada. DNA from blood samples (25 mL preserved in EDTA) was extracted manually using a high salt method (Lahiri & Nurnberger, 1991). DNA from saliva samples was extracted as per the manufacturer’s instructions. The 5-HTTLPR was assessed in a single assay using restriction fragment length polymorphism (RFLP) methods with polymerase chain reaction (PCR) primers originally described by Heils et al. (1996). Participants were classified according to their 5-HTTLPR genotype: l/l (n = 93); l/s (n = 132); s/s (n = 72). These frequencies did not differ from Hardy Weinberg equilibrium (x^2 = 3.38, p = .18). Consistent with the protocols of the majority of previous studies investigating the 5-HTTLPR, we compared l/l homozygotes (n = 93) to those with at least one s-allele (n = 204; see Hariri et al., 2005).

Data Analysis

Our analytic procedure involved a series of multiple linear regression models. In each model, dummy-coded study site (0-Toronto; 1-Kingston), dummy-coded depression status (0-non-depressed; 1-depressed), and total chronic difficulty threat were entered on Step 1. On step 2, we entered the dummy-coded genotype variable (0-l/l; 1- l/s or s/s) and the dummy-coded child maltreatment variable (0-absent; 1-present). The interaction of genotype and child maltreatment was entered on Step 3. Separate models were run to examine the relations of maternal emotional, paternal emotional, physical, and sexual maltreatment to indepen-

dent, dependent, and dependent-interpersonal event threat. Results of the models below including continuous BDI-II scores as a control variable instead of the dichotomous depression status variable are identical to those presented below.

Numerous papers have been published on the issue of false positive findings in candidate gene studies, with a key concern being replicability (e.g., Duncan & Keller, 2011). We instituted a number of measures to address this issue in the current study. First, we corrected for multiple tests using the false discovery rate (FDR; Benjamini & Hochberg, 1995) q-statistic. This statistic represents the minimum false discovery rate at which a test is considered significant, and is equal to a Bayesian derived quantity measuring the probability that a significant test is a true null hypothesis. We calculated the FDR q-statistic in the current study across all 12 observed p values reported below for the interactions of genotype and maltreatment (four types of maltreatment by three types of events). This yielded a q-statistic of .01. This is interpreted to mean that only 1% of all significant effects in this sample are true null hypotheses (i.e., false positives). Therefore, observed p values less than or equal to this value are considered significant (Storey, 2002).

Second, we performed bootstrapping on all of our primary analyses to determine a greater measure of accuracy to our estimates. We report bias statistics and bootstrapped confidence intervals for all of our primary significant tests below (DiCiccio & Efron, 1996).

Finally, and perhaps most importantly, we utilized the most valid and methodologically rigorous measures available to assess both childhood maltreatment and recent stressors. As noted above, the literature on gene by environment effects in depression has suffered from many failures to replicate (Munafo et al., 2009; Risch et al., 2009). In the life event literature, in general, spurious correlations, and corresponding false positive results, can emerge in studies that use self-report checklists to assess stress because responses on these measures are confounded with the individual’s depressive state (see Monroe, 2008; Monroe & Simons, 1991). Therefore, use of rigorously rated interview measures assures that we are, indeed, assessing the environmental context and not respondents’ biased perceptions of stress (see Caspi et al., 2010; Karg et al., 2011; Uher & McGuffin, 2010).

Results

Preliminary Demographic and Clinical Characteristics

Demographic and clinical characteristics of the sample stratified by 5-HTTLPR polymorphism are presented in Table 1. The s-allele carriers did not differ significantly from the l/l homozygotes in terms of sex, age, ethnicity, education level, BDI-II scores, depression status, or, among the depressed participants, number of previous episodes, age of first depression onset, or presence of a comorbid diagnosis (all ps > .09).

Females were significantly more likely than males to report a history of maternal emotional maltreatment, 29% versus 12%, x^2(1) = 8.08, p = .004, and sexual maltreatment, 13% versus 3%, x^2(1) = 5.60, p = .02. Furthermore, those who reported a history of physical maltreatment, Ms = 20.82, 19.53; SDs = 3.86, 3.50; n(295) = 2.25, p = .02, and sexual maltreatment, Ms = 21.18, 19.54; SDs = 4.38, 3.43; n(295) = 2.50, p = .01, were signifi-
cantly older than those who did not. In addition, those of non-White ethnicity were significantly more likely than those of White ethnicity to report a history of maternal emotional maltreatment, 35% versus 23%, $\chi^2(1) = 4.16, p = .04$, and paternal emotional maltreatment, 38% versus 22%, $\chi^2(1) = 6.63, p = .01$. As expected, participants with a depression diagnosis were significantly more likely than those without to report histories of maternal emotional, 39% versus 12%, $\chi^2(1) = 27.22, p < .001$, paternal emotional, 41% versus 10%, $\chi^2(1) = 34.29, p < .001$, physical, 24% versus 6%, $\chi^2(1) = 18.46, p < .001$, and sexual, 20% versus 2%, $\chi^2(1) = 24.24, p < .001$, maltreatment.

None of the life event variables were related to age or ethnicity. However, women reported significantly higher independent event threat than men, $M_s = 2.21, 1.77; SDs = 2.46, 2.34; t(193.41) = 4.50, p < .001$. Furthermore, consistent with the stress generation hypothesis, the depressed participants reported significantly higher dependent and dependent-interpersonal event threat in the past three months than those without. Those with a history of paternal emotional maltreatment and/or sexual maltreatment also reported higher independent event threat than those without. Furthermore, as expected, all types of maltreatment were significantly associated with more chronic stress.

In contrast, the 5-HTTLPR polymorphism was not significantly associated with any of the life event variables, including chronic stress. Furthermore, the 5-HTTLPR polymorphism was not significantly associated with a history of paternal emotional maltreatment, physical maltreatment, or sexual maltreatment. There was a small, but statistically significant, relation of genotype to a history of maternal emotional maltreatment.

### Gene by Child Maltreatment on Proximal Stressful Life Events

**Maternal emotional maltreatment.** Thirty-two (34%) of the l/l homozygotes reported a history of maternal emotional maltreatment, in comparison to 44 (22%) of the s-allele carriers. For the

---

### Table 1

Demographic and Study Characteristics of the Sample Stratified by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Sex: female n (%)</th>
<th>Age M (SD)</th>
<th>Years of education M (SD)</th>
<th>Ethnicity</th>
<th>BDI-II score M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>l/l</td>
<td>72 (77)</td>
<td>19.86 (3.72)</td>
<td>13.92 (2.68)</td>
<td>White</td>
<td>19.98 (16.04)</td>
</tr>
<tr>
<td>s/l or s/s (n = 204)</td>
<td>159 (78)</td>
<td>19.66 (3.52)</td>
<td>13.84 (2.69)</td>
<td>Asian-Canadian</td>
<td>16.70 (14.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>52 (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asian-Canadian</td>
<td>98 (48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>5.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asian-Canadian</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asian-Canadian</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asian-Canadian</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asian-Canadian</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black Canadian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Nations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other/Biracial</td>
<td></td>
</tr>
</tbody>
</table>

### Relations Among Primary Study Variables

The semipartial correlations among the primary study variables, controlling for site and depression status, are presented in Table 2. Consistent with the stress generation hypothesis, and previous research (Harkness et al., 2008), those with a history of maternal emotional, paternal emotional, and/or sexual maltreatment reported significantly higher dependent and dependent-interpersonal life event threat in the past three months than those without. Those with a history of maternal emotional maltreatment and/or sexual maltreatment also reported higher independent event threat than those without. Furthermore, as expected, all types of maltreatment were significantly associated with more chronic stress.

---

### Table 2

Semi-Partial Point-Biserial and Pearson Correlations Among Study Variables

<table>
<thead>
<tr>
<th>Variable 1</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>
</tr>
</thead>
<tbody>
<tr>
<td>HTTLPR l/l</td>
<td>-.12*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal emotion</td>
<td>-.08</td>
<td>.36***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical maltreatment</td>
<td>.001</td>
<td>.40***</td>
<td>.24***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual maltreatment</td>
<td>.03</td>
<td>.30***</td>
<td>.20***</td>
<td>.20***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent event threat</td>
<td>.01</td>
<td>.14*</td>
<td>.12*</td>
<td>-.002</td>
<td>.19***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent-interpersonal event threat</td>
<td>.05</td>
<td>.12*</td>
<td>.01</td>
<td>-.02</td>
<td>.23***</td>
<td>.79***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent event threat</td>
<td>.03</td>
<td>.06</td>
<td>.14*</td>
<td>-.02</td>
<td>.15**</td>
<td>.20***</td>
<td>.15**</td>
<td></td>
</tr>
<tr>
<td>Chronic difficulties</td>
<td>-.10</td>
<td>.33***</td>
<td>.25***</td>
<td>.20***</td>
<td>.31***</td>
<td>.27***</td>
<td>.23***</td>
<td>.22***</td>
</tr>
</tbody>
</table>

Note. Correlations are controlling for site and depression status.

*p < .05.  **p < .01.  ***p < .001.
model with dependent event threat, Step 1 including the relations of site, depression status, and chronic difficulties was significant, $R^2 = .09, F(3, 296) = 9.55, p < .001$, with only chronic difficulties emerging as a significant unique predictor, $\beta = .23, t(295) = 3.79, p < .001$. The second step of the model containing genotype and maternal emotional maltreatment did not add significant predictive power to the model, $\Delta R^2 = .009, \Delta F(2, 291) = 1.40, p = .25$. Step 3 indicated a genotype by maternal emotional maltreatment interaction that approached the significance level set by the FDR q-statistic, $\Delta R^2 = .02, \Delta F(1, 290) = 4.28, \beta = .21, t(295) = 2.21, p = .03$.

For the model including dependent-interpersonal threat, over and above the variance explained by site, depression status, and total chronic difficulties in the first step, $R^2 = .07, F(3, 293) = 7.83, \beta = .18, t(295) = 3.01, p = .003$, the independent effects of genotype and maternal emotional maltreatment entered on Step 2 were not significant, $\Delta R^2 = .01, \Delta F(2, 291) = 1.90, p = .15$. However, Step 3 indicated a significant genotype by maternal emotional maltreatment interaction, $\Delta R^2 = .02, \Delta F(1, 290) = 6.39, \beta = .24, t(295) = 2.53, p = .01$. As displayed in Figure 1, the s-allele carriers had higher levels of dependent-interpersonal events in the past three months than the l/l homozygotes, but only among those with a history of maternal emotional maltreatment, $R^2 = .03, \beta = .22, t(290) = 2.85, CI_{90} = .10, 2.06, p = .005$. This comparison was not significant among those with no history of maltreatment, $R^2 < .001, \beta = -.02, t(290) = -.24, p = .81$. Bootstrapping the significant comparison over 1,000 samples revealed a bias statistic that approached zero (.005), and a bootstrapped confidence interval for the mean difference nearly identical to the observed (CI$_{90} = -.08, 2.36, p = .01$).

In contrast, in the model for total independent threat, over and above the variance explained by site, depression status, and total chronic difficulties, the first step, $R^2 = .06, F(3, 293) = 6.62, \beta = .22, t(295) = 3.62, p < .001$, there was no evidence for significant improvements to the model by adding genotype or maltreatment, $\Delta R^2 = .002, \Delta F(2, 291) = .34, p = .71$, and only trend improvement for the interaction, $\Delta R^2 = .01, \Delta F(2, 290) = 3.26, p = .07$.

**Paternal emotional maltreatment.** Thirty (32%) of the l/l homozygotes and 47 (23%) of the s-allele carriers reported a history of paternal emotional maltreatment. As above, the first step of each model containing site, depression status, and total difficulties was significant, indicating a significant relation of total difficulties to dependent, dependent-interpersonal, and independent events. However, neither Step 2 nor Step 3 of the models for dependent, dependent-interpersonal, or independent event threat added significant predictive power ($\Delta R^2 = .001 - .01, ps = .10 - .74$).

**Physical maltreatment.** Fifteen (16%) of the l/l homozygotes and 30 (15%) of the s-allele carriers reported a history of physical maltreatment. As above, the first step of each model containing site, depression status, and total difficulties was significant, indicating again a significant relation of total difficulties to dependent, dependent-interpersonal, and independent events. However, neither Step 2 nor Step 3 of the models for dependent, dependent-interpersonal, or independent event threat added significant predictive power ($\Delta R^2 = .001 - .01, ps = .08 - .70$).

**Sexual maltreatment.** Ten (11%) of the l/l homozygotes and 23 (11%) of the s-allele carriers reported a history of sexual maltreatment. For the model with dependent event threat, over and above the Step 1 effects of site, depression status, and chronic difficulties, Step 2 was significant, such that those with a history of sexual maltreatment had significantly higher dependent event threat scores than those without, $\beta = .15, t(295) = 2.57, p = .01$. Furthermore, Step 3 indicated a significant genotype by sexual maltreatment interaction, $\Delta R^2 = .03, \Delta F(1, 290) = 7.55, \beta = .30, t(295) = 2.89, p = .004$. As displayed in Figure 2a, the s-allele carriers had higher levels of dependent events in the past three months than the l/l homozygotes, but only among those with a history of sexual maltreatment, $R^2 = .03, \beta = .25, t(290) = 2.87, CI_{90} = .11, 4.65, p = .004$. This comparison was not significant among those with no history of maltreatment, $R^2 < .001, \beta = -.04, t(290) = .56, p = .58$. Bootstrapping the significant comparison over 1000 samples revealed a bias statistic of .03, and a bootstrapped confidence interval for the mean difference nearly identical to the observed (CI$_{90} = -.34, 5.46; p = .03$).

For the model with dependent-interpersonal event threat, over and above the variance explained by total chronic difficulties in the first step, sexual maltreatment entered on Step 2 added significant predictive power, $\Delta R^2 = .04, \Delta F(2, 291) = 6.87, \beta = .21, t(295) = 3.51, p = .001$. Furthermore, Step 3 indicated a significant genotype by sexual maltreatment interaction, $\Delta R^2 = .03, \Delta F(1, 290) = 10.26, \beta = .33, t(295) = 3.20, p = .002$. As displayed in Figure 2b, the s-allele carriers had higher levels of dependent-interpersonal events in the past three months than the l/l homozygotes, but only among those with a history of sexual maltreatment, $R^2 = .04, \beta = .25, t(290) = 3.37, CI_{90} = .44, 3.59, p = .001$. This comparison was not significant among those with no history of maltreatment, $R^2 < .001, \beta = -.004, t(290) = .05, p = .88$. Bootstrapping the significant comparison over 1,000 samples revealed a bias statistic that approached zero (.003), and a bootstrapped confidence interval for the mean difference nearly identical to the observed (CI$_{90} = -.03, 4.26; p = .02$).

**Figure 1.** Serotonin transporter gene polymorphism by maternal emotional maltreatment on exposure to dependent-interpersonal event threat ($n = 297$).

---

This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.
Maltreatment may be more primary in setting the stage for pathological outcomes. Further, these two types of maltreatment co-occurred, with 23 participants reporting both types of maltreatment (70% of those with sexual maltreatment also reported maternal emotional maltreatment; 30% of those with maternal emotional maltreatment also reported sexual maltreatment). Furthermore, maternal emotional maltreatment and sexual maltreatment were highly related in both l/l homozygotes, \( r = .33, p = .001 \) and s-allele carriers, \( r = .38, p < .001 \). These issues, taken together, raise the question of whether or not these two forms of maltreatment have independent effects on stress generation.

We explored the above issue in a preliminary manner by running our model for dependent-interpersonal event threat including both maternal emotional maltreatment and sexual maltreatment, and their interactions with genotype. These results should be interpreted with caution given the strong correlation between sexual and maternal emotional maltreatment (tolerance > .85). Results for overall dependent event threat followed the same pattern and are available by request. The interaction step of this model was associated with a significant improvement in prediction, \( \Delta R^2 = .03, \Delta F(2, 288) = 5.61, p = .004 \). The interaction of genotype and sexual maltreatment was significant, \( \beta = .26, t(295) = 2.47, p = .01 \), whereas the interaction of genotype and maternal emotional maltreatment was not, \( \beta = .12, t(295) = 1.27, p = .20 \). Nevertheless, for both maternal emotional maltreatment and sexual maltreatment, the pattern of results was identical to that displayed in Figures 1 and 2; among the s-allele carriers, those with a history of maternal emotional (\( p = .001 \)) or sexual maltreatment (\( p = .002 \)) reported significantly higher levels of dependent-interpersonal events than those without, even after controlling for the influence of the other form of maltreatment and its interaction with genotype.

**Discussion**

The current study is the first to demonstrate that a history of maternal emotional and sexual maltreatment moderates the relation of the 5-HTTLPR polymorphism of the SCL6A4 gene to proximal stressful life events. Consistent with the stress generation hypothesis, this relation was specific to events that were, at least in part, dependent on the individual’s own behavior, particularly in the interpersonal domain. No evidence was found for a significant relation of genotype, maltreatment, or their interaction to independent or dependent-noninterpersonal events. These results met powerful correction for multiple testing (Benjamini & Hochberg, 1995), and were robust to bootstrapping. Therefore, our findings suggest that a genetic vulnerability for altered serotonergic neurotransmission is associated with proximal stress generation, but only among those who also have an early history of maternal emotional and/or sexual maltreatment.

While the precise mechanism underlying the relation of genes and the early environment to proximal stress was not the focus of the current study, several possible and complementary mechanisms may be in operation. For example, the 5-HTTLPR polymorphism of the SCL6A4 gene has been theorized to mediate a serotonergic amygdala-ACC-cortical circuit that promotes sustained cognitive-emotional processing, or rumination (e.g., Pezawas et al., 2005; Siegle et al., 2002). Rumination is related to the generation of dependent-interpersonal (but not noninterpersonal or independent) stress in several prospective studies (Flynn et al.,...
2010; Hamilton et al., 2014; Hankin et al., 2010; Shapero et al., 2013). Furthermore, rumination is a significant cognitive consequence of maltreatment, particularly emotional and sexual maltreatment (Conway, Mendelson, Giannopoulos, Csanak, & Holm, 2004; Spasojevic & Alloy, 2002), and significantly mediates the relation of maltreatment to depression over other cognitive variables (Raes & Hermans, 2008). Of specific relevance to the current results, Antypa and Van der Does (2010) reported that young adults with a history of emotional maltreatment reported higher rates of rumination than those without, but only among s-allele carriers of the 5-HTTLPR. This interaction was specific to rumination and was not seen for other depressotypic variables. Rumination may mediate the relation of early risk to interpersonal stress generation through several mechanisms; for example, by promoting maladaptive interpersonal behavior and, thus, compromising interpersonal functioning and/or by eroding social support networks (Flynn et al., 2010; Lyubomirsky & Nolen-Hoeksema, 1995). Therefore, an important direction for future research is to determine whether this serotonin-driven neurocognitive process mediates the generation of proximal stress in those with a history of maltreatment and the 5-HTTLPR diathesis.

It is also possible that s-allele carriers of the SCL6A4 gene may be more likely to have been raised in a negative and/or depressogenic family context than l/l homozygotes, which could then independently heighten their risk of both emotional or sexual maltreatment and dependent life events (Hammen, Brennan, & Le Brocque, 2011). Perhaps, for example, the association of genotype and maltreatment to stress generation can be explained by disrupted patterns of attachment (e.g., Cicchetti, Rogosch, & Toth, 2011). However, although not widely studied to date, there is no evidence to suggest that s-allele carriers are more likely to have a parental history of depression than l/l homozygotes (see Gibb, Uhrllass, Grassia, Benas, & McGearry, 2009), and evidence regarding the relation of this polymorphism to later attachment insecurity in adolescence or adulthood is mixed (Caspers et al., 2009; Reiner & Spangler, 2010). Therefore, an important area of future research concerns the extent to which intergenerational transmission of risk for adverse environments can further moderate the effect of genes on stress generation. Regardless of the precise mechanism, the current results provide a novel advance to models of stress generation by suggesting that a genetic diathesis may only be related to heightened generation of future stress in the context of adverse early experience.

A further novel contribution of the current study is the finding that the moderating effect of maltreatment on the relation of 5-HTTLPR variants and dependent and dependent-interpersonal stress was specific to maternal emotional maltreatment and sexual maltreatment. First, maternal emotional maltreatment and sexual maltreatment co-occurred to a significant extent. Maltreatment co-occurrence is very common and makes it difficult to examine the relative contributions of different types of maltreatment outside of very large epidemiological samples. Nevertheless, we provided tentative evidence in secondary analyses that sexual maltreatment may have a somewhat more powerful role than maternal emotional maltreatment in this model.

Prospective studies have also reported a significant relation between emotional maltreatment and later sexual maltreatment (e.g., Rich et al., 2005). Therefore, these two types of maltreatment may work together to heighten risk for pathological outcomes. In our sample, in those with both forms of maltreatment, the age of onset of maternal emotional maltreatment significantly preceded that for sexual maltreatment, suggesting that emotional maltreatment in the home may set the stage for later sexual maltreatment. Maternal emotional maltreatment could be related to risk for sexual victimization through a number of mechanisms, including the contribution of emotional maltreatment to the development of negative self-schemas (Lumley & Harkness, 2009) and maladaptive interpersonal behaviors (e.g., Rich et al., 2005) that may lead individuals into risky relationships. Interestingly, in the current sample, we found that maternal emotional maltreatment and sexual maltreatment were highly related in both l/l homozygotes and s-allele carriers. This suggests that a genetic diathesis involving the 5-HTTLPR is not responsible for their co-occurrence, although it does not rule out the contribution of other genetic mechanisms in driving this relation.

Previous studies of the relation of child maltreatment to stress generation have also found a strong and preferential role for emotional maltreatment. However, in the current study, the relation of emotional maltreatment to dependent and dependent-interpersonal stress only emerged in interaction with the genetic diathesis. In contrast, sexual maltreatment was significantly associated with dependent and dependent-interpersonal stress independent of genotype, and this effect was robust even when controlling for chronic stress and depression status. This emphasizes the strong deleterious effect that sexual victimization can have on interpersonal functioning, and the damage that it can exert on individuals’ interpersonal relationships (DiLillo, 2001).

To our knowledge, the current study is the first to report that the relation of emotional maltreatment to proximal stress generation is specific to maternal emotional maltreatment. The reasons why maternal, and not paternal, emotional maltreatment was associated with stress generation in those with a genetic diathesis are unclear and require further study. The frequency of the overall presence of maternal versus paternal maltreatment (both 26%), and the presence of marked levels of maternal versus paternal maltreatment (10% vs. 11%), did not significantly differ, and thus differences in early maltreatment load cannot account for the discrepancy in findings. The primacy of maternal versus paternal emotional maltreatment may be due to the primary role of mothers as attachment figures and sources of emotional support throughout childhood and adolescence (e.g., Rosenthal & Kobak, 2010). Indeed, in a recent longitudinal study, maternal physical and emotional maltreatment was more strongly predictive of depression symptoms and affect dysregulation than was paternal maltreatment, and, furthermore, paternal maltreatment was only predictive of outcomes in boys (Moretti & Craig, 2013). In the current study, participant sex did not emerge as a significant covariate. However, our sample included a very low number of males with maltreatment and, thus, our study had low power to detect any effects stratified by sex. Examining sex differences remains a very important area of inquiry that could help to further understand stress generation mechanisms. The current results do suggest, however, that a chronic history of emotional and sexual victimization, in the context of a genetic diathesis that enhances reactivity to threat, may be particularly damaging to individuals’ interpersonal relationships as it is associated with the generation of stress preferentially in this domain.
It is important to note that given the large age range of the current sample, some of the participants' experiences of maltreatment may have been contemporaneous in time with the interpersonal stressors covered by the LEDS, whereas for others the maltreatment may have occurred some years earlier. We confirmed that age did not act as a significant covariate in any of our models. Nevertheless, it is possible that the psychobiological mechanisms that mediate stress generation in those at genetic and early environmental risk may differ based on developmental stage. For example, developmental processes that may be influenced by serotonin, such as cortico-limbic neurodevelopment (e.g., Lesch & Waider, 2012), schema consolidation (Beck, 2008), and emotion regulation (Canli & Lesch, 2007), continue to solidify into early adulthood. We did not have the statistical power to examine age as a further moderator of the effects presented here. Therefore, examination of the ontogenetic processes underlying the role of child maltreatment in stress generation remains an important area for future research (Bergen, Gardner, & Kendler, 2007).

The current results should be interpreted in light of the following limitations. First, the sample size was small for genetic work, and we acknowledge that small cell sizes are the primary limitation of the current study. We sought to address this issue by performing a powerful correction for multiple comparisons and by performing bootstrapping analyses on all of our primary comparisons. In our data, the experiment-wide false discovery rate was .01. Furthermore, results of the bootstrapping analyses revealed that our sampling estimates contained very little bias and, as such, are likely to be replicated. As Caspi and colleagues (2010) note in their exhaustive review of the literature on the 5-HTTLPR by environment interaction in depression, “...large sample size tends to coincide with poor measurement quality [of stressful life events]” (p. 515). Our goal was to use the most rigorous methods available to provide a targeted analysis of a circumscribed and impactful question, and to provide a fine-grained analysis of the limits of gene by early environment effects in terms of the types of stressors that most strongly drive these relations. Such fine-grained questions are not possible to address using broad checklist assessments of stress. Therefore, we believe that the power benefit in employing strong contextual life event measurement was likely what helped to offset the power cost of the small sample relative to other genetic studies. Caspi and colleagues (2010) also note that small-scale studies of gene by environment effects are possible when these studies are hypothesis-driven and use strong measurement of both phenotype and the environment. Our analyses were strongly hypothesis-driven, and results were consistent with the large empirical literature on stress generation. Nevertheless, future studies with larger samples will permit the examination of further moderators of the above effects, such as sex, age, and depression status. Furthermore, the current study comprised a large proportion of individuals with depression. Therefore, future population-based samples are required to confirm the generalizability of the current findings.

Second, only one genetic polymorphism was examined in the current study. There is evidence for epistasis between the serotonin transporter gene and genes in other complementary neural systems, including brain-derived neurotrophic factor (Grabe et al., 2012). Very large sample sizes are required to detect such gene by gene by environment effects, and such questions went beyond the goals of the current study. Therefore, future studies building on the current results are necessary to further articulate the interacting neural systems involved in stress generation. Furthermore, due to power concerns we did not have a sufficient sample size to permit replication of the current findings using the triallelic assay of the serotonin transporter gene (Praschak-Rieder et al., 2007; Zalsman et al., 2006) and, thus, this remains an important question for future research. We focused on conducting an in-depth analysis of the specific types of early stress that moderate the relation of serotoninergic gene polymorphism to specific types of proximal stressors. This fine-grained specification of the environment is important and is often ignored in studies of biomarkers (see Monroe & Reid, 2008). Broad general constructs such as “childhood adversity” or “stress” encapsulate widely varying environmental contexts that may have markedly different pathological consequences. Specifying the environments most relevant to interactions with biomarkers will enable the identification of individuals at greatest risk for the pathological effects of these interactions.

Third, this study relied on retrospective self-reports of childhood maltreatment and stressful life events, raising the issue of recall bias. To address bias, the CEEA and LEDS interviews probe for both positive and negative contextual detail. In addition, interviewers are trained to not query about participants’ emotional reaction to stressors or the relation of stressors to depression. Threat ratings are based on manualized examples that raters use to justify their decisions, helping to ensure standardization. There is extensive documentation that the LEDS and CEEA have superior validity and reliability over self-report questionnaire assessments of environmental experiences, particularly in genetic research (Brown, Craig, Harris, Handley, & Harvey, 2007; Karg et al., 2011; Monroe & Reid, 2008). Furthermore, longitudinal research has found that reports of past maltreatment are largely accurate and stable across time when intensive interviews and investigator-based ratings are used (e.g., Dube, Williamson, Thompson, Felitti, & Anda, 2004).

The results of the current study suggest that the impact of the 5-HTTLPR polymorphism of the serotonin transporter gene on dependent and dependent-interpersonal stress generation is moderated by the early environment, such that this relation is only seen in s-allele carriers with a history of maternal emotional maltreatment or sexual maltreatment. These results have important implications for understanding why some children are resilient to the severe effects of maltreatment, whereas others develop pathological sequelae. They also underscore the importance of fine-grained analyses of maltreatment type to more directly pinpoint the early contexts from which such pathological sequelae emerge. As such, the current results have potentially important translational implications. Biomarkers of depression vulnerability, such as particular genetic polymorphisms, are fixed. However, the phenotypic vulnerabilities that emerge from the transactional relation between genes and the early environment may be more amenable to change. In particular, behavioral strategies that focus on how maladaptive patterns of interpersonal interaction that developed through negative parenting may be impacting on current relationship functioning have the potential to prevent the generation of the sorts of stressful life events that trigger onsets and recurrences of major depression in young people (Monroe, Rohde, Seeley, & Lewinsohn, 1999). As such, these strategies may help to prevent the onset of a potentially lifelong pattern of illness.
References


This document is copyrighted by the American Psychological Association or one of its allied publishers. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.


Received July 14, 2014
Revision received November 25, 2014
Accepted November 26, 2014