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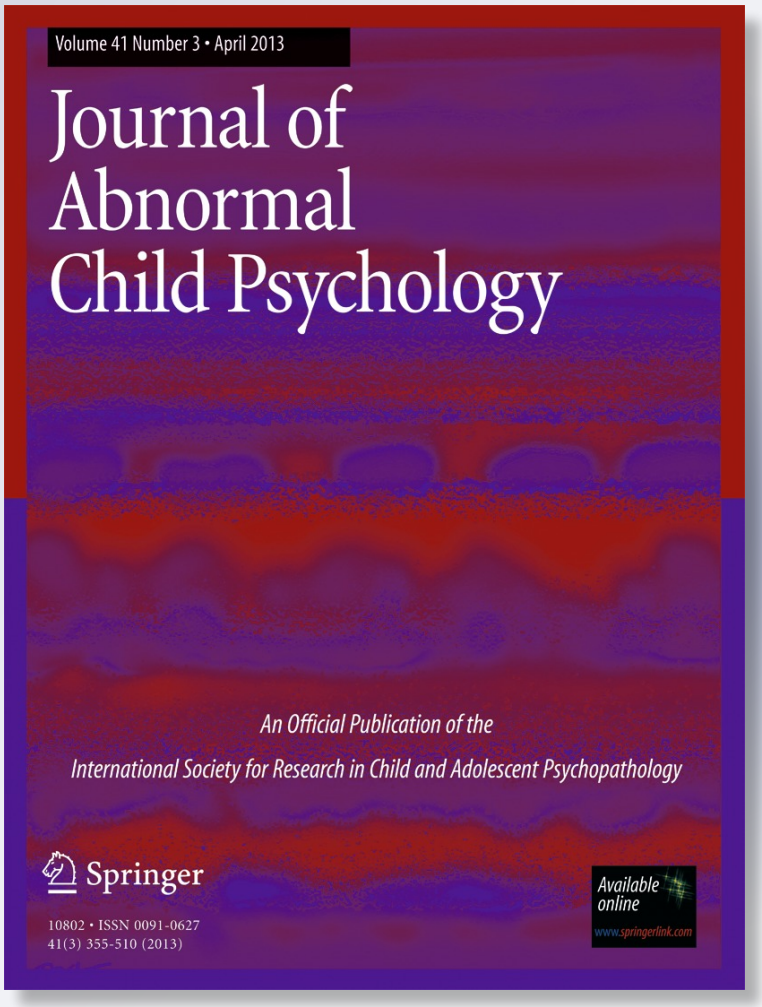

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Relational Security Moderates the Effect of Serotonin Transporter Gene Polymorphism (5-HTTLPR) on Stress Generation and Depression among Adolescents

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Abstract Previous research demonstrates that carriers of the short allele of the serotonin transporter gene (5-HTTLPR) show both greater susceptibility to depression in response to stressful life events and higher rates of generation of stressful events in response to depression. The current study examines relational security (i.e., self-reported beliefs about attachment security) as a moderator of these effects, building on emerging research suggesting that the short allele acts as a marker of sensitivity to the social environment. Participants were 354 Caucasian adolescents oversampled for maternal depression (137 male, 217 female), assessed at ages 15 and 20. Results indicated that the short allele predicted increased stress generation at age 20 among those with low age 15 security but decreased stress generation among those with high security, and revealed a three-way interaction between age 15 depression, age 15 security, and genotype, where depression predicted stress generation only among short allele carriers with low security. Further, among boys only, security interacted with genotype to predict longitudinal changes in depression diagnosis, with the *s*-allele predicting relative increases in probability of depression among boys with low security but decreases among boys with high security. Results support the notion of the short allele as a marker of social reactivity, and suggest that attachment security may buffer against the genetic vulnerability introduced by the short allele, in line with predictions of the differential susceptibility theory.

Keywords Serotonin transporter gene · 5-HTTLPR · Attachment security · Depression · Stress generation

Moderation by the short (*s*) allele of the promoter region of the serotonin transporter gene (5-HTTLPR) of the association between stress and depression has now been well established (Caspi et al. 2003; Hammen et al. 2010; Kendler et al. 2005; Kilpatrick et al. 2007; Nakatani et al. 2005; see Karg et al. 2011, for a recent meta-analysis), with *s*-carriers showing greater reactivity to stressors than long (*l*) homozygotes. A recent study (Starr et al. 2012) suggested that the association between stress, depression, and 5-HTTLPR genotype may be bidirectional, as the short allele may contribute to stress generation in addition to stress reactivity. *Stress generation* implies that stress acts not only as a predictor of depression, but as a consequence of it as well, as individuals with depression are more likely to generate stressful contexts and life events (Hammen 1991, 2006; Liu and Alloy 2010). Starr et al. (2012) found that short allele presence interacts with depressive symptoms at age 15 to predict generation of dependent (i.e., caused in at least part by the person's actions or characteristics) and interpersonal events, but not independent (i.e., fateful) events, at age 20, suggesting that 5-HTTLPR plays a role in stress generation in depression. This finding implies that 5-HTTLPR contributes to a reciprocal relationship between stress and depression, in which genotype interacts both with stress predicting depression and with depression predicting stress.

The notion that 5-HTTLPR marks both stress reactivity and stress generation implies a more complex, dynamic

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association between this genetic vulnerability, depression, and the social environment than previously envisioned. It also suggests that stress reactivity and stress generation may be rooted in the same genetically-mediated traits or behaviors. However, further research is needed to pinpoint specific conditions that amplify the likelihood that the *s*-allele will lead to negative outcomes, both emotional and behavioral.

Furthermore, it is unclear whether the short allele is primarily predictive of increased negative outcomes or if it may also lead to decreased negative outcomes (such as decreased depression and stressor levels) under certain circumstances. Initial research on 5-HTTLPR operated within the traditional diathesis-stress model, conceptualizing the short allele purely as a punitive factor that elevates risk of negative psychopathological outcomes under stressful environmental conditions but offers no obvious benefits. More recent work has re-construed the *s*-allele as a marker of sensitivity to the social environment, predicting negative outcomes under negative interpersonal circumstances, but potentially buffering against negative outcomes under warm, nurturing interpersonal conditions (Way and Taylor 2010), consistent with the differential susceptibility model (Belsky et al. 2007; Belsky and Pluess 2009; Ellis et al. 2011), which proposes that many so-called vulnerability factors may actually reflect plasticity to environmental influences.

For example, *s*-homozygotes with a history of a supportive family environment or recent positive events show lower levels of depression than *l*-carriers (Taylor et al. 2006), and the *s*-allele appears to be related to greater sensitivity to the buffering effects of social support (Kaufman et al. 2004; Kilpatrick et al. 2007) and the beneficial effects of positive parenting (Hankin et al. 2011). In addition, a recent study suggested that *s*-carriers' moods fluctuate in greater concert with their romantic partners' affect (Schoebi et al. 2011), further supporting the idea that the *s*-allele confers interpersonal sensitivity. Also in line with the idea that 5-HTTLPR marks differential susceptibility, Pluess, Belsky, Way and Taylor (2010) found both a G × E between the short allele and *negative* life events predicting *higher* neuroticism as well as an additional G × E between the short allele and *positive* life events predicting *lower* neuroticism. The notion that 5-HTTLPR confers sensitivity to social cues is new and relatively untested. More research is needed to determine whether, for example, the *s*-allele leads to decreased depression under positive interpersonal conditions, and specifically, whether it also predicts lower levels of stress generation when the individual has warm, nurturing relationships.

The current study expands upon previous findings (Starr et al. 2012) to attempt to identify interpersonal contexts under which the short allele may alter risk of both depression and stress generation. Starr et al. (2012) suggested that *s*-carriers are more prone to stress generation in part because they are more behaviorally as well as affectively reactive to the negative interpersonal correlates of depression, and that this behavioral reactivity culminates in the generation of acute life events. If so, it would be useful to identify the specific interpersonal factors that may modify *s*-carriers' risk for negative outcomes, as a step toward isolating mechanisms or intermediate phenotypes.

Here, we specifically focus on the role of relational security, or self-perceived beliefs about attachment. Based on attachment theory (Bowlby 1980), secure relational style implies the presence of positive working models of both oneself and other people, resulting in comfort with both closeness and separation (Bartholomew and Horowitz 1991; Bowlby 1969, 1980; Griffin and Bartholomew 1994). People with secure relational styles are able to build intimate, warm, and relatively harmonious relationships; relational insecurity, conversely, is associated with a host of interpersonal problems (Griffin and Bartholomew 1994). Disruptions in security have been strongly associated with depression (Davila et al. 2005), and likely play a role in stress generation, as insecure relational style predicts later negative interpersonal events (Bottonari et al. 2007; Hankin et al. 2005). Although secure relational style is not a direct measure of the interpersonal environment, it likely in part reflects a history of warm, nurturing relationships dating back to early childhood, as well as personality traits and competencies that allow the individuals to build positive relationships and maintain an agreeable interpersonal environment. Thus, it may be representative of the type of positive social milieu in which *s*-carriers flourish, and conversely, low security may reflect the types of negative interpersonal relationships that amplify the non-adaptive outcomes of the *s*-allele. Supporting this notion, security is associated with numerous indicators of positive relationship functioning, including higher quality and perceived support (Collins and Read 1990; Noftle and Shaver 2006; Ognibene and Collins 1998).

Research on genetic factors related to security is somewhat limited, as attachment has traditionally been conceptualized as a purely environmental phenomenon, stemming directly from interactions with early caregivers (Bowlby 1980). More recently, however, researchers have begun to explore its genetic underpinnings and interactive effects with genetic factors; for example, Brussoni et al. (2000) found a heritability of 37 % for adult attachment security. Researchers have also begun to explore specific candidate genes, and have linked poor attachment security to serotonin-related genes including 5-HTTLPR (Caspers et al. 2009; Gillath et al. 2008), although results have been mixed and existing support is fairly weak, with replication problems (Luijk et al. 2011; Reiner and Spangler 2010).

Other evidence suggests that genetic vulnerability combines with environmental risk factors to predict insecure attachment (although here too support has been mixed; Luijk et al. 2011). Barry et al. (2008) found that maternal nonresponsiveness predicted insecure attachment among those with the short allele, but not long homozygotes, in line with the idea that the short allele marks sensitivity to social cues. All in all, emerging but limited research suggests that genetic factors, including 5-HTTLPR, could potentially contribute to the development of relational security, suggesting that this is a relevant context under which to examine the impact of 5-HTTLPR genotype.

In addition, attachment may moderate the degree to which the short allele predicts negative outcomes. As a marker of the early social environment and interpersonal functioning, secure relational style may attenuate the short allele's impact on negative outcomes such as stress generation. Supporting this notion, Gilissen et al. (2008) found an interaction between 5-HTTLPR genotype and attachment security in predicting children's transdermal activity in response to a public speaking task, such that L/L homozygotes with high security showed the least stressed responses. *S*-allele presence may also interact with attachment to predict specific interpersonal behaviors (which may in turn contribute to stress generation). Zimmermann et al. (2009) found that attachment security significantly interacted with 5-HTTLPR genotype to predict adolescent autonomy behaviors, with security predicting decreased hostile behaviors and increased agreeable behaviors among *s*-carriers but not among long homozygotes. This again fits with the idea that the short allele may have a positive impact under positive interpersonal circumstances while also eliciting negative behaviors under more dysfunctional interpersonal conditions.

Taken together, this research suggests that secure relational style may be an example of a construct that helps to explain 5-HTTLPR's role in stress generation; however, this literature remains extremely limited. Of note, there have been no longitudinal studies examining the role of security in attenuating the impact of 5-HTTLPR genotype, and few studies examining this topic in adolescence, a time period critical to the development of important interpersonal processes and the emergence of psychopathology. The current study examines several research questions relating to the role of self-reported relational security in the association between 5-HTTLPR and negative outcomes in a longitudinal sample of adolescents, oversampled for maternal depression and assessed at ages 15 and 20.

First, we examined whether 5-HTTLPR genotype interacts with ratings of security to predict generation of stressful events. We predicted that *s*-allele presence would predict stress generation (increases in reports of dependent but not independent acute events) among those with less secure relational style. Conversely, we anticipated relatively lower levels of dependent and interpersonal stressors among *s*-carriers with higher attachment security. Next, we examined whether relational security moderated previously published findings. Using the current database, Starr et al. (2012) showed that self-reported depressive symptoms were more likely to lead to greater dependent and interpersonal stressors among *s*-carriers, speculating that interpersonally-sensitive *s*-carriers may be more likely to engage in depression-related dysfunctional interpersonal behaviors, placing a strain on their relationships and eventuating in acute events. If so, *s*-carriers with greater security (reflecting a more harmonious relationship style) may be protected against this process and show reduced stress generation. To examine this idea, we tested a three-way interaction between age 15 depression, security, and genotype, predicting that depressive symptoms would lead to particularly pronounced stress generation among *s*-carriers with low security.

Finally, we tested whether attachment security interacted with genotype to predict depression. Among those with low security, the *s*-allele presence was hypothesized to predict increased likelihood of depression diagnosis (controlling for baseline diagnosis), but among those with high security, we anticipated that the *s*-allele status would predict decreased likelihood of depressive diagnosis. Because numerous reports have suggested gender differences in constructs of interest, including differential impact of 5-HTTLPR by gender (e.g., Araya et al. 2009; Brummett et al. 2008; Sjöberg et al. 2006), as well as gender differences in depression, stress levels, reactivity to interpersonal vulnerabilities, and stress generation among adolescents (Nolen-Hoeksema and Girgus 1994; Rudolph 2002; Rudolph and Hammen 1999), for all hypotheses we examined whether results differed for boys and girls.

Methods

Participants

Three hundred and fifty-four Caucasian youth were included in the current analyses; these participants were part of a long-term, longitudinal study. The original sample (n=816) was a subset of the Mater University Study of Pregnancy, a large cohort study of children born at Mater Misericordiae Mother's Hospital in Brisbane, Australia (Keeping et al. 1989). Fifteen years after birth, mothers and offspring were recruited to participate in a follow-up study. To ensure heightened risk for depression within the sample, participants were oversampled for maternal depression assessed during pregnancy, postpartum, and 6 months and 5 years after birth. At each of these time points, mothers completed the Delusions-Symptoms-States Inventory (DSSI; Bedford and Foulds 1978; note that the DSSI was used for sample

inclusion decisions but maternal depression was later confirmed using clinical interviews). With the goal of oversampling mothers with clinically significant depression but also including a range of maternal depression levels, women were invited to participate in a follow-up if their DSSI scores suggested severe depression at two or more data collection points, severe depression only once between pregnancy and offspring age 5, moderate depression twice or more, or low depression at all time points. 991 mother-offspring pairs were targeted for participation and 816 participated.

At youth age 20, 705 families elected to participate in an additional follow-up (see Keenan-Miller et al. 2007 for sample and recruitment details). These participants were subsequently re-contacted between the ages of 22 and 25 and invited to participate in genotyping. Five hundred twelve youth chose to provide a DNA sample; these participants did not differ from non-genotyped participants on maternal or youth depression status, but were more likely to be female (χ^2=21.29, p<0.001). For financial and logistical reasons, genotyping was restricted to a single plating of 384 samples; these samples were selected randomly from the genotyped sample. Three samples yielded invalid readings, creating a genotyped sample of 381 participants (149 males and 232 females). To avoid population stratification artifacts, participants who were non-White (n=19) or who did not report race (n=7) were excluded (although analyses on the full sample produced similar results), leaving 354 Caucasian participants in the final sample (137 male, 217 female). For greater detail, see Hammen et al. (2010).

Procedure

Similar procedures were followed at the age 15 and 20 follow-ups. Research staff collected informed consent/assent and separately interviewed adolescents, mothers, and available fathers (at age 15 only) in their homes, and participants completed questionnaires. All youth interviewers were blind to maternal diagnoses. Two to 5 years (mean= 3.32 years, SD=1.02) after the age 20 follow-up, participants were mailed consent forms and blood collection kit for DNA samples. Blood samples were drawn at local facilities and retrieved by courier. Genotyping was conducted at the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research. This research was approved by the Institutional Review Boards of UCLA, Emory University, and University of Queensland.

Measures

Secure Relational Style The Bartholomew Relationship Questionnaire (Bartholomew and Horowitz 1991) is a widely-used self-report measure listing descriptions of attachment style prototypes, which participants rate on a Likert-type scale (1=*not at all like me* to 7=*very much like me*). For the current study, we used ratings of secure attachment style ("*It is easy for me to be close to others. I am comfortable counting on others and having others count on me. I feel accepted by others. When I am alone it does not bother me*."). The Relationship Questionnaire converges with other forms of attachment assessment, such as interviews (Bartholomew and Shaver 1998), and has demonstrated adequate psychometric properties in adult and adolescent populations (Bartholomew and Horowitz 1991; Davila et al. 2004).

Depression Youth lifetime depressive diagnoses were assessed at age 15 using the Schedule for Affect Disorders and Schizophrenia for School-Age Children-Revised Epidemiologic version for the DSM-IV (K-SADS; Orvaschel 1995). The K-SADS is a widely-used semi-structured interviews assessing past and present clinical disorders, and has demonstrated excellent psychometric properties (Kaufman et al. 1997). Interviews were administered separately to both parent and child; diagnostic decisions were reached by clinical team consensus using all available information. Interviews were conducted by advanced clinical psychology graduate students, supervised by clinical psychologists via audiotape and periodic visits. In the current study, depressive disorder is defined as a diagnosis of major depressive episode or dysthymic disorder. Weighted kappas were 0.82 for current depression diagnoses and 0.73 for past diagnoses. Forty-nine youth met lifetime criteria for depression by age 15. At age 20, current or past depression diagnosis occurring between ages 15 and 20 was assessed using the Structured Clinical Interview for the DSM-IV (SCID; Spitzer et al. 1995). Of the 354 youth included in the current analyses, 94 participants met criteria for major depression or dysthymia between ages 15 and 20. Ten percent of interviews were recoded by a second rater, a kappa of 0.89 for depression. Self-reported depressive symptoms were assessed at age 15 using the Beck Depression Inventory (BDI; Beck et al. 1996), a widely used 21-item with strong psychometric properties (Beck et al. 1988). Cronbach's alpha was 0.92. Maternal depression diagnosis was also assessed using the SCID, with 44 % of mothers meeting criteria for major depression or dysthymia by youth age 15.

Negative Life Events Acute stressors were assessed at ages 15 and 20 using the UCLA Life Stress Interview (Hammen et al. 2000), a semi-structured interview assessing acute stressful events based on the contextual threat approach (Brown and Harris 1978). The interview was adapted for use with adolescents, as supported by previous studies (e.g., Shih et al. 2006). Interviewers assess life events occurring

over the preceding 12 months, and prepare a written narrative of each event, its circumstances, and context to be rated by an independent team of raters who have no knowledge of the person's actual reactions to the event. The team rates each event for severity, ranging from one (*no impact*) to five (*extremely severe*; half-points were also assigned) that reflect each event's objective impact given contextual factors. Intraclass correlation for independent rating teams was 0.95. In the current analyses, severity scores across events were summed. Teams also rated events as independent (caused primarily by external situations) versus dependent (caused significantly by the individual's traits or actions), and identified interpersonal content events (a subset of dependent events). Reliability was excellent for both independence (ICC=0.97) and interpersonal (kappa=0.89) ratings.

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 (acgttggatgTCCTG CATCCCCCAT, acgttggatgGCAGGGGGGATACTGCGA, lower case sequence is non-templated) that gave products of 198 and 154 bp for Long and Short versions respectively and primer set 2 (acgttgg atgTCCTGCATCC CCCAT, acgttggatgGGGGATG CTGGAAGGGC) 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 %.

Genotypes for the full genotyped sample were distributed as follows: *l*/*l*=122 (32 %), *s*/*l*=178 (47 %), and *s*/*s*=81 (21 %). Proportions were in Hardy-Weinberg equilibrium (χ^2 (1, 381)=1.61, p=0.20). Studies suggest that the *l* form variants designated as L_G operate similarly to the *s* allele (Wendland et al. 2006); as such, 21 L_G variants were re-classified as *s* forms, producing the following updated genotype frequencies: *l*/*l*=101, *s*/*l*=189, *s*/*s*=91. As noted above, non-Caucasian participants were subsequently excluded, leaving a final distribution of *l*/*l*=96 (27 %), *s*/*l*=178 (50 %), *s*/*s*=80 (23 %). Following common convention (e.g., Caspi et al. 2003; Hammen et al. 2010; Starr et al. 2012), genotypes were dichotomized into groups reflecting *l*/*l* (*n*=96) versus *s*/*s* or *s*/*l* (*n*=258). Genotype was unrelated to maternal depression status.

Results

Table 1 displays descriptive data and bivariate correlations for all study variables. Of note, 5-HTTLPR genotype was not directly associated with any study variables. Relational security was inversely related to age 15 depressive symptoms, age 20 depression diagnosis, and age 20 interpersonal

Table 1 Bivariate associations among study variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. 5-HTTLPR Genotype (*s*-allele presence)	—										
2. Age 15 security	0.08	—									
3. Age 15 depression diagnosis	-0.03	-0.05	—								
4. Age 15 BDI	-0.05	-0.29***	0.20***	—							
5. Age 15 independent events	-0.03	0.05	0.17**	0.05	—						
6. Age 15 dependent events	0.06	-0.01	0.23***	0.21**	0.04	—					
7. Age 15 interpersonal events	0.06	0.04	0.23***	0.16**	0.34***	0.72***	—				
8. Age 20 depression diagnosis	0.07	-0.11*	0.25***	0.27***	0.21***	0.10	0.19***	—			
9. Age 20 independent events	-0.06	-0.05	0.15**	0.01	0.17***	0.03	0.11*	0.04	—		
10. Age 20 dependent events	0.02	-0.09	0.18**	0.13*	0.11*	0.09	0.16**	0.25***	0.08	—	
11. Age 20 interpersonal events	-0.03	-0.12*	0.17**	0.16**	0.11*	0.10	0.20***	0.28***	0.26***	0.77***	—
M	N/A	5.21	N/A	6.17	3.41	2.81	2.79	N/A	3.16	4.24	3.24
SD	N/A	1.57	N/A	6.37	3.09	2.63	2.84	N/A	2.87	3.64	3.12

*$p<0.05$, **$p<0.01$, **$p<0.001$

N/A descriptive data not applicable to categorical data

events. Security was also related to maternal depression, $t(347)=2.04$, $p=0.042$, with lower security among offspring of depressed mothers, mean difference=0.34.

Gene × Age 15 Security Predicting Generation of Age 20 Stressful Events

To assess whether the short allele interacted with secure relational style to predict total dependent stress at age 20, we conducted hierarchical linear regression analyses; main effects of age 15 relational security (centered) and genotype were entered as the first step, and gene × security interactions were entered as the second step. There were no significant main effects, but the interaction term was significant, *Beta*=-0.29, $p=0.002$. Following Aiken and West's (1991) procedures, it was determined that at low levels of security (one SD below the mean), *s*-allele presence predicted significantly higher stress levels at age 20, *Beta*=0.19, $p=0.013$; conversely, at high levels of security (one SD above the mean), *s*-allele presence predicted marginally significantly lower dependent stress, *Beta*=-0.14, $p=0.067$. Next, as a more conservative test, we examined the gene×security interaction predicting changes in stress levels over time, by entering age 15 dependent stress as a control variable in step 1 and then proceeding as above. Again, genotype and security interacted to predict changes in dependent events, *Beta*=-0.28, $p=0.003$. Following the same pattern, *s*-allele presence predicted significant increases in dependent stress among those with low security, *Beta*=0.18, $p=0.018$, but marginally significant decreases among those with high security, *Beta*=-0.14, $p=0.067$. Results did not differ by gender.

Next, analyses were repeated with interpersonal events as the outcome variable. In step 1, there was a significant effect of security, *Beta*=-0.12, $p=0.025$, but not for genotype. In step 2, genotype and security significantly interacted to predict interpersonal events, *Beta*=-0.31, $p=0.001$. Among participants with low security, *s*-allele presence predicted *higher* interpersonal stress, *Beta*=0.15, $p=0.046$; for those with high security, *s*-allele presence predicted *lower* levels of interpersonal stress, *Beta*=-0.20, $p=0.008$. Figure 1 illustrates this interaction. Again, for a more conservative test, we repeated these steps controlling for age 15 interpersonal events. There were no main effects for genotype, but relational security predicted significant decreases in interpersonal events over time, *Beta*=0.13, $p=0.017$. Again, security interacted with genotype to predict interpersonal events, *Beta*=-0.29, $p=0.002$, and decomposition showed genotype predicted marginally significant increases in interpersonal events among individuals with low security, *Beta*=0.12, $p=0.091$, but significant decreases among those with high security, *Beta*=-0.20, $p=0.007$. Results again did not differ by gender.

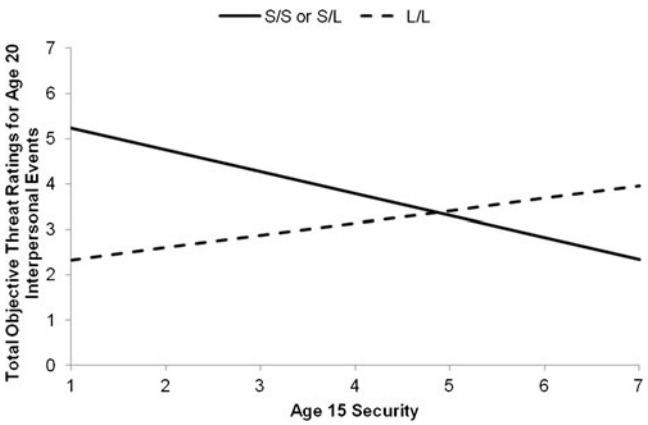

Fig. 1 Association between age 15 security ratings and total objective threat ratings for interpersonal events at age 20, as a function of genotype. Lines represent linear regression functions for each genotype. Regression coefficient is significant for *S/S* or *S/L* function (*Beta*=-0.25, $p<0.001$), but not for *L/L* function (*Beta*=0.13, $p=0.23$)

When total independent stress was included as the outcome, there were no significant main effects or interactions ($ps>0.05$).

Gene × Age 15 Security × Age 15 BDI Predicting Age 20 Stress

To determine whether the interaction between age 15 BDI and genotype differed as a function of security, main effects for BDI, genotype, and age 15 security were each entered in the first step, two-way interactions (gene × BDI, gene × security, and BDI × security) were entered in the second step, and a three-way interaction was added in the third step. The three-way interaction was not significant in predicting dependent events, *Beta*=-0.11, *ns*, but it was significant in predicting interpersonal events, *Beta*=-0.19, $p=0.036$. BDI predicted significant increases in interpersonal stress among those with both low security (1 *SD* below mean) and *s/s* or *s/l* genotype, but not among those with high security and/or *l/l* genotype. There were no significant gender effects.

Gene × Age 15 Security Predicting Age 20 Depression Diagnosis

Next, we conducted logistic regression analyses to determine whether age 15 security interacted with *s*-allele presence to predict increased likelihood of depression diagnosis. Following similar steps as above, we entered depression diagnosis by age 15 in the first step, and centered age 15 security and genotype in the second step, followed by their interaction, with depression diagnosis between ages 15 and 20 as the outcome. The interaction term was not significant; *B*=-0.10, *SE*=0.18, Wald=0.32, $p=0.573$. However, the interaction significantly differed by gender, as evidenced

by a significant three-way interaction between gender, security, and genotype, B=-0.88, SE=0.42, Wald=4.28, p=0.038. Among girls, the main effect for security (but not genotype) was significant, B=-0.27, SE=0.10, Wald=7.14, p=0.008, but the two-way interaction between genotype and security was not, B=0.21, SE=0.24, Wald=0.78, p=0.377. In contrast, among boys, there were no significant main effects for genotype or security, but *s*-allele presence interacted with age 15 security to predict increased likelihood of depression diagnosis, B=-0.73, SE=0.37, Wald=3.84, p=0.05. Among boys with low security (one *SD* below mean), *s*-allele presence predicted non-significant increases in depression diagnosis likelihood, B=1.37, SE=0.84, Wald=2.63, p=0.105; among boys with high security, it predicted non-significant decreases, B=-1.023, SE=0.83, Wald=1.54, p=0.215 (note that nonsignificant simple effects are not uncommon for crossover effects).

All analyses were repeated controlling for maternal depression; results were not impacted.

Discussion

Previous studies have shown that the *s*-allele of the 5-HTTLPR polymorphism confers increased risk of depression in conjunction with negative life events (Karg et al. 2011), and a recent study using the current dataset suggested that it also amplifies risk of stress generation in those with depression (Starr et al. 2012). The current findings tested a moderator of this effect, suggesting that secure relational style may enhance the impact of the *s*-allele on both depressive diagnosis and stress generation outcomes. First, genotype interacted with secure style at age 15 to predict changes in self-generated stressors by age 20, with the short allele predicting increased stressors among those with low security, and decreased stressors among those with high security. Second, we revealed a three-way interaction between genotype, age 15 depressive symptoms, and age 15 security predicting interpersonal stressors at age 20, with only insecure *s*-carriers showing a positive association between depressive symptoms and later generation of interpersonal events (with no association between depressive symptoms and stress generation for those with either *l/l* genotype or high security). Finally, showing a similar pattern with a different outcome, among boys (but not girls) presence of the *s*-allele interacted with secure style to predict depression diagnosis, with secure boys showing decreased likelihood of depression diagnosis by age 20, and insecure boys showing increased depression rates.

These results are notable for several reasons. First, they expand upon Starr et al.'s (2012) previous findings, laying the foundation for an explanatory model for the role of 5-HTTLPR in stress generation. Insecure relational style likely reflects a constellation of interpersonal risk factors, including poor interpersonal competencies, a history of relationship dysfunction with caregivers and other significant individuals, and interpersonally disruptive personality traits. These risk factors may activate the genetic vulnerability conferred by the *s*-allele, leading to increases in everyday behaviors (such as conflict, hostility, and reassurance-seeking) that eventuate in the generation of stressful events. Second, previous research has found that the *s*-allele interacts with stressful life events or early adversity to predict depressive onset (e.g., Karg et al. 2011), and our results suggest that it also interacts with insecure relational style to predict the same outcomes, although only among boys. This may be because insecure relational style is in part a proxy variable for negative early experiences, but may also mean that the ability to build and maintain fulfilling interpersonal relationships protects against the genetic vulnerability to depression introduced by the *s*-allele.

Further, results are consistent with Way and Taylor's (2010) model conceptualizing the *s*-allele as a marker of sensitivity to the social environment. Under negative social conditions (as reflected by age 15 insecure relational style), the *s*-allele predicted negative outcomes, including both depressive diagnosis (among boys) and increased stressors caused by the person. Conversely, under positive interpersonal conditions (represented by age 15 secure relational style), *s*-carriers showed improvement in functioning over time, including decreased likelihood of depression diagnoses among boys (especially notable given that youth in this sample were at high risk for depression as a consequence of maternal depression diagnosis) and decreased levels of self-generated stressors. Future research should replicate these results, and examine whether under positive social conditions the *s*-allele predicts overtly positive outcomes, in addition to protecting against negative outcomes (supporting this idea, Hankin et al. 2011 found that supportive parenting predicted higher positive affect among adolescents). Current findings provide early support for a more nuanced conceptualization of the phenotypic expression of the *s*-allele, suggesting it may have an adaptive function that emerges under some circumstances.

The interaction pattern revealed in the current study is consistent with the expectations of the differential susceptibility hypothesis (Belsky et al. 2007; Ellis et al. 2011), in contrast to most prior work on this genotype, which has implicitly operated under the assumptions of the diathesis-stress model (Monroe and Simons 1991). The differential susceptibility model suggests that many risk factors assumed to purely raise vulnerability (such as the 5-HTTLPR short allele) may actually reflect plasticity to environmental conditions. An important implication of this model is the importance of assessing constructs in relation to 5-HTTLPR, including environmental modifiers and

outcome variables, that reflect positive (including supportive relationships, nurturing parenting, positive life events, and successful outcomes) as well as negative (depression, stress) aspects of functioning and the environment. A few recent studies have begun to examine 5-HTTLPR using this approach (Hankin et al. 2011; Pluess et al. 2010), but far more work is needed.

It is somewhat counterintuitive that the interaction between genotype and secure relational style in predicting depressive disorder change was significant among boys but not girls. Several studies have found effects of 5-HTTLPR for girls but not boys (Brummett et al. 2008; Eley et al. 2004; Grabe et al. 2004; Hammen et al. 2010; Sjöberg et al. 2006), although a few have found more pronounced effects for boys (Araya et al. 2009; Du et al. 2000). Further, girls are more sensitive to interpersonal stressors and show heightened rates of depression as well as interpersonal stress (Lewinsohn et al. 1994; Nolen-Hoeksema and Girgus 1994; Rudolph 2002; Rudolph and Hammen 1999; Shih et al. 2006). It may be that girls are vulnerable to the effects of low security regardless of their 5-HTTLPR genotype, whereas boys are only adversely impacted by poor security when they also carry a genetic vulnerability that confers sensitivity to the social environment (supporting this notion, low security predicted depression as a main effect among girls but only in interaction with genotype for boys). A wealth of research delineates risk factors for depression that are specific to girls (e.g., Nolen-Hoeksema et al. 1999; Prinstein et al. 2005), but it is also important to identify contexts that amplify risk for depression among boys, and the current study suggests that the *s*-allele may reflect one such factor.

Several study limitations must be acknowledged. We assessed self-reported cognitions about attachment security, or secure relational style, rather than using interview or observationally based measures. The general consensus among attachment scholars is that attachment interviews (Bartholomew 1998; George et al. 1985) reflect the "gold standard" for attachment assessments for adolescents or adults. The self-report measure used here (Griffin and Bartholomew 1994) is widely used and strongly related to interview-assessed attachment (Bartholomew and Shaver 1998), but is subject to the limitations of self-presentation or lack of awareness or insight. As a result, we recommend that future studies attempt to replicate current findings using attachment interviews and other behaviorally indicated assessment techniques (e.g., script assessment; Waters et al. 1998). In addition, the sample size was relatively small for a candidate gene study, and effects were predictably small. Also, women were overrepresented in the genotyped sample. Finally, given the complexities inherent to three-way interactions, replication of these effects will be particularly important.

Current findings raise a number of important avenues for future research. Secure relational style represents just one possible context that elevates the likelihood of stress generation among *s*-carriers; future research should look at other moderators and mediators, including other forms of interpersonal problems and personality traits, such as neuroticism. We focused on generation of acute stressors, but it may also be informative to examine the interaction between genotype and security in predicting specific interpersonal behaviors (such as relational conflict, reassurance seeking, dependency, or hostility) that may ultimately accumulate into the generation of stressful events. Finally, further research should probe the idea the *s*-allele is a marker of reactivity to the social environment (Way and Taylor 2010), with potential to protect against negative outcomes. For example, while our findings provided support for the idea that under certain interpersonal conditions, the *s*-allele may predict reductions in negative outcomes (such as stress generation or depression), additional studies should clarify whether there are conditions where 5-HTTLPR genotype is predictive of changes in positive outcomes, such as well-being, relationship satisfaction, and academic and occupational success. Further research is needed to specify the different conditions that provoke a diversity of outcomes among 5-HTTLPR *s*-allele carriers.

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