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Serotonin Transporter Gene as a Predictor of Stress Generation in Depression

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Research suggests that a polymorphism in the promoter region of the serotonin transporter promoter (5-HTTLPR) interacts with stressful life events to predict depressive onset, with short (*s*) allele presence associated with greater susceptibility to stressors. However, this research has not considered that depressed individuals often actively generate stressful contexts. Furthermore, little is known about the genetic basis of stress generation. The current study explored the role of 5-HTTLPR genotype in stress generation in a longitudinal sample of 381 adolescents, oversampled for maternal depression, assessed at ages 15 and 20. Genotype did not correlate directly with number or ratings of stressful life events. However, 5-HTTLPR genotype interacted with depression at age 15 to predict dependent stressful events at age 20. Specifically, participants with one or more *s* alleles showed a stronger association between age 15 depression and age 20 dependent and interpersonal events than long allele homozygotes. Results imply that the 5-HTTLPR genotype predicts reciprocal associations between stress and depression, indicating a more complex relationship between stress, depression, and their genetic underpinnings than previously suggested.

Keywords: serotonin transporter gene, 5-HTTLPR, stress generation, depression, adolescents

Stress has been studied within the context of depression for decades, and has long been accepted as a critical etiological factor (e.g., Brown & Harris, 1978). More recently, research has identified genetic factors (most notably, the serotonin transporter gene) that increase susceptibility to depressive reactions to stress (Karg, Burmeister, Shedden, & Sen, 2011); however, this research has generally not considered findings showing that depressed individuals have an elevated tendency to generate stress within their environments (Hammen, 1991). Furthermore, although research has strongly established that depression predicts later generation of stress (see Hammen, 1991, 2006; Liu & Alloy, 2010), little is known about the genetic underpinnings of this process. The current study addresses these gaps in the literature by examining the potential role of the serotonin transporter gene in stress generation.

Stress Generation

In much of the literature on stress and depression, stress is construed as a fundamentally independent variable, with various reactions to stressful events (such as depression) as primary outcomes. Prior research has often implied that individuals are passive players in their own lives, neglecting to explore the ways in which individuals play an active role in contributing to the stressors they experience. Based on the observation that depressed individuals tend to experience disproportionate amounts of stressful life events, Hammen (1991) formulated the *stress generation* model, showing that individuals with unipolar depression have an elevated tendency to promote stressors in their environments (even outside of current depressive episodes). Numerous studies have supported the stress generation model in clinical and community samples (for reviews see Hammen, 2006; Liu & Alloy, 2010). The existence of stress generation implies a far more complex and dynamic association between stress and depression than is often presented in the literature, and suggests that examining stress exclusively as an independent variable and depression as a dependent variable can obscure important associations and clinical implications via the reverse direction of causality.

Little is known about potential genetic correlates of stress generation. However, twin and family studies suggest significant heritability in the occurrence of stressful events (estimated around

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20%; Kendler, Neale, Kessler, Heath, & Eaves, 1993) and in the elevated exposure to stressful life events among depressed individuals (Kendler, Karkowski, & Prescott, 1999; Kendler et al., 1993; McGuffin, Katz, & Bebbington, 1988). For example, Kendler et al. (1999) showed that about one third of the association between stressful life events and depression could be accounted for by shared genetic components that increase risk of both depression and dependent events. Furthermore, genetic liability for major depression predicts elevated occurrence of stressful life events (Kendler & Karkowski-Shulman, 1997). Importantly, genetic influence on stressful events appears to be mediated by personality characteristics (Saudino, Pedersen, Lichtenstein, McClearn, & Plomin, 1997), suggesting that genetically influenced personality characteristics increase the likelihood of selection into stressful circumstances. Several personality and cognitive factors have been shown to predict stress generation, including neuroticism, negative cognitive styles, and Axis II pathology (Daley, Hammen, Burge, & Davila, 1997; Poulton & Andrews, 1992; Safford, Alloy, Abramson, & Crossfield, 2007). In turn, each of these variables appears to have a heritable component, with heritability estimates ranging from about 30% to 60% (Jang, Livesley, Vernon, & Jackson, 1996; Lahey, 2009; Lau & Eley, 2008; Sen, Burmeister, & Ghosh, 2004). Given that numerous predictors of stress generation are genetically influenced, it would logically follow that stress generation itself is genetically mediated. Overall, however, research on genetic factors in stress generation is extremely limited, and in particular, there have been no candidate gene studies exploring specific genotypes associated with increased risk of stress generation.

Serotonin-Transporter-Linked Polymorphic Region and Depression

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) is widely believed to play an integral role in emotion and mood regulation (see Neumeister, Young, & Stastny, 2004). Based on this evidence, substantial research has explored genes associated with 5-HT as potential genetic markers of depression risk. Specifically, much work has focused on the allelic variants of the serotonin-transporter-linked polymorphic region (5-HTTLPR), the polymorphic promoter region of the serotonin-transporter gene (5-HTT), which facilitates synaptic reuptake of serotonin (Lesch et al., 1996). The 5-HTTLPR region includes two major allelic variations: long (*l*) and short (*s*) forms. Compared to the long form, the short form is associated with less efficient 5-HTT transcription and in turn 5-HT reuptake. Caspi et al. (2003) proposed that the 5-HTTLPR polymorphism represents a diathesis that interacts with environmental factors to predict depression (a gene-environment interaction [GxE]), and found that the presence of one or more *s* alleles interacted with stressful life events to predict increased odds of depressive onset, implying that this genotype reflects sensitivity to environmental stressors. Since Caspi et al.'s seminal findings, numerous studies have attempted to replicate this GxE model. Different meta-analyses have yielded different results, but the most recent and comprehensive reviews (e.g., Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Karg et al., 2011) have supported the interaction between 5-HTTLPR polymorphisms and stressful life events in the prediction of depression, with particularly supportive results from studies using high quality stress measures (e.g., interviews rather than checklists).

Given its role in the association between stressful life events and depression, 5-HTTLPR is a logical starting point for exploring candidate genes implicated in stress generation. If the link between stress and depression is bidirectional, and if 5-HTTLPR moderates the link between stress and later depression, it is reasonable to question whether it also moderates the link between depression and later stress. There are several reasons to believe that 5-HTTLPR may play a role in stress generation. The 5-HTTLPR genotype is presumed to predict emotional reactions to environmental stressors, and Way and Taylor (2010) have also emphasized that the 5-HTTLPR short alleles particularly modify sensitivity to social situations. Heightened reactivity to negative social experiences may promote negative interpersonal interactions that can culminate in stressful life events. Presence of a short allele may indicate personality or emotion regulation characteristics that put individuals at risk for generating stress. For example, the 5-HTTLPR *s* allele has been associated with neuroticism (albeit inconsistently; Du, Bakish, & Hrdina, 2000; Lesch et al., 1996; Schinka, Busch, & Robichaux-Keene, 2004; Sen et al., 2004; Willis-Owen et al., 2005), and neuroticism may increase likelihood of stress generation (Davila, Karney, Hall, & Bradbury, 2003; Gunthert, Cohen, & Armeli, 1999). More broadly, the *s* genotype may represent a general environmental sensitivity (Caspi et al., 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005), which may exacerbate reactions to mild negative events or ongoing strains, magnifying them into acute life events. Thus, perhaps the same genetic factors affect both depression and stress occurrence. Kendler (2011) noted this possibility, and suggested that if shared genetic liability increases risk of both stress occurrence and depression, the rGE may produce a statistical confound that may be falsely construed as a GxE.

There are two principal ways in which 5-HTTLPR could be associated with stress generation. First, the *s* allele may directly place individuals at greater risk for stressful life experiences, possibly due to passive (genetically associated parental traits affecting maladaptive parenting that results in social difficulties) or evocative (genetically associated youth traits that elicit negative reactions from others) gene-environment correlations (rGE). Although research has not directly focused on this hypothesis, studies that have examined stress $\times$ 5-HTTLPR interactions in predicting depression often report associations between stress and genotype, and generally these studies have not supported a main effect of genotype on stress (e.g., Kendler et al., 2005; Kilpatrick et al., 2007; also see Aguilera et al., 2009), although existing studies have not distinguished between dependent versus fateful events.

Second, 5-HTTLPR genetic vulnerability may interact with depressive symptoms to predict generation of stressful events. This idea differs from the above model (although the two are not necessarily mutually exclusive), in that instead of suggesting that 5-HTTLPR directly puts people at risk for generating stress, it proposes that the vulnerabilities introduced by the *s* allele presence will activate or amplify the stress-generating characteristics associated with depression, which may in turn put people at greater risk for increased depression. For example, Way and Taylor (2010) proposed that the *s* variant increases psychological sensitivity to the social environment. Elevated sensitivity to negative social circumstances may instigate depression-related interpersonal processes (e.g., attachment disruptions, reassurance seeking) that may in turn generate stress (Eberhart & Hammen, 2009, 2010; Potthoff,

Holahan, & Joiner, 1995). Importantly, this hypothesis essentially expands and inverts existing 5-HTTLPR models, which have shown that the *s* alleles moderate the association between stressful life events and later depression, suggesting that the association between prior depression and stress generation is moderated by the *s* alleles. In fact, Caspi, Hariri, Holmes, Uher, and Moffit (2010) noted the failure to account for depression's effects on stress occurrence as an important shortcoming of existing research on 5-HTTLPR.

The stress generation literature has illuminated the importance of careful assessment of qualitative aspects of stressful events. In particular, events differ in the extent to which they are independent (i.e., fateful or caused mainly by external forces) or dependent (i.e., caused at least in part by the person's actions or characteristics; Hammen, 1991, 2006). Depression appears to particularly predict dependent events (those due at least in part to the person), but not necessarily independent events (Hammen, 1991; Hammen, Mayol, deMayo, & Marks, 1986; see also Harkness & Stewart, 2009). Furthermore, interpersonal events, a subset of the general category of dependent events, are especially likely to be elevated among people with prior depression (e.g., Davila, Bradbury, Cohan, & Tochluk, 1997; Hammen, 2005; Potthoff et al., 1995), fitting with general models highlighting the importance of interpersonal factors in the development and maintenance of depression (e.g., Joiner & Timmons, 2009). Failing to distinguish between these variants of stressful life events may conceal associations between stress and depression. Notably, the 5-HTTLPR literature, perhaps as a result of its focus on the consequences rather than the precipitants of stress, has not specifically distinguished between independent and dependent events. In the current study, in line with the stress generation literature, we separately examined generation of independent, dependent, and interpersonal events, as each may have differing genetic contributions.

The Current Study

The current study tests these questions in a longitudinal study of a sample followed from birth to early adulthood (with major study data collected at ages 15 and 20), who are at elevated risk for depression because of oversampling for maternal depression. The following specific hypotheses are tested: First, participants with at least one *s* 5-HTTLPR allele are predicted to show elevated rates of dependent stress across time points (including episodic stress at ages 15 and 20). Second, the presence of at least one 5-HTTLPR *s* allele is hypothesized to interact with depressive symptoms at age 15 to predict dependent (but not independent) stress at age 20. Based on studies suggesting that both stress generation (Davila et al., 1997; Rudolph & Hammen, 1999) and 5-HTTLPR (Du et al., 2000; Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010) may have stronger effects for women than men, gender effects were explored.

Method

Participants

Participants were 381 youth who were a subset of a larger sample ($n = 815$) that was recruited from the Mater University Study of Pregnancy, a study following the development of a cohort of children born between 1981 and 1984 at Mater Misericordiae Mother's Hospital in Brisbane, Australia (original N = 7,775; Keeping et al., 1989). A subset of the original sample (including mothers and offspring) was recruited for participation in a follow-up 15 years after birth ($n = 815$), oversampling for maternal depression to ensure elevated vulnerability to depressive symptoms within the sample. Selection was based on maternal self-reported depression assessed during pregnancy, post-partum, and at six months and five years after birth using the Delusions-Symptoms-States Inventory (Bedford & Foulds, 1978). Maternal depression diagnoses were confirmed at the age 15 follow-up using the Structured Clinical Interview for the *DSM–IV* (Spitzer, Williams, Gibbon, & First, 1995). For greater detail on recruitment procedures and sample characteristics, see Hammen and Brennan (2001).

Families were recontacted and invited to participate in an additional follow-up at age 20, and 705 participated (see Keenan-Miller, Hammen, & Brennan, 2007, for details). Participants were further recontacted between ages 22 and 25 and invited to provide a DNA sample for genetic analysis. Of these, 512 participants provided a DNA sample. The nonparticipating remainder of the sample could not be contacted, no longer lived in the geographical area, withdrew from the study, had significant medical problems, or were deceased. Compared to the 193 additional participants who were included at the age 20 follow-up, the 512 participants who provided DNA did not differ on depression history or maternal depressive status, but were more likely to be female ($\chi^2 = 21.29$, $p < .001$).

Because of budgetary and procedural constraints, genotyping was restricted to a single full plating of 384 samples; 384 participants were selected randomly for genotyping from the pool of participants who provided blood-based DNA samples. Three samples produced invalid readings, leading to a final sample of 381 participants. Although selection for genotyping was random, by chance more female participants were selected than males ($\chi^2 = 16.49$, $p < .001$); otherwise, the genotyped and nongenotyped participants did not differ by their own depression status at previous follow-ups or by maternal depression status.

The final sample included 149 males and 232 females. Of those reporting race, the sample was 95% Caucasian (minority groups represented included Asian, Maori/ Pacific Islander, and Aboriginal) and predominantly reported middle or lower income. Race (Caucasian vs. other) was not associated with dichotomous genotype, $\chi^2 = 0.95$, *ns*. Of the genotyped sample, 43% of mothers met criteria for depression between the participant's birth and age 15 follow-up (see Hammen & Brennan, 2001 for greater detail on maternal depression rates).

Procedure

Youth, mothers, and available fathers were separately interviewed in their homes after the children turned 15 years old. Youth interviewers were blind to maternal depression status, and separate interviewers assessed mothers and children. Participants also completed a battery of questionnaires. Similar procedures were followed when youth turned 20. At each follow-up, participants provided informed consent (or assent, as appropriate). Two to five years after the age 20 follow-up (mean interval = 3.32 years, $SD = 1.02$) participants provided DNA samples for genetic anal-

ysis and completed questionnaires. Participants were mailed blood collection kits and consent forms, and had blood samples drawn at local facilities, which were later retrieved by courier. Genotyping procedures were conducted at the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research, as described below. The Institutional Review Boards of the University of Queensland, UCLA, and Emory University approved this research.

Measures

Youth depressive symptoms. The Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996) is a widely used measure of depressive symptoms. Studies have extensively documented the BDI's excellent psychometric properties, including reliability and validity, as well as strong sensitivity and specificity for detecting depression in community samples (Beck, Steer, & Garbin, 1988; Lasa, Ayuso-Mateos, Vazquez-Barquero, Diez-Manrique, & Dowrick, 2000). Here, Cronbach's alpha was .92 at both age 15 and age 20. The BDI was employed instead of depression diagnoses because (a) relatively few participants met full criteria for major depressive episode (MDE) by age 15 ($n = 35$ or 9.2% of the sample), (b) BDI is a valid measure of risk for diagnosable depression (Beck et al., 1988) and is also, in the current study, predictive of current and future impairment in functioning, and (c) the BDI provides continuous symptom data, which are inherently more powerful for detecting interaction effects. Furthermore, in the current sample, the BDI scores were stable (scores at age 15 correlated with those at age 20 at $r = .41$) and BDI at 15 predicted later onset of MDE, after controlling for current MDE (*Beta* = .23, $p < .001$).

Negative life events. The UCLA Life Stress Interview (Hammen, Henry, & Daley, 2000), a semistructured assessment of acute and chronic stress, was adapted for adolescents and administered at ages 15 and 20. Previous studies have supported the UCLA Life Stress Interview as a reliable and valid assessment of life events in adolescents (e.g., Shih, Eberhart, Hammen, & Brennan, 2006). The current analyses used objective ratings of acute life events. Based on the contextual threat approach to the assessment of life events (Brown & Harris, 1978), interviewers elicited occurrences of life events over the past 12 months and carefully probed for its dating, nature, and circumstances. Interviewers documented responses carefully and provided written synopses to a rating team of trained raters. The rating team generated a consensus severity score based on the event's objective impact on the person's life given contextual factors. Scores ranged from 1 (*no impact*) to 5 (*extremely severe*), and half-point ratings were also utilized. Interrater reliability for independent rating teams was excellent (intraclass correlation = .95). Sums of severity ratings were analyzed as a continuous variable. Events were judged as independent (i.e., fateful or caused primarily by external forces) or dependent (caused in significant part by the individual's actions or characteristics); reliability was .97. As a subset of dependent events, events were also classified as interpersonal or noninterpersonal. Overall, participants reported a range of zero to 11 events; mean number of events in the current sample was 3.22 ($SD = 1.95$).

Genotyping. Genotyping was conducted using agarose gel analysis of polymerase chain reaction products spanning the central portion of the repeats in the 5-HTTLPR. Polymerase chain reaction utilized Qiagen enzyme and buffer, with 30% deazaguanine and with 10 cycles of Touchdown protocol beginning at 67 °C and finishing at 62 °C with a further 32 cycles. Samples were subject to independent duplicate polymerase chain reaction with primer set 1 (acgttggatgTC CTG CATCCCCCAT, acgttggatgGCAGGGGGGATACTGCGA, lower case sequence is nontemplated) that gave products of 198 and 154 bp for Long and Short versions, respectively, and primer set 2 (acgttggatgTCCTGCATCC CCCAT, acgttggatgGGGGATGCTG GAAGGGC) for products of 127 and 83 bp. Gel analyses were conducted in triplicate for most samples. At least two matching independent results were required for inclusion. Final call rate was 96.4%. To estimate accuracy, duplicate samples were genotyped for 764 individuals in a different study in the same laboratory, following above procedures, with discordance rates of 0.45%. In the current sample, frequency of genotypes was *l*/*l* = 122 (32%), *l*/*s* = 178 (47%), and *s*/*s* = 81 (21%), with proportions in Hardy-Weinberg equilibrium, $\chi^2(1, 381) = 1.61$, $p = .20$. Based on evidence suggesting that the *l* form variants designated as L_G function similarly to the *s* allele (Wendland, Martin, Kruse, Lesch, & Murphy, 2006), 21 L_G variants were reclassified as *s* forms. Following this reclassification, updated allele frequencies were *l*/*l* = 101 (27%), *s*/*l* = 189 (50%), *s*/*s* = 91 (24%). As in many studies (e.g., Caspi et al., 2003; Hammen et al., 2010), we collapsed categories into dichotomous groups of absence ($n = 101$) verses presence ($n = 280$) of one or two short alleles (supporting this choice, analyses using the three-group classification indicated that the S/L and S/S groups showed similar associations to key study variables).

Results

Descriptive Statistics

Means, standard deviations, and ranges for study variables are presented in Table 1. Genotype did not differ by gender (χ^2 (2, 381) = 1.89, $p = .39$) nor by maternal depression status (χ^2 (2, 381) = 0.66, $p = .42$), and *s* allele presence was not associated with BDI scores at ages 15 or 20 ($ps > .05$). Bivariate correlations between study variables are presented in Table 2. Cross-sectional correlations between BDI scores and stress indices at age 20 were

Table 1
Descriptive Statistics for Study Variables

	M	*SD*	Range
Age 15 BDI	6.17	6.26	0–32
Age 20 BDI	7.71	8.74	0–52
Age 15 Attachment security	5.22	1.55	1–7
Objective Threat Ratings			
Age 15 All events	6.06	4.14	0–22.5
Age 15 Independent events	3.05	2.79	0–20.0
Age 15 Dependent events	2.95	2.71	0–15.5
Age 15 Interpersonal events	2.70	2.72	0–16.5
Age 20 All events	7.36	4.79	0–30.0
Age 20 Independent events	3.16	2.84	0–12.0
Age 20 Dependent events	4.23	3.62	0–21.5
Age 20 Interpersonal events	3.20	3.12	0–23.0

Table 2
Bivariate Correlations Among Study Variables

	1	2	3	4	5	6	7	8	9
Age 15 Variables									
1. Independent Stress	—								
2. Dependent stress	.06	—							
3. Interpersonal stress	.36***	.71***	—						
4. BDI	.05	.19***	.16**	—					
5. Attachment security	.05	.00	.05	−.30***	—				
Age 20 Variables									
6. Independent stress	.18	.04	.11*	−.01	−.04	—			
7. Dependent stress	.11*	.09	.15**	.12*	−.09	.08	—		
8. Interpersonal stress	.12*	.09	.19***	.16**	−.12	.25***	.78***	—	
9. BDI	.15**	.20***	.20***	.41***	−.20***	.06	.28***	.28***	—

* $p < .05$. ** $p < .01$. *** $p < .001$.

moderate for dependent and interpersonal events (*r*s were .23 to .25, respectively, *p*s $< .001$), and weak for ratings of independent events ($r = .10$, $p = .01$).

Genotype as a Correlate of Episodic Stressors

To test for correlations between genotype and environmental stressors, *t* tests were conducted comparing participants with the *l*/*l* genotype to participants with one or two *s* alleles. Outcome variables included all stress variables at ages 15 and 20, including total objective threat ratings of the subcategories of independent, dependent, and interpersonal events. Notably, no *t* tests emerged as significant, suggesting a lack of correlation between genotype and stressful life event occurrence. There were no significant interactions between genotype and gender, all *p*s $> .05$.

Genotype as a Moderator of Association Between Depressive Symptoms and Later Acute Stressors

Several linear regressions were conducted to test the interaction between depressive symptoms and 5-HTTLPR. Age 15 BDI (centered) and dichotomized genotype (indicating presence or absence of at least one *s* allele) were entered as a first step, and their interaction was entered as a second step.

First, age 20 total ratings of independent events were included as the outcome variable. In the first step ($R^2 < .01$), there were no main effects for genotype ($B = -.002$, $SE = .02$, $Beta = -.01$, *ns*) or age 15 BDI ($B = -.46$, $SE = .34$, $Beta = -.07$, *ns*), and in the second step ($\Delta R^2 < .01$), genotype did not interact with depression ($B = .04$, $SE = .03$, $Beta = .08$, *ns*).

Next, total ratings of dependent events were included as the outcome variable. In the first step ($R^2 = .01$), the main effect for age 15 BDI score was significant, supporting stress generation, $B = .07$, $SE = .03$, $Beta = .12$, $p = .03$. The main effect for genotype was not significant, $B = .18$, $SE = .43$, $Beta = .02$, *ns*. In the second step ($\Delta R^2 = .02$, total $R^2 = .03$), genotype and age 15 depressive symptoms significantly interacted to predict age 20 dependent stress ($B = .09$, $SE = .03$, $Beta = .14$, $p = .009$). Decomposition of the significant interaction revealed a significant, positive association between age 15 depression and age 20 stress ratings of dependent events for participants with the *s* allele ($B = .10$, $SE = .03$, $Beta = .18$, $p = .003$), compared to a nonsignificant negative association for l/l participants ($B = -.004$, $SE = .06$, $Beta = -.01$, $p = .96$), as illustrated in Figure 1a. Controlling for race did not impact results. Results were not replicated using depression diagnoses as outcome variables (interaction $B = .87$, $SE = 1.15$, $Beta = .07$, *ns*).

Finally, age 20 objective threat ratings for interpersonal events were included as a dependent variable, entering the same predictors as above. In the first step of the regression ($R^2 = .03$), the main effect for age 15 depressive symptoms was significant ($B = .08$, $SE = .03$, $Beta = .16$, $p = .003$), again supporting stress generation, but the main effect for the genotype was not significant ($B = -.06$, $SE = .37$, $Beta = -.01$, *ns*). In the second step ($\Delta R^2 = .01$, total $R^2 = .04$), the interaction term was significant ($B = .07$, $SE = .03$, $Beta = .12$, $p = .02$). Once again, as displayed in Figure 1b, age 15 depression significantly predicted age 20 stress ratings only for those with an *s* allele ($B = .11$, $SE = .03$, $Beta = .24$, $p < .001$), and not for those with two *l* alleles ($B < .001$, $SE = .06$, $Beta < .001$, $p = .99$).[1] Results were not altered when controlling for race.

Results were similar when analyses were repeated controlling for age 15 stress levels to predict whether there were increases in stressors by age 20. Depressive symptoms significantly interacted with genotype to predict increases in (a) dependent stress (interaction term $B = .09$, $SE = .03$, $Beta = .13$, $p = .01$), and (b) interpersonal stress (interaction term $B = .06$, $SE = .03$, $Beta = .11$, $p = .03$); in both cases, age 15 depressive symptoms predicted increases in stress at age 20 for those with one or more *s* alleles, but not for those with the *l*/*l* genotype. Consistent with previous results, depression did not interact with genotype to predict changes in independent stress.

In addition, to ensure that results are not affected by covariance between stressful life events and continuing depressive symptoms at age 20, we reran analyses controlling for age 20 BDI as an

[1] As previously noted, L_A and L_G allelic variants were recoded as *s* variants, following the common practice and the recommendations of Wendland et al. (2006). Results were similar when using non-reclassified genotype, with age 15 depressive symptoms interacting with genotype to predict interpersonal stress ratings ($Beta = .12$, $p < .05$), except that the interaction between genotype and age 15 depressive symptoms only marginally predicted dependent stress ratings ($Beta = .16$, $p = .08$).

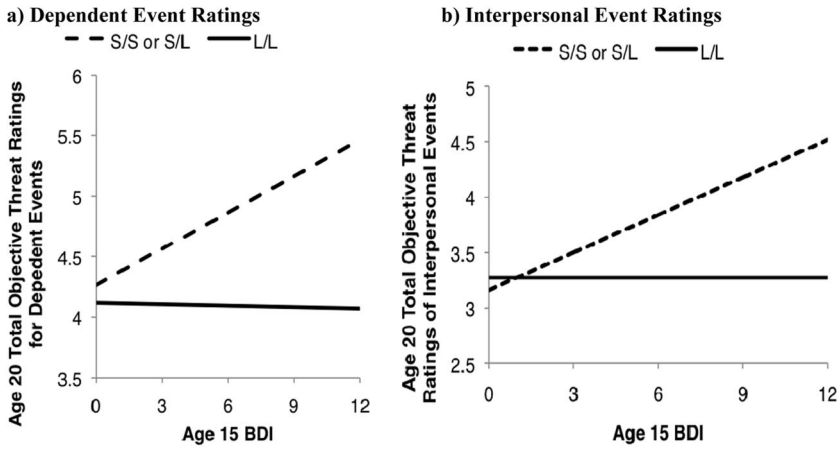

Figure 1. Interaction between 5-HTTLPR genotype and age 15 depressive symptoms, predicting dependent and interpersonal stressful events at age 20. Lines represent linear regression functions for each genotype.

additional predictor. Regression equations included (a) main effects of genotype, (b) main effects for age 15 BDI (centered), (c) the interaction between BDI and genotype, and (d) age 20 BDI, and separate regressions were conducted for independent, dependent, and interpersonal events at age 20 as outcomes. Again consistent with prior results, the interaction between genotype and depressive symptoms were significant in predicting dependent ($B = .09$, $SE = .03$, $Beta = .26$, $p = .009$) and interpersonal events ($B = .06$, $SE = .03$, $Beta = .11$, $p = .039$), but not in predicting independent events ($p > .05$). Decomposition of significant interaction revealed similar patterns to those described previously.

The potential role of gender was tested with the additional predictors of (a) a main effect of gender, (b) two-way interactions between gender and genotype and between gender and depression, and (c) a three-way interaction between gender, genotype, and depression. The three-way interaction was not significant in any model, and significance of two-way interactions between genotype and depression was not impacted by the inclusion of gender effects. In addition, results did not differ when controlling for maternal depression.

Discussion

The current study examined the role of the 5-HTT gene in stress generation. Previously published results using the current dataset (Hammen et al., 2010) have replicated Caspi et al.'s (2003) seminal findings, showing that 5-HTTLPR genotype interacted with stress to predict later depression. In the current study we found evidence for genetic moderation of the reverse direction of causality: The association between depressive symptoms at 15 and stressors at 20 was moderated by 5-HTTLPR genotype. Specifically, depression predicted stress generation among youth with one or more *s* alleles, but not among those with the *l*/*l* genotype. Importantly, genotype moderated the association between depressive symptoms and later generation of dependent events, including interpersonal stress, but not independent events, consistent with the stress generation model (Hammen, 1991, 2006). The results indicated no significant gender interactions, suggesting similar patterns for males and females.

The finding that the 5-HTTLPR genotype moderates the association between depression and later stress is important for several reasons. First, although several studies have suggested that stress generation has a heritable component (Kendler et al., 1999; Kendler et al., 1993; McGuffin et al., 1988), this study is the first to link stress generation with a specific candidate gene. Furthermore, the results may imply that the serotonergic system plays a role not only in depression itself (Neumeister et al., 2004), but in the emergence of psychosocial correlates and consequences of depression. Notably, the 5-HTTLPR genotype explained only a small portion of the variance of stressful event generation (around 2%), although this is consistent with candidate gene research, as studies examining single genotypes and complex phenotypes typically yield small effect sizes (Ioannidis, Trikalinos, & Khoury, 2006).

In addition, the findings have important consequences for research on 5-HTTLPR, stress, and depression. Previous studies have investigated and supported a model in which genetic vulnerabilities interact with the occurrence of stressful events within the environment (Caspi et al., 2003; Karg et al., 2011; Kendler & Karkowski-Shulman, 1997). The current study found evidence for an inverted version of this moderational model, in which depression becomes the predictor and stressful events the outcome. Importantly, it would be impossible to distinguish between these two models using a cross-sectional design; the current study's longitudinal sample allowed detection of the differences between the two directions of effect. Numerous studies on the association between 5-HTTLPR, stress, and depression have relied on cross-sectional designs (see Karg et al., 2011 for a review); the current findings suggest that these studies may have generated incomplete results by considering only one direction of effect, underscoring the importance of primarily relying on prospective datasets in future work. At minimum, researchers should carefully assess temporal sequencing of stressful events and depressive onset (Monroe & Reid, 2008). Furthermore, Kendler (2011) noted that gene-environment correlations have the potential to generate spurious GxE results. Researchers exploring interactions between 5-HTTLPR and stress in predicting depression should carefully control for the effects of genotype on environmental stressors.

The current study revealed a bidirectional association between stress, depression, and the 5-HTTLPR genotype, suggesting a dynamic, reciprocal association between gene and environment, with genetic vulnerabilities making the individual not only more likely to become depressed in response to stress, but also to generate more stress within his or her environment, and then, presumably, more apt to become depressed as a result of this generated stress. The notion that stress and depression operate under such reciprocally causal conditions is widely understood by depression researchers; the current findings suggest that 5-HTTLPR may impact the likelihood of such vicious cycles. Future research should explore the role of the 5-HTT gene in the bidirectional associations between stress and depression in greater detail. For example, daily diary or experience sampling methods could reveal, at a more intricate level, differences in how individuals with and without the *s* alleles react to stress and, in turn, generate stress in response to negative mood.

An important next step is to clarify mechanisms by which the 5-HTTLPR *s* allele moderates the link between depression and later stressors. Although further research is needed, we can speculate on a few possibilities. First, although much research has focused on emotional reactivity conferred by 5-HTTLPR, *s* allele presence may impact a more general reactivity in response to negative environmental circumstances—not just emotional reactivity, but also cognitive and behavioral reactivity that contributes toward the generation of stressful events (e.g., Way & Taylor, 2010). In turn, depression is associated with a constellation of cognitive, behavioral, and interpersonal vulnerabilities that may interact with the reactivity introduced by the short allele, eventuating in episodes of adverse experiences, such as stressful life events. Similarly, heritable personality traits may promote both depression and stress generation. A key example is neuroticism, which has been implicated in stress generation (Davila et al., 2003; Gunthert et al., 1999) and associated with the 5-HTT gene (although evidence for its link to the 5-HTT gene has been inconsistent and may be measure-dependent; Du et al., 2000; Lesch et al., 1996; Schinka et al., 2004; Sen et al., 2004; Willis-Owen et al., 2005). The current dataset did not include a neuroticism measure at the appropriate time points, but future research should explore whether neuroticism and related constructs help explain the association between 5-HTTLPR genotype and stress generation.

In an additional possibility, the short allele may affect how individuals react to their own dysphoric mood, which may in turn eventuate in socially dysfunctional behavioral patterns that promote stressful life events. Numerous studies of depressed adults and children have demonstrated dysfunctional emotion-regulation and information-processing strategies that interfere with "mood repair" and disengagement from negative material (Gotlib & Joormann, 2010; Kovacs, Joormann, & Gotlib, 2008). Such patterns may not only intensify and prolong depressive symptoms, but also have negative effects on social relationships. Similarly, the occurrence of depressive symptoms may activate a variety of genetically conferred, socially dysfunctional coping efforts. For example, several depression-related behaviors have been associated with stress generation, including excessive reassurance seeking, dependency, and insecure attachment behaviors (Eberhart & Hammen, 2009, 2010; Holahan, Moos, Holahan, Brennan, & Schutte, 2005; Joiner, Wingate, & Otamendi, 2005; Potthoff et al., 1995; Safford et al., 2007), and future studies should explore whether 5-HTTLPR genotype elevates risk for these behaviors.

In addition to psychosocial mechanisms, future research should explore physiological mechanisms underlying the possible role of 5-HTTLPR in stress generation. In a significant shortcoming of the literature, there have been no prior studies examining biological underpinnings of stress generation, so it is difficult to speculate on which factors may contribute. However, recent research has linked HPA axis reactivity to the stress reactivity associated with 5-HTTLPR (Gotlib, Joormann, Minor, & Hallmayer, 2008); future studies should investigate whether HPA axis functioning also plays a role in stress generation.

Gene-environment correlation as a main effect—that 5-HTTLPR genotype would correlate directly with stressful life events—was not supported. Genotype was not independently associated with stressors at 15 or 20. Given that the genotyped sample was relatively small, these findings should be viewed as tentative prior to replication. However, paired with other findings, these results may suggest that the 5-HTT gene only increases the likelihood of stress occurrence under certain circumstances, such as among those with high levels of depressive symptoms. Future research should identify further conditions under which people with short 5-HTTLPR alleles are at amplified risk for stress generation. For example, the 5-HTT gene may interact with other genes or with environmental conditions to increase risk of producing stressful contexts.

Several important study limitations must be acknowledged. First, the portion of the sample that was genotyped was fairly small, and underpowered gene candidate studies can produce misleading results (Munafò, Durrant, Lewis, & Flint, 2009). The current findings require replication, and should be interpreted in conjunction with data from larger-scale studies. Relatedly, although no gender differences were observed in the moderating effect of 5-HTTLPR on the association between depression and later stress, note that the sample size of males was smaller than for females, and future research with larger male samples might yield different patterns. Second, BDI scores were used in lieu of depression diagnoses, largely because their continuous nature offered greater statistical power (indeed, using depression diagnoses did not generate similarly supportive results, likely related to their low base rate and lack of power). Some argue, however, that self-reported symptom measures inappropriately pathologize what may be transient distress (Coyne, 1994), although as participants in this study were oversampled for maternal depression, their self-reported symptoms may be more likely to represent clinically significant depression. Furthermore, given that depression in this study was a predictor and not an outcome, the possibility that symptoms captured may be subclinical does not necessarily detract from its importance. The notion that 5-HTTLPR genotype could elevate risk of negative consequences of low-grade depressive symptoms has important implications. Still, future work should clarify genetic influences of stress generation among those with clinically significant depression, in addition to self-reported symptoms.

Furthermore, the sample was overselected for depression risk based on maternal depression status, and, therefore, results may not generalize to nonselected samples. Similarly, the study was limited to adolescents, who typically have relatively elevated levels of stressful life events compared to older and younger samples

(e.g., Hammen, 2009), and research is needed to determine whether similar patterns of moderation by the 5-HTTLPR polymorphisms would occur in different ages. Finally, candidate gene research carries inherent limitations, as any single gene has only small effects that can be difficult to link to heterogeneous, descriptively defined phenotypes such as depression and stressful events. Other genes and combinations of genes should be explored in future studies.

In sum, the current study suggests the *s*-allele bidirectionally affects the association between depression and stress. This underscores an important point: Associations between depression and its psychosocial etiological factors rarely follow a simple causal pathway, and failing to account for the dynamic, reciprocal effects between depression and the environment may obscure important associations. Results indicate the need for a broadened perception of the mechanisms of the effect of the 5-HTTLPR polymorphisms. We hope that future studies will not only take into account the complex transactions among variables, but also shed further light on the nature of the mechanisms of this and other possible candidate genes in the stress-depression process.

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