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The Serotonin Transporter Promoter Variant, Stress, and Attentional Biases in Middle Childhood

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Abstract

Although evidence suggests that 5-HTTLPR variants may shape risk for depression, the influence is likely complex, and involves effects on endophenotypes. We examined associations between 5-HTTLPR and biases in attention to affective stimuli in a sample of girls and a sample of both boys and girls. Children with at least one short (S) variant of the 5-HTTLPR polymorphism had lower positive attentional bias scores in both samples. This association was qualified by an interaction with stress in one sample, such that links between the S allele and decreased positive attentional bias was significant only when life stress was elevated. This difference in findings between the two samples was explained by sex differences in samples; the GXE interaction was significant only in boys. Findings are discussed in the context of sex differences in GXE.

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Keywords

serotonin transporter promoter; attentional biases; middle childhood

The promoter region of the serotonin transporter gene (5-HTTLPR) is one of the most studied and controversial polymorphisms in psychiatric genetics. Most studies have contrasted the influence of the long (L) allele, composed of 16 copies of a ~22 bp repeat unit, with that of the short (S) allele, consisting of 14 copies (for a review, see Hariri & Holmes, 2006), on such phenotypes as major depression and anxiety (Clarke, Flint, Attwood, & Munafo, 2010; Albert, Vahid-Ansari, & Luckhart, 2014). The S allele conveys diminished transcription, lower transporter levels, and reduced serotonin uptake, with putatively functional effects on neural circuits relevant to mood regulation (Hariri & Holmes, 2006). However, because psychiatric disorders are complex phenotypes that result from interactions between biological and environmental factors, attempting to identify specific gene variants associated with diagnostic constructs is challenging. Indeed, studies of associations between the 5-HTTLPR S allele and depression have yielded inconsistent findings (for a review, see Kiyohara & Yoshimasu, 2010). An alternative strategy to dissecting the genetic bases of disorder is to focus on intermediate phenotypes, or endophenotypes (Gottesman & Gould, 2003), fundamental characteristics that are more likely to have a parsimonious genetic basis than are psychiatric diagnoses.

Psychiatric genetics research has drawn from the vast literature on cognitive models of depression to identify relevant endophenotypes. These models (Beck, 1976; Teasdale, 1988) emphasize biases in information processing (e.g., attentional biases), beliefs about one's ability to influence outcomes, and attributions for events in conferring vulnerability to depression. Constructs drawn from information-processing models of depression may prove to be useful endophenotypes for several reasons. First, attentional biases in information processing are known to characterize depression (Mathews, Ridgeway, & Williamson, 1996; MacLeod, Mathews, & Tata, 1986; Mogg, Millar, & Bradley, 2000; Rinck & Becker, 2005). Specifically, researchers have documented attentional biases towards negative stimuli in depressed adults and youth (e.g., Hommer et al., 2014; Joormann, Talbot, & Gotlib, 2007; Lonigan & Vasey, 2009; Mathews et al., 1996; Rinck & Becker, 2005, although see also MacLeod et al., 1986; Mogg et al., 2000; Neshat-Doost et al., 2000). Other studies have found that depressed adults have decreased attention towards positive stimuli (e.g., Gotlib, McLachlan, & Katz, 1988). Thus, there are differences in attentional biases between depressed and nondepressed adults and youth, albeit with some inconsistencies in terms of the valence of the stimuli.

Given the role of serotonin in influencing attention (e.g., Wingen, Kuypers, Formisano, & Ramaekers, 2008), investigators have examined whether the 5-HTTLPR S variant is associated with biases in the processing of emotional stimuli (Antypa & Van der Does, 2010; Beevers, Wells, Ellis, & McGeary, 2009; Hariri & Holmes, 2006), which could be a mechanism or endophenotype by which 5-HTTLPR influences depression vulnerability. In fact, studies of adults have found associations between 5-HTTLPR polymorphisms and attention for emotional stimuli. Beevers et al. (2009) found that young adults with the S

variant of 5-HTTLPR had difficulty disengaging from positive and negative stimuli, and Kwang et al. (2010) replicated Fox, Ridgewell, and Ashwin's (2009) findings, documenting that adults with the L allele oriented their attention away from negative word stimuli. Importantly, however, research on the relation between 5-HTTLPR and attentional biases earlier in development is scant. While some studies of youth have found that the 5-HTTLPR S variant is associated with attentional biases towards negative emotional stimuli (e.g., Perez-Edgar et al., 2010; Thomason et al., 2010), others found that the S variant is associated with attention away from negative stimuli (Gibb, Benas, Grassia, & McGeary, 2009). Finally, one study found that, while attentional biases towards negative stimuli were associated with the S variant, the L variant was linked to biases favoring positive stimuli (Perez-Edgar et al., 2010).

The inconsistencies linking 5-HTTLPR to attentional biases may be due to the failure to account for environmental influences. Theorists have argued that the S allele is associated with increased susceptibility to environmental influences (Belsky & Pluess, 2009; Fox, Zougkou, Ridgewell, & Garner, 2011), suggesting that the association between 5-HTTLPR and attentional biases in information processing is stronger in the context of stressful life events. Indeed, a small literature supports this notion; studies of adults suggest that persons with at least one S variant of the 5-HTTLPR polymorphism show greater attentional biases towards negative stimuli in the context of stressful life events than do those who are homozygous for the L allele (e.g., Disner et al., 2013; Markus & Raedt, 2011; Osinsky, Lösch, Hennig, Alexander, & MacLeod, 2012). Only one study has addressed this question in youth: Gibb et al. (2011) found that children with the S allele whose mothers' speech samples were characterized by high criticism showed attentional avoidance of angry faces.

Thus, we know little about gene-environment interactions in shaping early attentional biases that have been linked to depression. In the present study, therefore, we examined main effects of 5-HTTLPR and stress, as well as their interaction, in predicting attentional biases to threat and positive stimuli in community-dwelling children. We predicted that children with at least one S allele of the 5-HTTLPR polymorphism would show attentional biases consistent with those that have been associated with depression; further, we expected that such biases would be heightened in the context of stress. We did not have a specific hypothesis regarding whether these biases would be evident for positive versus negative stimuli, given the mixed literature on this issue. In light of the importance of replication in this field, we tested models in two independent samples of children.

Method

Participants

Data were collected at two sites: XXXXXX University (XXXXXX) and XXXXXX University (XXXXXX), henceforth referred to as Sample 1 and Sample 2, respectively. As this was not a planned, two-site study, methods differ slightly across the samples as described below. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Sample 1—Participants were 191 girls ($M_{age} = 12.52$; $SD = 1.61$; Caucasians = 134, 70%; Hispanics = 8, 4%; Asian Americans = 13, 7%; African Americans = 10, 5%; biracial ethnicity = 24, 13%; missing ethnicity data = 2, 1%), without significant medical problems, who completed the dot-probe task (MacLeod et al., 1986). Girls performed in the above average range (Scaled Score $M = 14.34$; $SD = 2.26$) on the vocabulary section of the verbal subtest of the Wechsler Intelligence Scale for Children – 4th edition (Wechsler, 2003). Approximately one-fifth (20%) of families reported an income between \$50,000-\$100,000, 45% of families reported a family income greater than \$100,000, 14% of families reported a family income of less than \$50,000, and 21% of the sample was missing income data. Girls self-reported about depressive symptoms and stressful life events and provided buccal cells for genetic analyses. Approximately half of the girls had mothers who had experienced recurrent episodes of depression during their daughters' lifetime; the other half had mothers with no Axis I disorder. None of girls met criteria for a current or past DSM diagnoses.

Sample 2—Participants were 205 7-year-old boys and girls without significant psychological or medical problems, determined during telephone recruitment interviews; 156 of these children (56% girls; $M_{age} = 7.70$ years; $SD = 3.45$; Caucasians = 137; 88%; Asian Canadians = 4; 3%; biracial ethnicity = 11; 7%; missing ethnicity data = 4; 2%) provided buccal cells for genetic analyses and comprise the current sample. Children performed within the normal range ($M = 112.06$; $SD = 11.66$) on the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV; Dunn & Dunn, 2007). Approximately half (52.90%) of the families that participated reported a family income ranging from \$40,000-\$100,000, 27.10% of families reported a family income greater than \$100,000, 13.50% of families reported a family income of less than \$40,000, and 6.5% of the sample was missing family income data. This study design differed from Sample 1 in that data were drawn from two waves, the second of which occurred at child age 9, two years after the first wave ($N = 156$; $M_{age} = 9.90$ years; $SD = 3.51$). Participants who completed both waves did not differ from those who participated only in the baseline session in terms of proportion of boys participating, PPVT scores, depressive symptoms, or family income (all $ps > .19$).

Genetic Data

Sample 1—Saliva was collected using the Oragene Kit (DNA Genotek, Ottawa, Ontario, Canada); DNA extracted by this method is of high quality and allows for a high success rate of genotyping (Rylander-Rudqvist, Hakansson, Tybring, & Wolk, 2006). Oligonucleotide primers flanking the 5-HTT-linked polymorphic region (Heils et al., 1996) and corresponding to the nucleotide positions -1416 to -1397 of the 5-HTT gene 5'-flanking regulatory regions were used to generate 484-bp or 528-bp fragments. The polymerase chain reaction products were electrophoresed through 5% polyacrylamide gel (Acrylamide/bis-Acrylamide ratio 19:1) at 60 V for 60 min. There were three groups of girls based on 5-HTTLPR: S/S = 39 (20%), L/S = 93 (49%), and L/L = 59 (31%). This distribution is in Hardy-Weinberg equilibrium ($\chi^2(1, N = 191) = .05, p = .83$).

Sample 2—Buccal cells were collected for genetic analysis by rubbing the inside of each child participant's cheek with two swabs. The Qiagen DNA Micro Kit (Qiagen, Valencia, CA) was used to extract genomic DNA from buccal swab samples. Extracts were kept at

4 °C when being actively used for analysis, and were held at –80 °C for long-term storage. The extracted DNA was used to genotype subjects for the 5-HTTLPR polymorphisms. Polymerase chain reaction (PCR) was carried out using the Applied Biosystems thermal cycler Gene Amp 9700, and PCR products were separated on polyacrylamide gels, stained with ethidium bromide, and visualized and documented by a UV imaging system (Bio-Rad Labs, Richmond, CA). Genomic DNA was purified from buccal swab cellular extracts and stored according to manufacturer instructions (Qiagen). Following Chorbov et al. (2007), the primers used for amplification were 5'-GGCGTTGCCGCTCTGAATGC-3' (forward) and 5'-GAGGGACTGAGCTGGACAACCAC-3' (reverse). The PCR conditions used were: 5 min of initial denaturation at 94 °C followed by 30 cycles of 30 s of denaturation at 94 °C, 20 s annealing at 58 °C and 20 s of extension at 72 °C, and a final extension of 5 min at 72 °C. 5-HTTLPR distributions were: S/S = 30 (30%), L/S = 80 (51%), and L/L = 46 (19%); this distribution is in Hardy-Weinberg equilibrium ($\chi^2(1, N = 156) = 2.34, p = .13$).

Assessment of Attentional Biases

Sample 1—Brief film clips (6 minutes long) were used to induce a negative mood in girls before the dot-probe task, including one depicting children saying goodbye to their terminally ill mother and another one depicting an adolescent girl learning that her best friend has died. To determine change in mood following the mood induction procedure, participants were asked to rate their mood on a 5-point scale that was anchored in faces reflecting 1 = very sad, 2 = a little sad, 3 = neutral, 4 = a little happy, and 5 = very happy. Following the negative mood induction, girls' mood declined from a mean of 4.15 ($SD = .65$) to a mean of 2.83 ($SD = 1.05$); this difference was significant ($t(178) = 16.10, p < .001$; Cohen's $d = 1.52$). Change in mood was not significantly associated with any other study variables. A more detailed review of this procedure is described by Joormann et al. (2007).

The dot-probe task was administered immediately after the mood induction. A set of 20 faces, each expressing happy, angry, and neutral emotions, was selected from the MacArthur Network Face Stimuli Set 1 (<http://www.macbrain.org/faces/index.htm>) developed by the Research Network on Early Experience and Brain Development. An equal number of male and female faces that each had a neutral, happy, and angry expression, as well as an equal number of faces of different ethnicities were selected. Each of the 40 picture pairs (20 happy and 20 angry expressions paired with the neutral expression of the same actor) was presented twice, for a total of 80 trials, which were presented in a new, fully randomized order for each participant. Participants were told to detect a small dot as quickly as possible, that the dot could appear in the left or right position on the screen, and that their job was to respond as quickly as possible when they saw the dot by pressing the button labeled “left” on the keyboard in front of them if the dot appeared on the left side of the screen, and the button labeled “right” if the dot appeared on the right side.

Each trial started with a display of a white fixation cross in the middle of the screen for 1,000 ms., followed by a pair of pictures displaying the same person with a neutral and an emotional expression presented for 1,500 ms. Following the offset of the pictures, a small gray dot appeared in the center of the screen location (left or right) where one of the pictures had been, and it remained on the screen until the participant pressed one of two response

keys on the keyboard to indicate the position of the dot—on the left or the right side of the screen. Accuracy and latency of each response were recorded. The emotional stimulus faces (angry or happy) appeared in the right and the left positions with equal probability, with the matched neutral face of each pair appearing in the other position. The dot probe was also presented in both positions with equal probability.

Only response latencies from correct responses were analyzed (2.68% of all responses were excluded). To minimize the influence of outliers, reaction times that were less than 100 ms. were considered anticipation errors and subsequently excluded from the analyses. Similarly, reaction times that were greater than 1,000 ms. were excluded since they likely reflected lapses of concentration. Overall, the exclusion of these extreme reaction times also resulted in the deletion of .94 % of errorless responses. This method of removing extremely fast and slow trials is consistent with data cleaning procedures in published studies using the dot-probe paradigm with children (e.g., Dagleish et al., 2003; Heim-Dreger, Kohlmann, Eschenbeck, & Burkhart, 2006; Hunt, Keogh, & French, 2007; Joormann et al., 2007; Kimonis, Frick, Fazekas, & Loney, 2006).

Attentional bias scores were computed separately for each facial expression (happy and angry), using the following equation (Mogg, Bradley, & Williams, 1995): Attentional bias score (positive attentional bias scores indicated attention to happy faces; negative attentional bias scores indicated attention to angry faces) = $\frac{1}{2}[(RpLe - RpRe) + (LpRe - LpLe)]$, where R = right position, L = left position, p = probe, and e = emotional face. In this equation, RpLe corresponds to the mean latency when the probe is in the right position and the emotional face is in the left position, and so on. This equation calculates the “attention-capturing” quality of emotional faces by subtracting the mean probe detection times for probes appearing in the same position as the emotional face from the mean probe detection times for probes appearing in a different position from the emotional face. Positive values of this bias score indicate a shift of attention toward the spatial location of emotional faces relative to matched neutral faces, and negative values indicate a shift of attention away from the spatial location of emotional faces relative to matched neutral faces. Mean bias scores (milliseconds) for happy and angry face trials are presented in Table 1.

Sample 2—At ages 7 and 9, children completed a slightly different version of the dot-probe task from that described above. Four types of picture pairs (neutral-neutral, positive-neutral, and threat-neutral) were created using images (e.g., animals, scenes) taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997). Thus, in contrast to Sample 1, stimuli were emotionally valenced images rather than faces. The IAPS provides normative data for both the valence (i.e., pleasant versus unpleasant) and intensity of emotional arousal evoked by each image. Pleasant images (e.g., fireworks, ice cream) ranged from 6.39 to 8.33 on the valence dimension; they were rated as low to moderate in arousal and ranged from 3.06 to 7.11. Threat stimuli were those rated in the course of the IAPS validation procedures as both unpleasant (i.e., ranging from 2.33 to 4.39 on the valence dimension) and high in arousal (arousal ranging from 4.33 to 7.78) (e.g., a picture of a house on fire).

Presentation procedures in Sample 2 were similar to those described for Sample 1. On each trial, picture pairs were presented on the left- and right-hand sides of the screen against a black backdrop for 1200 ms., after which both images disappeared and one was replaced with a probe stimulus (a small white dot). Children were required to indicate the location of the probe via button press. The probe stimulus remained on the screen until children responded. The task consisted of three blocks of 60 trials (15 of each pairing type). New picture pairings were created for each of the three blocks so that no two images were paired on more than one trial. The probe location (left or right) was counterbalanced, and half of the neutral-valence trials were congruent (i.e., the probe was located at the same location as the emotional image) and half were incongruent (i.e., the probe was located at the same location as the neutral image). Trials within each block were presented in a fully randomized order for each participant. Blocks were separated by a one-minute break.

Data collected in Sample 2 were cleaned by removing RT data for trials in which children committed errors (2.89% of trials at time 1 and % at 5.14% time 2) and for correct trials in which children responded faster than 100 ms. or slower than 2000 ms. (1.27% of correct trials at time 1 and .76% of correct trials at time 2). Similar to the procedure used in Sample 1, traditional bias scores (MacLeod & Mathews, 1988) were calculated for positive and threatening stimuli valence, which reflect response time differences between congruent and incongruent trials, controlling for probe location. Mean bias scores (in milliseconds) at time 1 and time 2 for positive and threat trials are reported in Table 2.

Assessment of Depressive Symptoms

Given that depression has been found to be associated with attentional biases (e.g., Joormann et al., 2007), depressive symptoms assessed concurrently with the attentional bias scores were included as predictors in both samples.

Sample 1—Depressive symptoms were assessed using self-reports based on the short form of the Children's Depression Inventory (CDI; Kovacs; 1981). The mean of the CDI score is reported in Table 1 ($\alpha = .80$); this mean is consistent with results reported in other non-clinical samples of similar age (e.g., Cannon & Weems, 2006; DuBois, Felner, Bartels, & Silverman, 1995).

Sample 2—At age 9, children self-reported symptoms of depression using the Depression Self-Rating Scale (DSRS; Birlleson, 1981; $\alpha = .86$ in present sample). The mean score (see Table 2) was consistent with non-clinical samples (Asarnow & Carlson, 1985; Hayden, Klein, Durbin, & Olino, 2006).

Assessment of Stressful Life Events

Sample 1—Life Events Checklist (LEC; Johnson & McCutcheon, 1980) is a self-report measure of the frequency and severity of positive and negative life events. The LEC is a modification of the Life Event Record (LER; Coddington, 1972) containing 46 life events. The participants in the study were asked to indicate if the event was positive or negative and the degree to which the event was stressful or unpleasant on a 4-point scale. Severity (level of stress/unpleasantness) of negative life events scale (descriptive statistics are provided in

Table 1) from LEC was used in this study. As the events assessed by the LEC are viewed as likely independent, we do not report internal consistency for this measure, as is standard (Compas, 1987). Because a significant number of participants did not have the LEC data (37%; $n=71$), expectation maximization (EM) algorithm was run in SPSS22 to estimate the missing data. Similarly, due to high levels of skewness (3.76) and kurtosis (17.97), LEC severity was transformed by applying a Log_{10} transformation which reduced skewness to .01 and kurtosis to 1.05.

Sample 2—Child stress was assessed at age 9 using the Adolescent Life Events Questionnaire (ALEQ; Hankin & Abramson, 2002). This self-report assesses a broad range of life events (total of 70), including school problems, friendship, romantic difficulties, and family problems. The ALEQ was modified to be suitable for the younger children in the current sample (e.g., items such as “boyfriend/girlfriend broke up with you but you still want to go out with them” were dropped). The global composite was used in the present study ($\alpha = .93$; see descriptive data presented in Table 2).

Data Analyses

Similar regression models were tested in both samples. Specifically, outcome variables were positive and negative bias scores reflecting attentional biases towards positive and negative stimuli; predictors were 5-HTTLPR, stress, child depressive symptoms, and the interaction between 5-HTTLPR and stress. In Sample 2, dot-probe data were available from two different time points; thus, in order to investigate change over time, bias scores from age 7 were also included in models predicting attentional biases at age 9. To probe any significant GXE, Hayes and Matthes' (2009) guidelines (MODPROBE macro) were used to test regions of significance in two-way interactions according to the Johnson-Neyman technique (Johnson & Fay, 1950). This procedure uses the asymptotic variances, covariances, and other regression parameters to determine the upper and lower boundaries of the focal predictor variable at which groups representing a multi-level moderator differ significantly ($p < .05$) in terms of the outcome of interest. 5-HTTLPR genotype was the focal predictor variable and the moderator was child self-reported stress centered around zero (i.e., LEC severity scores in Sample 1 and ALEQ scores in Sample 2). Consistent with most other investigations of 5-HTTLPR (e.g., Gibb, McGeary, Beevers, & Miller 2006; Willeit et al., 2003), children with two L variants were compared to all other children (coded as s/s and l/s = 1, l/l = 0). Thus, testing regions of significance shows which levels of child self-reported stress are differentially associated with attentional biases for the two 5-HTTLPR groups. In both samples, analyses were repeated with Caucasian participants only; because these yielded virtually identical results, they are not described here but are available from the first author.

Results

Sample 1

Bivariate associations among the major study variables in Sample 1 are presented in Table 1. S allele carriers showed higher levels of negative attentional bias. Higher self-reported depressive symptoms were associated with greater severity of negative stressful life events, and were also unexpectedly positively associated with positive attentional bias scores.

Regressions (Table 3) predicting attentional biases towards angry faces indicated that girls with at least one 5-HTTLPR S allele had higher negative bias scores ($B = 10.31$; $p = .01$), reflecting greater attentional biases towards angry faces. This main effect was not qualified by a significant interaction with LEC severity of negative life events. There were no significant main effects of child self-reported stress or depressive symptoms on attentional biases towards angry faces.

In analyses predicting attentional biases towards happy faces (see Table 4), girls with at least one S allele tended to have lower positive bias scores ($B = -6.97$; $p = .08$). The main effect of 5-HTTLPR was not qualified by a significant interaction with LEC severity of negative life events. Self-reported depressive symptoms also positively predicted higher positive attentional bias scores ($B = 1.93$; $p = .02$). There was no significant main effect of self-reported stressful life events.

Sample 2

Bivariate associations between Sample 2 variables are presented in Table 2. S-allele carriers showed higher levels of threat bias scores at age 7 and lower levels of positive bias scores at age 9. Higher levels of child self-reported depressive symptoms at age 9 were associated with higher levels of stressful life events reported concurrently on the ALEQ, and lower positive attentional bias scores at age 9. Positive and threat attentional biases assessed at the two waves of data collection were not significantly correlated, consistent with extant literature (Schmukle, 2005; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014).

In the first regression, threat bias scores at age 9 were the outcome variable and threat bias scores at age 7, DSRS (child self-reported depressive symptoms) at age 9, 5-HTTLPR, ALEQ at age 9, and 5-HTTLPR $\times$ ALEQ age 9 were included as predictors. There were no significant main effects or interactions in this model (see Table 3).

In the regression (see Table 4) predicting age 9 positive bias scores, similar to Sample 1, children with at least one S variant of 5-HTTLPR had lower positive bias scores at age 9 ($B = -22.11$; $p = .04$). In addition, the 5-HTTLPR-ALEQ age 9 interaction was significant ($B = -1.10$; $p = .01$), indicating the presence of a GXE interaction. Thus, children with at least one S variant of 5-HTTLPR had lower positive bias scores at age 9 ($p = .04$) and this effect was qualified by a significant interaction with child self-reported level of stress ($p = .01$; see Figure 1). The effect of 5-HTTLPR on positive bias scores became significant at higher levels of child self-reported stress (ALEQ > 2.18 ; see Figure 1).

Sample 1 was composed solely of girls; given that a GXE predicting positive bias scores was not found in this sample, we conducted exploratory analyses to see whether the two-way interaction found in Sample 2 was qualified further by a three-way interaction with child sex, thus explaining the difference in findings across the two samples. Indeed, the interaction among sex, 5-HTTLPR, and ALEQ scores at age 9 was significant ($B = -1.91$; $p = .03$). To interpret this three-way interaction, the two-way interaction of 5-HTTLPR and stress was examined separately in boys (see Table 5; $n = 69$; $n_{\text{boys l/l}} = 23$; $n_{\text{boys s/l, s/s}} = 46$) and girls (see Table 5; $n = 87$; $n_{\text{girls l/l}} = 24$; $n_{\text{girls s/l, s/s}} = 63$). Whereas no significant main effects or interactions were found for girls (see Table 5 and Figure 3), boys with at least one S variant

of 5-HTTLPR had lower positive bias scores at age 9 at a strong trend level ($B = -34.19$; $p = .06$). This main effect was qualified by a significant interaction of 5-HTTLPR and ALEQ at age 9 ($B = -1.90$; $p = .01$), shown in Figure 2. The effect of 5-HTTLPR on boys' positive bias scores becomes significant at higher levels of self-reported stress ($ALEQ > .814$; see Figure 2).

Discussion

We examined the roles of the 5-HTTLPR, stress, and their interaction in predicting children's positive and negative attentional processing. Youth with at least one S variant of 5-HTTLPR had lower positive bias scores, consistent with literature implicating the serotonin transporter promoter polymorphism in shaping attentional biases (e.g., Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012; Perez-Edgar et al., 2010; Thomason et al., 2010). This finding was replicated across the two samples despite differences in stimuli and methods used in the two samples. It is important to note, however, that this main effect of the 5-HTTLPR on positive attentional biases was qualified by a significant interaction with stressful life events in one of our samples: S carriers in Sample 2 showed lower levels of positive attentional bias scores in the context of stressful life events. Further, this GXE appeared to operate only in boys; a three-way interaction of 5-HTTLPR, stressful life events, and sex indicated that only boys who were S carriers showed a significant reduction in positive attentional biases from age 7 to age 9. This is the first study to report an interaction of this kind for attentional biases in middle childhood.

The current study is not the first, however, to report sex differences in interactions between environmental stress and 5-HTTLPR (Aslund et al., 2009; Brummett et al., 2008; Sjöberg et al., 2006; Uddin, de los Santos, Bakshis, Cheng, & Aiello, 2011). For example, Sjöberg et al. (2006) found that, in a large sample of adolescents (16- to 19-year-olds), the S allele was related to increased depressive symptoms for females in the context of interpersonal stressful life events, but not for males. Similar findings were obtained by Brummett et al. (2008) in adults. Other investigators did not find significant interactions between 5-HTTLPR and the environment in predicting depressive symptoms in males (e.g., Aslund et al., 2009; Uddin et al., 2011). However, none of these studies investigated sex differences in how such an interaction might affect depression endophenotypes, such as attentional biases. While previous work has documented GXE in predicting attentional biases (e.g., Disner et al., 2013; Markus & Raedt, 2011; Osinsky et al., 2012), sex differences in GXE were not examined in these samples. Only one study has investigated similar questions in children using the dot-probe task: Gibb et al. (2011) found that 8-12-year-old children with at least one S allele showed attentional avoidance of angry faces in the context of maternal criticism, and tests of sex differences in GXE were not significant. It is important to note, however, that our methods differed in several respects from those used by Gibb et al. In particular, we used a self-report measure that assessed various stressful life events (e.g., school stress and stress associated with relationships with parents and peers) as opposed to focusing on a specific type of stressor, i.e., maternal criticism. Overall, it will be important in future work to examine whether the obtained interactions between 5-HTTLPR and stressful events are sex-specific in their impact on attentional biases.

In contrast to several previous studies (e.g., Perez-Edgar et al., 2010; Thomason et al., 2010), we found mixed support linking the S variant of 5-HTTLPR to negative bias scores; in Sample 1 only, the S variant was associated with negative bias scores, while no such effect was found in Sample 2 for age 9 threat bias scores (although there was a significant bivariate correlation between threat bias scores at age 7 and the 5-HTTLPR in this sample in a consistent direction). This could reflect differences in stimuli used between the two samples, if the 5-HTTLPR is more relevant to negative facial stimuli than to negative stimuli more broadly. Such a possibility is consistent with past work linking this variant to negative attention biases (e.g., Perez-Edgar et al., 2010; Thomason et al., 2010), in that these studies have used faces as stimuli.

Our study has numerous strengths, including the use of two community samples of children in middle childhood. Middle childhood is associated with increased interpersonal and self-regulatory demands (Angold, Costello, Erkanli, & Worthman, 1999; Lansford, Malone, Dodge, Pettit, & Bates, 2010; Turner & Cole, 1994), and precedes a time of marked increases in depressive symptoms (Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993); hence, this may be a time when associations between putative risk markers and depressive symptoms are more readily identified. Similarly, we used a well-validated task to assess attentional biases in both of our samples (i.e., the dot-probe task; McLeod, 1986). Further, the pattern of findings obtained showed some consistency despite different methods in the two studies; differences in the role of GXE in the two samples may be interpretable within the context of important sex differences in attentional biases in the context of stress.

Despite these strengths, this study also has several limitations. Measures of stress and depressive symptoms differed between the two studies; thus, differences in methodology may have influenced the pattern of findings between the two samples. Given the small samples for genetic studies, it will be important to replicate our findings in larger samples. Additionally, examining more diverse samples is needed, since both samples in the present study consisted of mainly affluent families with children in the average to high-average range of cognitive functioning, thus potentially limiting generalizability. The mood induction procedure was administered directly prior to the dot-probe in Sample 1 only; while a negative mood induction was used in Sample 2 (and shown to have been effective), this was prior to another task that preceded the dot-probe task, and its effects seemed unlikely to last throughout the dot-probe as well. However, recent research (e.g., Dozois, 2007) indicates that cognitive structures relevant to vulnerability to depression can be validly assessed in the absence of negative mood induction. Finally, we administered self-report measures of stress. In future studies it will be important to replicate our findings using interview-based measures of stress that would also allow researchers to distinguish among different types of stress.

In conclusion, we found evidence for a conditional GXE depending on child sex, suggesting that, for male S carriers, attentional biases implicated in depression increase as a result of heightened stress. These findings suggest that future studies of GXE in depression should attend to sex differences; such analyses have the potential to contribute greater precision to our understanding of which individuals are most likely to experience adverse consequences in the context of negative life events.

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Highlights

- Associations between 5-HTTLPR and attentional biases were examined
- Analyses were performed in a sample of girls and a sample of both boys and girls
- S variant of the 5-HTTLPR was associated with lower positive attentional bias scores
- This link was significant only when life stress was elevated
- This GXE interaction was significant only in boys

5-HTTLPR x Child Stress Predicting Positive Bias Scores

Figure 1.

5-HTTLPR interacting with child self-reported levels of stress at age 9 predicting change in positive bias scores from age 7 to age 9 (full Sample 2); the dotted line represents the region of significance, i.e., at the level of stress that is higher than 2.18 on the ALEQ (centered around zero), the S allele carriers experience a significant decline in their positive bias scores from age 7 to age 9

5-HTTLPR x Child Self-Reported Stress Predicting Positive Bias Scores at Age 9 (Boys Only)

Figure 2.

5-HTTLPR interacting with child self-reported levels of stress at age 9 predicting change in positive bias scores from age 7 to age 9 (boys only Sample 2); the dotted line represents the region of significance, i.e., at the level of stress that is higher than .81 on the ALEQ (centered around zero), boys who are S allele carriers experience a significant decline in their positive bias scores from age 7 to age 9

5-HTTLPR x Child Self-Reported Stress Predicting Postive Bias Scores at Age 9 (Girls Only)

Figure 3.

5-HTTLPR interacting with child self-reported levels of stress at age 9 predicting change in positive bias scores from age 7 to age 9 (girls only Sample 2); this interaction is not significant

Table 1
Bivariate Correlations between Variable and Their Means and Standard Deviations in Sample 1

	5-HTTLPR	LEC Severity	CDI	PosBias	NegBias	Mood Change
5-HTTLPR	--	-.08	.08	-.09	.20**	-.03
LEC Severity		--	.26**	.03	-.02	.04
CDI			--	.17*	.04	.13
PosBias				--	-.10	.04
<i>M</i>		8.00	1.97	4.21	-1.87	-1.30
<i>SD</i>		10.12	2.55	25.70	26.13	1.09

Note.

5-HTTLPR coded as s/s and l/s = 1, l/l = 0; NegBias = attentional bias towards sad faces; PosBias = attentional bias towards happy faces; LEC Severity = Negative Life Events Severity scale from the Life Event Checklist; CDI = Children's Depression Inventory total score; Mood Change = change in girls' mood after the negative mood induction

* $p < .05$,

** $p < .01$;

Table 2
Bivariate Associations between Variables and Their Means and Standard Deviations in Sample 2

	5-HTTLPR	ALEQ	DSRS	Pos.Bias1	Pos.Bias2	ThreatBias1	ThreatBias2	Sex
5-HTTLPR	--	-0.1	0.11	-0.05	-0.15 [†]	0.14 [†]	-0.02	-0.06
ALEQ		--	0.44 ^{**}	-0.12	-0.24 ^{**}	0.06	-0.02	0.03
DSRS			--	-0.02	-0.20 [*]	0.18 [*]	0.07	0.10
Pos.Bias1				--	-0.09	0.09	-0.05	-0.03
Pos.Bias2					--	-0.10	-0.08	-0.06
ThreatBias1						--	0.11	-0.09
ThreatBias2							--	0.04
Sex								
<i>M</i>		33.24	14.72	8.92	0.92	15.24	3.22	
<i>SD</i>		23.62	7.37	62.86	59.58	72.53	52.28	

Note.

5-HTTLPR coded as s/s and l/s = 1, l/l = 0; ALEQ = Adolescent Life Events Questionnaire at age 9; DSRS= Depression Self-Rating Scale at age 9; Pos.Bias1 and Pos.Bias2 = dot-probe positive bias score at ages 7 and 9; ThreatBias1 and ThreatBias2 = dot-probe threat bias score at ages 7 and 9; sex – child sex coded as 1 = boy; 0 = girl

* *p* .05,

** *p* .01,

[†].10 < *p*;

Table 3
Regression Analyses Predicting Negative Bias Scores in Samples 1 and 2

Sample 1:				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
CDI	.29	.81	.36	.72
5-HTTLPR	10.31	4.05	2.56	.01
LEC Severity	.77	8.55	.09	.93
5-HTTLPR $\times$ LEC Severity	-2.50	10.50	-.24	.81
Sample 2:				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
ThreatBias1	.08	.06	1.21	.23
DSRS	.48	.70	.69	.49
5-HTTLPR	-3.52	9.99	-.35	.73
ALEQ	-.28	.29	-.97	.33
5-HTTLPR $\times$ ALEQ	.28	.39	.71	.48

Note. 5-HTTLPR coded as s/s and l/s = 1, l/l = 0; LEC Severity = Negative Life Events Severity scale from the Life Event Checklist; CDI = Children's Depression Inventory total score; ALEQ = Adolescent Life Events Questionnaire at age 9; DSRS= Depression Self-Rating Scale; Pos.Bias1 and Pos.Bias2 = dot-probe positive bias score at ages 7 and 9; ThreatBias1 and ThreatBias2 = dot-probe threat bias score at ages 7 and 9

Table 4
Regression Analyses Predicting Positive Bias Scores in Samples 1 and 2

Sample 1:				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
CDI	1.93	.81	2.40	.02
5-HTTLPR	−6.97	4.01	−1.74	.08
LEC Severity	−7.20	8.48	−.85	.40
5-HTTLPR × LEC Severity	11.50	10.42	1.10	.27
Sample 2:				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Pos.Bias1	−.10	.08	−1.26	.21
DSRS	−.50	.75	−.67	.50
5-HTTLPR	−22.11	10.75	−2.06	.04
ALEQ	−.03	.32	−.11	.92
5-HTTLPR × ALEQ	−1.10	.42	−2.59	.01

Note. 5-HTTLPR coded as s/s and l/s = 1, l/l = 0; LEC Severity = Negative Life Events Severity scale from the Life Event Checklist; CDI = Children's Depression Inventory total score; ALEQ = Adolescent Life Events Questionnaire at age 9; DSRS= Depression Self-Rating Scale; Pos.Bias1 and Pos.Bias2 = dot-probe positive bias score at ages 7 and 9; ThreatBias1 and ThreatBias2 = dot-probe threat bias score at ages 7 and 9

Table 5
Regression Analyses Predicting Positive Bias Scores in Sample 2: Examining the
interaction between 5-HTTLPR and Child Self-Reported Stress in Boys and Girls

Sample 2: 3-way interaction				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Pos.Bias1	-.05	.08	-.62	.54
DSRS	-.51	.74	-.69	.49
Sex	11.06	17.47	.63	.53
5-HTTLPR	-7.47	14.71	-.51	.61
ALEQ	.08	.38	.20	.84
5-HTTLPR × ALEQ	.02	.57	.03	.99
5-HTTLPR × Sex	-26.80	20.85	-1.29	.20
ALEQ × Sex	-.16	.63	-.25	.80
5-HTTLPR × ALEQ × Sex	-1.91	.84	-2.28	.03
Sample 2: Boys				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Pos.Bias1	-.06	.15	-.37	.72
DSRS	-.52	1.18	-.44	.66
5-HTTLPR	-34.19	17.82	-1.92	.06
ALEQ	-.08	.63	-.12	.90
5-HTTLPR × ALEQ	-1.90	.73	-2.61	.01
Sample 2: Girls				
Predictors:	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Pos.Bias1	-.04	.08	-.52	.61
DSRS	-.52	.94	-.55	.59
5-HTTLPR	-7.34	12.62	-.58	.56
ALEQ	.08	.33	.25	.80
5-HTTLPR × ALEQ	.01	.49	.03	.98

Note. 5-HTTLPR coded as s/s and l/s = 1, l/l = 0; ALEQ = Adolescent Life Events Questionnaire at age 9; DSRS= Depression Self-Rating Scale; Pos.Bias1 and Pos.Bias2 = dot-probe positive bias score at ages 7 and 9; ThreatBias1 and ThreatBias2 = dot probe threat bias score at ages 7 and 9; 0 = girls; 1 = boys