Stress, relationship satisfaction, and health among African American women: Genetic moderation of effects

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Abstract
We examined whether romantic relationship satisfaction would serve as a link between early and later stressors which in turn would influence the Thyroid Function Index (TFI), an indicator of physiological stress response. Using the framework of genetic susceptibility theory combined with hypotheses derived from the vulnerability-stress-adaptation and stress-generation models, we tested whether the hypothesized mediational model would be conditioned by 5-HTTLPR genotype, with greater effects and stronger evidence of mediation among carriers of the “s” allele. In a sample of African American women in romantic relationships (n = 270), we found that 5-HTTLPR moderated each stage of the hypothesized mediational model in a “for better or for worse” manner. That is genetic polymorphisms function to exacerbate not only the detrimental impact of negative environments (i.e. “for worse effects”) but also the beneficial impact of positive environments (i.e. “for better effects”). The effect of early stress on relationship satisfaction was greater among carriers of the “short” allele than among those who did not carry the short allele, and was significantly different in both the “for better” and “for worse” direction. Likewise, the effect of relationship satisfaction on later stressors was moderated in a “for better” or “for worse” manner. Finally, impact on physiological stress, indexed using TFI level, indicated that the impact of later stressors on TFI level was greater in the presence of the short allele, and also followed a “for better” or “for worse” pattern. As expected, the proposed mediational model provided a better fit for “s” allele carriers.

Keywords
contextual stressors, romantic relationship satisfaction, 5-HTTLPR, Thyroid Dysfunction, genetic susceptibility model

Disciplines
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Contextual stresses have been hypothesized to have substantial impact on health outcomes (Chen & Miller, 2013). For example, economic pressure and perceived neighborhood disorder have been found to be associated with metabolic syndrome (Cutrona et al., 2014) and self-reported health (Ross & Mirowsky, 2001). Conversely, positive life events and supportive neighborhood networks may tend to counteract the impact of negative contextual stressors on well-being (Conger & Elder, 1994; Sampson & Graif, 2009). Further, numerous studies have also shown that relationship satisfaction is associated with metabolic syndrome (Whisman, Uebelacker, & Settles, 2010) and physical illness (Wickrama, Lorenz, Conger, & Elder, 1997).

Indeed, stressors external to the relationship, originating in economic, neighborhood, or other personal circumstances, may begin as individual stressors external to the relationship but become relationship stressors as they give rise to reductions in mutual support or increases in negative interactions within the dyad (Rauer et al., 2008). Studies have reported, for instance, that neighborhood crime and financial stress are associated with increased risk for negative interactions between spouses or romantic partners (Conger & Elder, 1994). Likewise, there is evidence that marital difficulties or reduced relationship satisfaction may increase chances of experiencing stressful events and economic pressure, moving house frequently, and altering working performance and lifestyles (Cacioppo et al., 2008; Karney & Bradbury, 1995).

Available research also suggests that links among stressors, relationship satisfaction, and physiological outcomes should be particularly pronounced for women. Specifically, Donoho, Crimmins, and Seeman (2013) reported that marital support was linked to reductions in two markers of inflammation, CRP and IL-6, in women but not men. Similarly, Melamed and colleagues (2004) found similar gendered effects when examining the link between contextual stressors and increased metabolic syndrome, with effects of distress greater for women than for men. Accordingly, those exposed to chronically elevated contextual stress due to negative stress processes may be at particular risk for both negative impact on relationships as well as long-term physiological effects. These considerations suggest that, among women, the effect of early stressors and physiological stress may be mediated by both relationship satisfaction and later stressors.

Unlike self-reported measures of general physical health, physiological manifestations of stress cannot be readily assessed using traditional survey methods. Therefore, some scholars (Bremner et al., 2012; Whisman et al., 2010) have attempted to incorporate biomarkers as indicators of physiological stress. One potential physiological response of interest is thyroid...
dysfunction, as indexed by Thyroid stimulating hormone (TSH) and free T4 (fT4). Thyroid dysfunction has been associated with various socioeconomic stressors (Knudsen et al., 2003; Tsatsoulis, 2006). Compared to other biomarkers, TSH and fT4 appear to be more sensitive as neuroendocrine indicators and are more common in women than men (Canaris et al., 2000; Bauer et al., 2014), and are related to depression, higher blood pressure, elevated cortisol, cardiovascular disease, and obesity (Fletcher & Weetman, 1998; Robin, McCain, & Elswick, 2012). TSH is secreted by the pituitary gland, and its function is to direct the thyroid gland to secrete thyroxine hormone. In turn, fT4 is a marker of the concentration of the free thyroxine produced by the thyroid gland. TSH secretion is stimulated by thyroid-releasing hormone (TRH), but is under negative feedback control by the amount of free thyroid hormone (fT4 and fT3) in circulation (Surks & Ocampo, 1996). Accordingly, higher levels of TSH are suggestive of low levels of free thyroid hormone. Aging and physiologic stress can reduce the circulating levels of thyroid hormone thus resulting in an increase of TSH (Bremner et al., 2012). Similarly, diseases of the thyroid such as autoimmune thyroiditis can decrease the release of T4 from the thyroid which also results in increased levels of TSH (Knudsen et al., 2003). Likewise, in response to inflammation, there can be increases in TSH and decreases in fT4. In addition, subclinical hypothyroidism is defined as an elevated TFI level and is associated with lipid abnormalities which may increase cardiovascular risk, and this may be a particular concern among older women (Kahaly, 2000; Robin, McCain, & Elswick, 2012). By combining TSH and fT4 to assess thyroid dysfunction it is possible to create an index of overall thyroid function (TFI) (Jostel, Ryder, & Shalet, 2009). In sum, TFI is a sensitive marker of physiological stress due to environmental sources and inflammation-related processes.

Complicating and enhancing our understanding of the way contextual stress may influence relationship satisfaction, and thyroid function, is the potential for contextual stress effects to be exacerbated or ameliorated by individual differences (see vulnerability-stress-adaptation model; Karney & Bradbury, 1995). In the past decade, a profusion of studies (Casi, Hairiri, Holmes, Uber, & Moffitt, 2010) have focused on gene-by-environment interactions (GxE), and have been incorporated into the social sciences through a stress vulnerability perspective. This perspective suggests that genetic “vulnerabilities” help to amplify the effects of negative circumstances. Contrary to this, Belsky and Pluess (2009) articulated the genetic susceptibility perspective, which suggests that genetic polymorphisms amplify the impact of the environment in a “for better” and “for worse” manner. That is, according to the genetic susceptibility perspective, genetic polymorphisms function to exacerbate not only the detrimental impact of negative environments (i.e. “for worse effects”) but also the beneficial impact of positive environments (i.e. “for better effects”). Support for this approach is evident when the slopes for a gene by environment interaction show a crossover shape, with the susceptible group showing worse outcomes than the comparison group when the environment is negative but demonstrating better outcomes than the comparison group when the environment is positive.

The current investigation contrasts predictions from vulnerability and susceptibility frameworks with respect to variability in the promoter region of the serotonin transporter gene (SLC6A4), also referred to as the 5-HTT-linked polymorphic region (i.e., the 5-
HTTLPR, a key regulator of serotonergic neurotransmission. 5-HTTLPR is localized to 17p13 and consists of 14 exons and a single promoter. Variation in the promoter region of the gene, the 5-HTTLPR, results in two main variants, a short (s) and a long (l) allele that differ in the number of copies each has of a 22-bp repeat element. The s variant has 12 copies, and the l variant has 14 copies. Among African Americans, a non-negligible portion of the population carries an extra-long variant that has 16 copies. The s variant is associated with lower availability of 5-HTT and reduced efficiency of 5-HT reuptake, supporting its potential relevance for a range of serotonergic-linked outcomes such as depression and impulsive aggression (Carver, Johnson, & Joormann, 2008). The extra-long variant, however, is not associated with reduced expression (Vijayendran et al., 2012), suggesting that contrasting the response of those carrying one or more short alleles to all others is appropriate in an African American Sample.

There also is considerable evidence that genetic variation in the serotonin transporter is related to differential response to stress (Caspi et al., 2010; van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012; Lei et al., 2014). At the level of stress neurophysiology, the s allele appears to be associated with increased connectivity between the amygdala and other brain regions (Heinz et al., 2005). At the level of reactivity, the s allele is associated with amplification of response to verbal and nonverbal threats, and enhanced reactivity to punishment cues (Hariri, Drabant, & Weinberger, 2006). Finally, s allele carriers are disposed to rumination, directing preferential attention toward threat-related stimuli and disengaging from such stimuli with greater difficulty (Osinsky et al., 2008). Taken together, this literature is consistent with the proposition that s allele carriers are more hypervigilant and more reactive to stress, leading to greater potential impact of contextual stress on relationship satisfaction and stress response, and suggesting the value of a focus on this particular candidate gene.

In addition, there is evidence suggesting that the effects of relationship satisfaction on stressors and physiological stress might differ between s allele carriers and l allele carriers. Genetic variation in 5-HTT has been found to influence responses to marital interaction (Schoebi, Way, Karney, & Bradbury, 2012) in a “for better” and “for worse” manner. That is, the marital satisfaction of 5-HTTLPR s allele carriers demonstrated greater response to both positive and negative marital context. Likewise, Haase et al. (2013) found that the marital satisfaction of individuals who were 5-HTTLPR s allele carriers were more strongly and negatively influenced by the presence of negative emotion and more strongly positively affected by the presence of positive emotion. Taken together, then, there appear to be effects of stressors on relationship satisfaction, of relationship satisfaction on stressors, and of stressors on physiological stress, with the potential for these effects to be amplified by variation at 5-HTTLPR.

Combining the vulnerability-stress-adaptation (VSA) framework (Karney & Bradbury, 1995) with the genetic susceptibility perspective (Belsky & Pluess, 2009) leads to an expectation of greater effect of contextual stress on relationship satisfaction among “susceptible” individuals as well as greater effect of poorer relationship satisfaction on long term stressors. Similarly, one would anticipate a greater effect of contextual stressors on physiological stress among susceptible individuals. On the other hand, stress generation
(Hammen, 2006) and stress propagation models (Joiner, 2000), suggest that effects of contextual stress on the accumulation of interpersonal stress may cascade, with the impact of contextual stress on relationship satisfaction conferring risk for long term physiological stress particularly among those who are more genetically susceptible to environmental influences. That is, interpersonal stressors may be particularly important in the stress accumulation process because they have the potential to be a more substantial source of lasting stress than non-interpersonal stressors (Frans et al., 2005). These considerations lead to the proposed model to be tested which is illustrated in Figure 1.

Figure 1 suggests that genetic variation at 5-HTTLPR may influence susceptibility to each of three key stages. If the effects follow a susceptibility pattern at each stage, those persons most vulnerable to relatively adverse contexts will also be more susceptible to the benefits of relatively more benign contexts, demonstrating a for better and for worse response. We hypothesize in stage 1 of Figure 1 that contextual stress will affect relationship satisfaction, and do so more strongly for s allele carriers. In stage 2, we hypothesize that relationship satisfaction will influence later assessments of contextual stress, and that this will be a more potent influence for individuals with the 5-HTTLPR s allele. In stage 3 of Figure 1 we hypothesize that later perception of contextual stressors will influence physiological stress as measured by the TFI, and do so more strongly for carriers of the s allele. In addition, the model suggests that the relationship between early and later stressors may be mediated by romantic relationship satisfaction, but to a greater degree for those who are genetically susceptible than for those who are not. Further, we hypothesize that perception of later stressors mediates the association between relationship satisfaction and TFI, and does so to a greater degree for those who are genetically susceptible. In sum, the model guiding the current examination of contextual amplification combines the vulnerability-stress-adaptation with a genetic susceptibility perspective to predict that early stress/support will influence relationship satisfaction, which in turn will influence later stress/support, which will ultimately influence thyroid function as a physiological stress response. Each stage of this process is hypothesized to be amplified by the presence of the 5-HTTLPR s allele.

In the current study, we focus on a single ethnic group, African Americans, for several reasons. First, we avoid tendencies to pathologize that often characterize race comparative studies (see Bryant et al., 2010) in which difference becomes a proxy for deficiency, a danger that is particularly relevant in studies that include genetic variables. In addition, studies that search for genetic effects using multiple distinct ethnic groups have increased potential to find spurious and misleading genetic effects due to background variation in gene frequencies across ethnic groups, (e.g., finding the gene that predicts use of chopsticks, Hamer & Sirota, 2000). Because of known differences in allele frequencies at 5-HTTLPR across different racial groups, this is a particular concern. In addition, TFI levels differ across ethnic groups (Boucai & Surks, 2009), suggesting that analyses within racial group is appropriate for this outcome. Further, clinically elevated TFI is associated with increased mortality among African Americans but not among other racial groups (Rhee et al., 2013). Finally, because differences in discrimination may condition response to, and interpretation of, contextual stressors (Veroff, Douvan, & Hachett, 1995), assessments of chronic stressors may not be fully comparable across ethnic groups even when using similar items.
Accordingly, a focus on a single ethnic group seems appropriate for examination of genetic vulnerability and susceptibility models that may have implications for health effects and possible points of intervention for African American dyads.

**METHODS**

**Sample**

The current investigation utilizes data from five waves of the Family and Community Health Study (FACHS), a multisite (Georgia and Iowa) investigation of neighborhood and family processes that contribute to African American families’ vulnerability and resilience (see Cutrona et al., 2000). The first wave of the FACHS data was collected in 1997-1998 from 889 African American families, all of whom had an African American child in the fifth grade (411 boys and 478 girls; 467 from Iowa and 422 from Georgia) and their primary caregivers (PCs) (60 men and 829 women). Data were collected from the child’s primary caregiver, and secondary caregiver in homes in which they were present. The second, third, fourth, and fifth waves of data were collected from 1999 to 2000, 2001 to 2002, 2004 to 2005, and 2007-2008, respectively. Within the sample, PCs self-identified as single parents in 54.9% of cases. Of the 889 PCs interviewed at Wave 1, 693 were interviewed again at Wave 5 (77.26% of the original sample). As part of Wave 5 data collection, the PCs were asked to provide blood samples. Of the 693 participants, 489 PCs (71%) agreed to biomarker collection, and a blood sample was obtained from 472 cases. Successful genotyping for both 5-HTTLPR and TFI was achieved for 460 females (a call rate of 97.5%). Of these, 270 were African American women in marital relationships, with an average marital duration of 8 years, or cohabiting relationships (a minimum duration of 7 months) and so were included in the current analyses.

Comparison of those individuals excluded from the current analyses due to missing data with those retained in the analyses did not identify any significant differences with regard to age, education, poverty, contextual stress at Wave 1, or Wave 2 relationship satisfaction. At Wave 1, the resulting sample had a mean age of 36.27 years, $SD = 7.73$, 57% of the families lived below 150% of the poverty line, 42.2% had earned a GED or completed high school, 39.1% had some education beyond high school, and 18.7% had not completed high school.

**Materials and Procedures**

As described elsewhere (Cutrona et al. 2000), to enhance rapport and cultural understanding, African American university students and community members served as field researchers to collect data from the FACHS families in their homes. The protocol and all study procedures were approved by the University institutional review board. The instruments were presented on laptop computers, allowing participants to enter anonymous responses.

**Contextual stress**—We examined both negative and positive contexts as tests of the susceptibility model require using the full range of the naturally occurring social context, from favorable to adverse (Belsky & Pluess, 2009). The specific items included in the FACHS measure can be found in the Appendix 1. First of all, we examined two negative contexts related to neighborhood and economic circumstances. The *neighborhood disorder*
and crime scale consisted of 7 items (Sampson & Raudenbush, 1999). This scale asks the extent to which each of the respondent’s neighborhood: trash or broken glass on the streets, graffiti on walls, vacant buildings, drinking in public, people selling or using drugs, groups of people hanging out and causing trouble, and gang violence. Cronbach’s alpha was .88 at wave 1, .90 at wave 2, .91 at wave 3, .86 at wave 4, and .87 at wave 5. Four items assessed economic pressure (Conger & Elder, 1994); e.g. “During the past 12 months, my family has not had enough money to afford the kind of home we need?” Cronbach’s alpha was .81 at wave 1, .80 at wave 2, .88 at wave 3, .85 at wave 4, and .86 at wave 5. On the other hand, we assessed positive contexts using two components. First, two items assessed the neighborhood social network (Sampson & Graif, 2009) e.g., “How many friends do you have in your neighborhood?” These two items were correlated from waves 1 to 5 ($r > .22, p < .01$). Then, we also assessed positive life events using a 4-item scale (Conger & Elder, 1994). An example item is, “Did you have a positive change in your employment situation in the past 12 months?” Cronbach’s alpha was about .62 across waves. Confirmatory factor analysis of the four composite measures (two negative stressors and two positive stressors) used to assess a composite of measure of contextual stress produced factor loadings that were significant and in the expected direction, $\lambda > .4$ across waves (i.e., model fit for wave 1: Chi-square = 1.619, $df = 2$, CFI = 1, RMSEA = .000). We reverse coded the positive environment measures, and then each component of compound chronic stress/support was standardized, and the four components were summed to form an overall index of this construct. The composite measure has the advantage of ranging from very positive to very negative, thereby providing the type of environmental measure necessary in order to test differential susceptibility theory. Finally, we then averaged scores from waves 1 and 2 to form a composite measure of early contextual stress. Later contextual stress was measured by averaging waves 4 and 5 scores. Using Nunnally’s (1978) reliability formula for composite variables, the reliability for the overall index was more than .80.

**Romantic relationship satisfaction** was assessed using two items (Conger et al., 1990): “How happy are you, all things considered, with your relationship?” and, “All in all, how satisfied are you with your relationship?” Responses ranged from 1 (extremely unhappy/not at all satisfied) to 5 (extremely happy/completely satisfied). This scale has been used previously and has strong reliability and validity (see Bryant, Conger, & Meehan, 2001). Cronbach’s alpha was .88 at wave 2 and .91 at wave 3. Scores were averaged waves 2 and 3 to form a measure of romantic relationship satisfaction. The correlation between waves 2 and 3 was .463, $p < .001$.

**Genotyping**—During the last wave of interviews, phlebotomy was performed to provide biomaterial for DNA and sera for the study. DNA was prepared from the blood specimens using cold protein precipitation (Lahiri & Schnabel, 1993). Genotype at the 5-HTTLPR was determined for each sample as described previously (Bradley et al., 2005) using the primers F-GGCGTTGCCGCTCTGAATGC and R-GAGGGACTGAGCTGGACAACCAC, standard Taq polymerase and buffer, standard dNTPs with the addition of 100 μM 7-deaza GTP, and 10% DMSO. The resulting polymerase chain reaction products were electrophoresed on a 6% non-denaturing polyacrylamide gel, and products were visualized using silver staining. Two individuals blind to the study hypotheses and other information...
about the participants called the genotypes. Consistent with prior research (Beach et al., 2012), the current study used the dominant model. We treated the 5-HTTLPR as dichotomous variables where individuals received a score of 1 if they were carrying at least one copy of the short allele and a score of 0 if they were homozygous for the long allele. Among the 270 respondents, 5.9% were homozygous for the short allele (ss), 38.9% were heterozygous (st), and 55.2% were homozygous for the long allele (ll). Using the Hardy-Weinberg equilibrium test, the observed distribution of 5-HTTLPR did not differ significantly from that predicted on the basis of simple Mendelian inheritance.

**Thyroid function index (TFI)** was measured with two biomarkers of thyroid function at wave 5. They were determined by the University of Iowa Clinical Pathology Laboratories using a clinical protocol previously described (Philibert et al., 2011). Thyroid stimulating hormone (TSH) is a sensitive marker of thyroid function. The TSH normal range is 0.5-4.7 U/L and is well known to have a non-linear distribution. Therefore, all TSH was log transformed before analysis as per standard protocols (Forman-Hoffman & Philibert, 2006). Free thyroxine (fT4) is the metabolically active form of T4 and is a marker of the concentration of biologically active thyroid hormones. The fT4 normal range is 7.8-14.3 U/L (d’Herbomez, Jarrige, & Darte, 2005). The two markers were inversely and significantly correlated ($r = -.240, p < .001$). Finally, thyroid function index (TFI) was calculated by the equation described by Jostel, Ryder, and Shalet (2009): $\text{TFI} = \log \text{TSH} + 0.1345 \times \text{fT4}$. The normal reference range was $-2 \pm 2$ SD. In the current study, seven individuals were out of a range (observed range $-4.15$ to $3.30$).

**Control Variables:** Our analyses included controls for several individual characteristics including obesity (body mass index $\geq 30$ kg/m$^2$, Center for Disease Control and Prevention [CDC], 2011), high school graduate, age, family income below 150% of the poverty line, and marital status.

**Analytic Strategy**

We used multiple imputation techniques to estimate missing data at the item level for control variables to avoid loss of subjects. Rates of missing data ranged from 6.2% for education, to 13.6% for poverty level. We did not use imputed data for primary predictor and dependent variables (contextual stress, relationship satisfaction, TFI at Wave 5).

To contrast predictions from vulnerability and susceptibility hypotheses, hierarchical regression were run using Mplus 7.2 (Muthén & Muthén, 2012) statistical software to test for the main and interactive effects of stressors and genotypes on outcomes of interest. We included two models for each stage. Main-effects-only models were conducted first to identify significant main effects. In keeping with guidelines for susceptibility analyses (Belsky & Pluess, 2009), we analyzed predicted interaction effects in a second step regardless of whether there was a main effect for the genetic polymorphism.

All independent variables were standardized (mean of 0 and $SD$ of 1) before the interaction terms were calculated making the simple slope easier to test and interpret. When interaction effects were present, we examined simple slopes and followed-up with the Johnson-Neyman (J-N) technique (Roisman et al., 2012) to distinguish significant “for better” and “for worse”
effects. This procedure identifies regions of significance for interactions between continuous and categorical variables (e.g. *5-HTTLPR*).

Structural equation modelling was employed to test the hypothesized relationships depicted in Figure 1. We began by estimating a model that separated *s*-allele and *l*-allele carriers. Next, we examined the conditional indirect effect (Preacher, Rucker, & Hayes 2007; Model 5, p. 194) to determine whether the indirect effect of contextual stress on TFI level through relationship satisfaction varied as a function of *5-HTTLPR*. To allow simultaneous estimates of all effects, we used bootstrapping methods with 1000 resamples of the data and bias corrected and accelerated bootstrap CIs (95%) to adjust for any bias in the sampling distribution.

**RESULTS**

**Descriptive and association analysis**

The means, standard deviations, and zero order correlations among the study variables are presented in Table 1. The average age of women in the study sample at the first assessment was about 36 years. Among the 121 women carrying the *s* allele, 74.6% had completed high school or had earned a GED, 61.2% of the families lived below 150% of the poverty line, 64.5% were classified as obese, and 43% of respondents reported that they were married. Mean TFI levels were .332, *SD* = .823. Mean level of romantic relationship satisfaction was 7.314 (*SD* = 1.833), with a range from 2 to 10. Using independent *t*-tests, there were no mean differences between carriers of the *s* allele and *l* allele homozygotes on any of the variables. As expected, contextual stress, relationship satisfaction, and TFI level were significantly intercorrelated for *5-HTTLPR s* allele carriers, but there were no significant intercorrelations among them for *l* carriers.

**Gene-environment correlations**

Because gene-environment correlations (*rGE*) can confound assessment of gene-environment interactions (Caspi et al., 2010), we examined bivariate associations. No direct associations of genotype with outcomes in the current study reached nominal levels of significance, suggesting that potential confounding effects of *rGE* effect on relationship satisfaction, selection into adverse or positive environments, or effects on TFI level were minimal. A marginal correlation with obesity was noted.

**Amplification of the effect of early contextual stress effect on relationship satisfaction**

Regression analyses were used in Models 1a and 1b in Table 2 given that romantic relationship satisfaction is the outcome. We first checked for potential multicollinearity among variables. VIF scores ranged between 1.026 for the *5-HTTLPR* and 1.245 for contextual stress, and all measures of tolerance were above .75, suggesting that multicollinearity is not present. To examine the shape of the interaction effect of contextual stress with genotype on relationship satisfaction, we first regressed the relationship satisfaction score at Waves 2 and 3 for each participant on level of contextual stress (averaged across waves 1 and 2) and *5-HTTLPR* genotype (*s* allele carriers = 1; others = 0), as well as on the control variables obesity, age, education, and family poverty. We then
examined the moderating effect of variation at the 5-HTTLPR by entering the interaction of contextual stress and genotype in the second step of the regression. As can be seen in Table 2, the main effect for contextual stress was significant in Model 1a, \( b = -0.417, p < .001 \); the effect of genotype was not significant; and the interaction with presence of an s allele at the 5-HTTLPR was significant in Model 1b, \( b = -0.525, p = .016 \). Figure 2a depicts this interaction effect. As can be seen, s allele carriers showed, on average, a greater response to contextual stress. The significant interaction effect is the result of a steeper, and significant slope for the association of increasing contextual stress with decreasing relationship satisfaction among those carrying the s allele (\( b = -0.743, p < .001 \)), and a less steep slope among ll allele homozygotes (\( b = -0.218, p = .138 \)). In addition, there was a crossover pattern. This pattern suggests, consonant with the susceptibility perspective, the possibility of both “for better” and “for worse” effects calling for additional examination.

To compare vulnerability (i.e., “worse only”) to susceptibility (i.e., “for better and for worse”) models, post hoc analyses of interaction terms were conducted using the Johnson-Neyman (J-N) technique. As shown in Figure 2, indicating susceptibility, the results present a substantial region of significant difference in both the “for better” and “for worse” direction.

**Amplification of relationship satisfaction effect on late contextual stress**

Turning to stage 2 of the model, using contextual stress (averaged across waves 4 and 5) as the outcome, we again began by checking for multicollinearity. The VIF ranged from 1.018 to 1.212, and all measures of tolerance were above .80, indicating no multicollinearity. As can be seen in Model 2a of Table 2, the main effect of relationship satisfaction (averaged across waves 2 and 3) was significant (\( b = -0.336, p = .002 \)), whereas the 5-HTTLPR genotype was not. Model 2b added the multiplicative interaction term formed by multiplying relationship satisfaction by the 5-HTTLPR genotype. As hypothesized, the interaction was significant (\( b = -0.450, p = .040 \), partial \( R^2 = .014 \)). To interpret this result, we plotted the effect in Figure 2b for levels of relationship satisfaction ranging from 3 SD below to 3 SD above from the sample mean. Using a simple slope test with the J-N technique, the significant interaction effect is the result of a steeper, and significant slope for the association of increasing romantic relationship satisfaction with later decreasing contextual stress among those carrying the short allele (\( b = -0.579, p < .001 \)), and a less steep, non-significant slope among those with only the long allele (\( b = -0.129, \text{NS} \)). The cross-over results in s allele carriers being more likely than ll allele homozygotes to experience high levels of contextual stress following periods of low relationship satisfaction, whereas s allele carriers are less likely than ll homozygotes to experience high levels of contextual stress following periods of high relationship satisfaction. Thus, the graph for this interaction indicates a pattern virtually identical to those depicted in Figure 2a, indicating that the results present the expected cross over effect and provide strong support for the genetic susceptibility perspective.

**Amplification of the effect of late contextual stress on TFI**

For stage 3 of the model, we tested the effect of contextual stress (averaged across waves 4 and 5) on a level of TFI at wave 5. As an initial step in Models 3a and 3b in Table 2, a test
of multicollinearity was performed. The VIF ranged from 1.026 to 1.256, and all measures of tolerance were above .80, indicating no multicollinearity. To examine the shape of the interaction effect of genotype with contextual stress on a level of TFI, we first regressed TFI on contextual stress for each participant and 5-HTTLPR genotype (s allele carriers = 1), as well as the control variables of obesity, age and gender in step one. We then examined the moderating effect of variation at the 5-HTTLPR by entering the interaction of contextual stress and genotype in the second step of the regression. As can be seen in column 5 of Table 2, the main effect for contextual stress was not significant in step one, \( b = .090, p = .079 \); but the interaction with presence of an s allele at the 5-HTTLPR was significant in step two, \( b = .245, p = .014 \). Figure 2c explicates the interaction effect. As can be seen, the effect of contextual stress on TFI was significantly steeper for respondents with at least one short allele at 5-HTTLRP \( b = .239, p = .003 \) than it was for those with only long alleles \( b = -.006, p = .923 \). In addition, as before there was a crossover pattern (i.e., the pattern potentially indicative of susceptibility effects).

To clarify whether the cross over effect represented “susceptibility,” we again highlighted the 95% confidence bands using the J-N technique. The shaded area in Figure 2c shows a significant region of significant difference in both the “for better” and “for worse” direction. As can be seen, the 5-HTT s allele is associated with significantly greater TFI when the context is more negative (i.e., if contextual stress is greater than 1.034 SD above the mean for the sample), whereas the 5-HTT s allele is associated with significantly lower TFI when the context is more positive (i.e., contextual stress is greater than .804 SD below the mean for the sample).

**Conditional indirect effect of contextual stress on TFI**

Given the presence of significant moderation by the 5-HTTLPR genotype at each stage of the model, we examined whether the mediational component of the model presented in figure 1 would function differently for s-allele carriers compared to ll-allele homozygotes. As Figure 3a shows, for the s-allele carriers the association between contextual stress (averaged across waves 1 and 2) and relationship satisfaction (averaged across waves 2 and 3) was significant \( (\beta = -.359, p < .0001) \), the relationship between relationship satisfaction and contextual stress (averaged across waves 4 and 5) was significant \( (\beta = -.209, p = .009) \), and the association between relationship quality and a level of TFI at wave 5 was also significant \( (\beta = .218, p = .033) \). At the same time, the significant association between contextual stress (averaged across waves 1 and 2) and TFI \( (b = .173, p = .049) \) became non-significant when romantic relationship satisfaction (averaged across waves 2 and 3) and contextual stress (averaged across waves 4 and 5) were introduced as mediators \( (\beta = -.013, p = .909) \). Further, we used a bootstrapping technique with 1,000 replications to test the indirect effects of contextual stress and TFI. First, contextual stress (averaged across waves 1 and 2) had a significant indirect effect on contextual stress (averaged across waves 4 and 5) through relationship satisfaction (indirect effect = .073, 95% CI [.018, .165]). Second, the indirect effect of relationship satisfaction on TFI through contextual stress (averaged across waves 4 and 5) was also significant (indirect effect = −.020, 95% CI [−.056, −.003]) \(^1\). Finally, the indirect effect of contextual stress (averaged across waves 1 and 2) on TFI through both relationship satisfaction and contextual stress (averaged across waves 4 and 5)
was significant, with a 95% confidence interval between .001 and .023. Accordingly, among s-allele carriers romantic relationship satisfaction and later contextual stress mediated the impact of early contextual stress on TFI level at wave 5.

We also examined the indirect effect models among I-allele carriers; results are presented in Figure 3, Model B. For the II-allele homozygotes, there were no significant indirect effects of early stress through relationship satisfaction and/or later stress on TFI, precluding mediation. Further, using tests of conditional indirect effects, the results showed that there were no indirect effects of contextual stress (averaged across waves 1 and 2) on TFI through both relationship satisfaction and contextual stress (averaged across waves 4 and 5) for II-allele homozygotes (indirect effect = .000, 95% CI [−.008, .011], NS). However, such indirect effects were significant and stronger among respondents carrying at least one copy of the 5-HTTLPR s allele (indirect effect = .014, 95% CI [.003, .049]) and accounted for 11.6% of the total variance.

Supplementary analysis

First, it is possible that nonlinearity could be introduced if a more extreme range of values were examined (Roisman et al., 2012). Not shown in table 2, we repeated the analyses including a squared term for the main effect of contextual stress or relationship satisfaction as well as an interaction term using the squared term and genotype to examine potential non-linear effects, but the non-linear effects were found to be non-significant. Specifically, there was no significant effect of a quadratic term for contextual stress or relationship satisfaction, nor did the quadratic term interact significantly with the 5-HTTLPR genotype. Therefore, the previously significant G×E effects were not better explained by nonlinear associations in the data. Second, to insure robustness of effects, we repeated all analyses excluding the seven individuals with clinical evidence of thyroid disease and having a history of thyroid disease or on thyrotropic agents (e.g. levothyroxine). The results showed no change in the pattern of effects (see appendix 2). Finally, given that the analyses presented in table 2 and figure 3 focus upon the respondents who reported at waves 2 and 3 that they were involved in a romantic relationship, we re-estimated the models using full information maximum likelihood (FIML) and using all respondents who provided a blood sample. Appendix 3 showed a pattern of results very similar to those for subsamples (n = 270). Thus, the results do not appear to be the result of sample selection bias. Since these analyses did not produce changes in patterns of results they are not discussed in detail.

DISCUSSION

Evidence is accumulating that contextual stressors may be problematic, in part, because they set in motion changes in relationship satisfaction. In turn, these changes in romantic relationship satisfaction may influence later stressors and prompt physiological changes reflecting elevated chronic physiological stress. In the current investigation, the impact of contextual stress on relationship satisfaction was significantly greater for individuals who carried the widely studied risk/susceptibility variant of 5-HTTLPR, i.e., the s allele. When

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1Although not presented for the purpose of brevity, our results indicated that individuals with the 5-HTTLPR s allele show a heightened impact of relationship satisfaction on TFI level. Detailed results are available upon request.
portrayed graphically, the effect took the form of a significant crossover effect with substantial regions of observed cross-over in both the “for better” and “for worse” directions. Accordingly the results are conservatively described as being consistent with a differential “susceptibility” explanation. That is, the current study suggests that the s allele may be best characterized as a “plasticity” or “susceptibility” allele rather than a “vulnerability” allele when the focus is understanding the impact of contextual stress on romantic relationship satisfaction. Thus, replicating prior work, and as predicted by the susceptibility model, variability at 5-HTTLPR may increase susceptibility to environmental influences, increasing the impact of perception of contextual stressors on relationship outcomes.

Further, as predicted in the second stage of the proposed model, supporting hypothesized reciprocal influences between stress and relationship satisfaction, relationship dissatisfaction was also related to a shift toward perception of greater negative life stressors, but only among those with the s allele carriers. As for the first stage of the model, our results also provided evidence for a “for better” effect in which greater romantic relationship satisfaction led to significantly less perceived contextual stress among those with the 5-HTTLPR s allele. Indeed, the degree of amplification of positive and negative effects was relatively symmetrical, suggesting that there may be as much of a positive effect of relationship satisfaction on reduced stress as there is a negative effect of relationship dissatisfaction on increased stress, with the effect in both directions concentrated among carriers of the s allele.

We also found amplification for carriers of the s allele when we examined the third stage of the model, i.e., the impact of contextual stressors on greater physiological stress, as indexed by TFI. In the prediction of physiological stress, the s allele again acted as one would expect a “susceptibility” allele to behave. Those with s alleles had significantly higher TFI in the presence of negative contextual stressors. However, those with s alleles and more positive contexts had significantly lower TFI. Thus, both “for better” and “for worse” effects were supported at all three stages of the model. This suggests that individuals with the 5-HTTLPR s allele are more sensitive to the effects of both positive and negative social environments, with amplification of effects occurring at multiple stages.

Distinguishing between the genetic vulnerability and susceptibility perspectives is important as they suggest very different implications about those who carry the allele. Whereas the genetic vulnerability perspective paints individuals with the s allele as difficult to change for the better given their genetic tendency to be hyper-responsive to adversity, the genetic susceptibility perspective argues that carriers of the susceptibility allele are particularly good candidates for intervention and are more likely than others to learn the lessons being taught by a new, more favorable environment. Several recent studies have reported evidence indicating that the serotonin transporter gene interacts with the environment in the manner predicted by the differential susceptibility approach (Beach et al., 2012; Belsky & Pleuss, 2009).

Together, the current findings suggest that the effect of early contextual stressors on health-related outcomes may be mediated by effects on romantic relationship quality and later
stressors, with this effect substantially greater among s allele carriers. A large and consistent literature documents the association between chronic stress and poor health outcomes (Kahn & Pearlin, 2006; Steptoe et al., 2005), but relatively little work has elaborated the potential for this association to be accounted for by the effect of early contextual stress on relationship processes and relationship satisfaction, which may in turn both produce a greater effect on late contextual stressors and physiological response. The current research suggests the value of future efforts to change physiological stress and enhance health outcomes through interventions targeting relationship processes and contextual stress. However, the current results suggest that effects may be more pronounced for those who are more susceptible to the impact of environments.

In addition, the results suggest the value of continuing attention to the multiple connections between neighborhood, family, and biological levels of analysis and the need to examine multiple levels simultaneously. Given the potential for neighborhood context to influence intimate relationships as well as parenting relationships (Beach et al., 2012), and the potential for these interpersonal effects to become self-perpetuating, it would be useful for future investigations to examine whether targeted interventions can disrupt this effect, and whether such interventions are particularly helpful for those who are both susceptible by virtue of their genetic make-up and experiencing less satisfying romantic relationships. Although it is premature to limit intervention to those with s alleles (Brody et al., 2013), both because the nature of susceptibility is not yet well characterized, and because it may be that susceptibility will prove to be more normally distributed than it currently appears, it is nonetheless useful to treat genetic susceptibility as a window on the extent to which intervention may have different effects for some people, thereby expanding our conceptual models (Howe et al., 2010).

Several limitations and qualifications of the current research deserve consideration. First, given that the adults in the sample were selected because of their status as primary caregivers, virtually all of them were women. This precluded analyses to test for gender differences. However, there is certainly a need for studies that focus upon women given that women are at higher risk than men for having thyroid dysfunction (Bauer et al., 2014; Robin et al., 2012), for exposure to poverty (Starrels, Bould, & Nicholas, 1994), and the negative impact of neighborhood disorder (Peterson & Krivo 2010). Second, when the same models were examined using variation at DRD4 as the genetic moderator rather than the 5-HTTLPR, the interaction effect was not significant at any of the three stages of the model (see Appendix 4). Accordingly, not all previously identified susceptibility alleles are interchangeable in their effects, and they appear to work through different mechanisms and have different effects on attention and urgency of reward seeking during interaction, leading them to have different implications for amplification of the biological stress response. Third, there was loss of sample due to attrition and to nonparticipation in genotyping and the blood collection that was the basis of TFI assessment. This does not seem to have biased the sample, but may have produced unknown effects on the results. In addition, the time lags between assessments in the current investigation may not have been ideal for capturing some “for better” or “for worse” effects. These effects may be amplified when shorter lag times are used or through the use of genetically informed experimental designs (e.g. Howe, Beach,
& Brody, 2010); and future research should also focus on these possibilities. Fourth, the sample is all African American, raising the question of whether observed effects would generalize to other racial and ethnic groups. However, given that conceptually similar amplification effects have been reported in samples with a low percentage of African American couples (e.g., Schoebi et al., 2012), it seems possible that effects would generalize, suggesting that this deserves attention in future research.

The current pattern of results suggests that there may be multiple opportunities to interrupt the processes that result in heightened physiological stress and risk for negative health outcomes, with the potential for more substantial effects among some “susceptible” individuals. Although some chronic stressors may be inevitable, downstream effects on physiological stress may be substantially influenced by later contextual stress and relationship quality – outcomes which are potentially modifiable, particularly among “susceptible” individuals. If so, intervention to enhance relationship quality or to decrease contextual stress should interrupt the amplification of stress over time and interrupt the process that leads to changes in TFI. In either case, successful intervention should exert a greater beneficial effect on those with the s allele of SLC6A4, suggesting that there is a group for whom a focus on marital and cohabiting relationship quality may be particularly powerful in terms of its health effects. These findings have particular relevance for prevention because they indicate that those at greatest risk for some negative outcomes may also be those who will benefit the most from positive change in the social circumstances linked to those outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES


Figure 1.
Theoretical model linking contextual stress to relationship satisfaction and ultimately chronic stress response. The model indicates that presence of the 5-HTT $s$ allele is associated with greater stress generation at all three stages of the contextual amplification process.
Figure 2.
a. The effect of contextual stress (higher scores more negative) at Waves 1 and 2 on romantic relationship satisfaction (higher scores more positive) at Waves 2 and 3 moderated by *5-HTTLPR* (s allele carriers vs non-carriers). b. Examination of the differential impact of romantic relationship satisfaction at Waves 2 and 3 on contextual stress at Waves 4 and 5 as a function of *5-HTTLPR*. c. The effect of contextual stress at Waves 4 and 5 on thyroid function (higher scores more negative) moderated by *5-HTTLPR*. Note. Analysis uses Johnson-Neyman 95% confidence bands; gray areas are significant confidence regions. Numbers in parentheses refer to simple slopes with 95% confidence intervals. * $p \leq .05$. ** $p \leq .01$. 
**Figure 3.**
Indirect effect model of contextual stress on thyroid function as a chronic stress response through the stress generation process. The values presented are standardized parameter estimates; obesity, education, age, family poverty, and married are controlled in the analyses; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3; W4 = Wave 4; W5 = Wave 5. * \( p \leq .05 \)  ** \( p \leq .01 \).
Table 1
Correlations, Means, and Standard Deviations among Study Variables by 5-HTTLPR

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>1. Contextual stress (W1-W2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>.627**</td>
<td>-.085</td>
<td>-.015</td>
<td>.270**</td>
<td>.013</td>
<td>.366**</td>
<td>-.217**</td>
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<td>2. Romantic relationship satisfaction (W2-W3)</td>
<td>-.359**</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-.062</td>
<td>-.033</td>
<td>.086</td>
<td>-.027</td>
<td>.047</td>
<td>-.004</td>
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<td>3. Contextual stress (W4-W5)</td>
<td>.519**</td>
<td>—</td>
<td>-.368**</td>
<td>—</td>
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<td>—</td>
<td>-.007</td>
<td>.012</td>
<td>-.128</td>
<td>.059</td>
<td>.315**</td>
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<tr>
<td>4. Thyroid function index (W5)</td>
<td>.173*</td>
<td>-.210†</td>
<td>.275**</td>
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<td>—</td>
<td>—</td>
<td>.066</td>
<td>.054</td>
<td>-.075</td>
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<td>5. Obesity (BMI ≥ 30) at W5</td>
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<td>-.090</td>
<td>.114</td>
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<td>—</td>
<td>.152†</td>
<td>-.120</td>
<td>-.075</td>
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<td>6. Education &gt; high school</td>
<td>-.328**</td>
<td>.122</td>
<td>-.141</td>
<td>-.073</td>
<td>.071</td>
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<td>—</td>
<td>-.081</td>
<td>-.272**</td>
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<td>7. Age at the first assessment</td>
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<td>-.047</td>
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<td>-.063</td>
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<td>-.053</td>
<td>36.772</td>
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<td>8. Poverty 150% below limit</td>
<td>.302**</td>
<td>-.121</td>
<td>.155†</td>
<td>.014</td>
<td>-.167†</td>
<td>-.255**</td>
<td>-.152†</td>
<td>—</td>
<td>—</td>
<td>-.319**</td>
<td>.538</td>
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<td>9. Married</td>
<td>-.365**</td>
<td>.038</td>
<td>-.218**</td>
<td>-.082</td>
<td>-.088</td>
<td>.093</td>
<td>.142</td>
<td>-.290**</td>
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<thead>
<tr>
<th></th>
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<td>.056</td>
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<td>.430</td>
<td>.497</td>
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</table>

Note. Correlations for the long allele of the 5-HTTLPR (n = 149) displayed above the diagonal; correlations for the at least one copy of the short alleles of the 5-HTTLPR (n = 121) displayed below the diagonal; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3; W4 = Wave 4; W5 = Wave 5.

* p ≤ .05.
** p ≤ .01.
† p ≤ .10, two-tailed.
Table 2
Moderated Regression Analyses Examining 5-HTTLPR as a Moderator at Three Stages

<table>
<thead>
<tr>
<th></th>
<th>Stage 1: Romantic relationship satisfaction at W2 and W3</th>
<th>Stage 2: Contextual stress at W4 and W5</th>
<th>Stage 3: Thyroid function index at W5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1a (Unstandardized b [95% CI])</td>
<td>.246 [-.415, .908]</td>
<td>.238 [-.419, .894]</td>
<td>.249 [-.048, .545]</td>
</tr>
<tr>
<td>Model 1b (Unstandardized b [95% CI])</td>
<td>.239 [-.054, .532]</td>
<td>.239 [-.054, .532]</td>
<td>.239 [-.054, .532]</td>
</tr>
</tbody>
</table>

- **Intercept**:
  - Main effect:
    - Contextual stress (W1-W2): −.417** [−.650, −.184]
    - Romantic relationship satisfaction (W2-W3): .336** [−.551, −.121]
    - Contextual stress (W4-W5): .090† [−.010, .190]
  - 5-HTTLPR (1= ss, sl):
    - .278 [-.702, .146]
    - −.336** [−.551, −.121]
    - −.033 [−.467, .391]
    - −.014 [−.208, .180]
  - Two-way interaction:
    - 5-HTTLPR × Contextual stress (W1-W2): −.025 [−.951, −.100]
    - 5-HTTLPR × Romantic relationship satisfaction (W2-W3): −.450 [−.879, −.021]
    - 5-HTTLPR × Contextual stress (W4-W5): .245* [.050, .440]

<table>
<thead>
<tr>
<th>R² increase because of interaction</th>
<th>.020*</th>
</tr>
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</table>

Note. CI = confidence interval; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3; W4 = Wave 4; W5 = Wave 5. Obesity, education, age, family poverty, and married are controlled in the analyses. Age, married, contextual stress, and romantic relationship satisfaction are standardized by z-transformation (mean = 0 and SD = 1).

* p ≤ .05
** p ≤ .01
† p ≤ .10, two-tailed. n = 270.