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Stressful Life Events Moderate the Relationship Between Genes and Biased Attention to Emotional Faces in Youth

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Abstract

Attention bias to emotion may be an intermediate trait for stress-reactive psychopathology associated with biologically plausible candidate genes, yet the precise direction of effects within the youth literature remains unclear. The present study investigated whether stressful life events (SLEs) moderate the link between genetic risk (5-HTTLPR and *COMT*) and attention bias to emotion among youth ($N = 467$). Analyses revealed a differential effect of gene. Among youth who had experienced more recent SLEs, those homozygous for the low expressing allele of 5-HTTLPR (S/S) demonstrated preferential attention toward negative emotional expressions, whereas youth homozygous for the high expressing *COMT* genotype (Val/Val) showed attentional avoidance of positive facial expressions. No interaction between 5-HTTLPR and *COMT* was found. These findings highlight the importance of investigating stress as a moderator within the intermediate trait literature and suggest that biologically plausible candidate genes may have a differential effect in the pathway to psychological disorders.

Keywords

intermediate trait, emotion processing biases, genetics, stress, youth

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Investigating the role of specific, biologically plausible candidate genes in the development of stress-reactive emotional disorders, such as anxiety and depression, is an important step to advance the understanding of both etiology and possible mechanisms of intervention. However, research has had little success in identifying a direct link between candidate genes and stress-reactive psychopathology, most likely due to the complex etiology of disorders (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Intermediate traits are thought to be more proximal to disorder (Gottesman & Gould, 2003) and part of developmental pathways to disorder initiated by candidate genes (Caspi et al., 2010; Gibb, Beevers, & McGeary, 2013). Biased processing of emotional information has been identified as a possible intermediate trait for both depression (Gibb, Benas, Grassia, & McGeary, 2009; Hasler, Drevets, Manji, & Charney, 2004) and anxiety (Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012) within the context of a measured genetic risk (e.g., serotonin-transporter-linked polymorphic region, or 5-HTTLPR). However, research findings have been mixed, with some studies showing individuals at high genetic risk to display preferential attention toward both positive and negative emotions (e.g., Beevers, Wells, Ellis, & McGeary, 2009) and other studies finding preferential attention specifically for negative emotion (e.g., Perez-Edgar et al., 2010). Given mixed findings within the literature, investigating the role of moderators associated with psychopathology onset and gene expression, such as environmental stress (e.g., Chaouloff, Berton, & Mormède, 1999; Grover, Ginsburg, & Ialongo, 2005), is an important next step. Therefore, the present study aimed to clarify the relationship between biologically plausible candidate

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genes and biased processing of emotional faces by examining the role of stressful life events (SLEs) as a possible moderator (i.e., G×E).

Attention bias to emotion

Cognitive theories of stress-reactive psychopathology posit that information processing of socially imbued affective cues, such as emotional facial expressions, may contribute to the development, maintenance, and recurrence of depression (Beck, 2008; Gotlib & Krasnoperova, 1998) and anxiety (MacLeod, Campbell, Rutherford, & Wilson, 2004). Indeed, there is a large body of studies with adults demonstrating that currently depressed and anxious adults exhibit an attention and memory bias for negative material (see Mathews & MacLeod, 2005, for a review). In addition, there is evidence supporting cognitive theories of anxiety and depression among youth (Hankin, Snyder, & Gulley, 2013). The dot-probe task is frequently used to measure aspects of cognitive mechanisms that are thought to function outside of one's awareness (e.g., encoding, attention) as this task is considered to be less susceptible to reporting biases as compared with self-report measures (Gotlib & Neubauer, 2000). Attentional bias for negatively valenced material has been observed among adults and youth diagnosed with stress-reactive clinical disorders and symptomatology. Within the depression and anxiety literature, it is theorized that attention biases to emotion demonstrate specificity related to symptom and etiologically based factors associated with each disorder, such as sadness and loss or threat and fear among depressed and anxious individuals, respectively. Research has generally supported attention bias specificity within disorder. Specifically, attention bias to sad emotional stimuli is found among adults experiencing depression or dysphoria (Beevers & Carver, 2003; Gotlib et al., 2004; Joormann & Gotlib, 2007) or who have a history of remitted depression (Joormann & Gotlib, 2007). In addition, two studies have found attentional bias for sad emotional faces in youth at-risk for depression (e.g., offspring of depressed mothers; Gibb et al., 2009; Joormann, Talbot, & Gotlib, 2007) as well as currently depressed youth (Hankin, Gibb, Abela, & Flory, 2010). Similar evidence has demonstrated attention bias for negative emotional material, specifically threat-related emotional stimuli, in anxious adults (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007) and youth (Hankin, Gibb, et al., 2010). Given the strong evidence that attentional bias for negative emotional material is linked to depression and anxiety in adults and youth, it is important to understand the underlying mechanisms, such as genetic risk factors, associated with attention bias.

Genetic risk and attention bias to emotion

It is important to consider the appropriate genetic methodology to examine attention bias to emotion as a possible intermediate trait. There are two typical approaches, including the theory-free examination of numerous single-nucleotide polymorphisms (SNPs) used in genomewide association studies (GWAS) and a theory-based selection of candidate genes approach. A major disadvantage of a theory-free GWAS approach includes the need for sample sizes that often prohibit the careful measurement of the phenotype examined. Alternatively, thoughtful selection of only a few genes theorized to be associated with a specific, carefully measured intermediate trait (i.e., attention bias to emotion) helps to minimize the possibility of Type I errors that can arise when conducting a number of statistical tests among a large data set of genes (Moffitt, Caspi, & Rutter, 2006; Van den Oord & Sullivan, 2003). Accordingly, for the present study we chose to examine whether two biologically plausible candidate genes, 5-HTTLPR and catechol-O-methyltransferase (*COMT*) gene, were associated with attention bias to emotion.

5-HTTLPR. 5-HTTLPR has been one of the most studied genes associated with risk for depression within the context of gene by environment interactions (G×E; e.g., Caspi et al., 2003; Hankin, Jenness, Abela, & Smolen, 2011; Jenness, Hankin, Abela, Young, & Smolen, 2011; see meta-analysis by Karg, Burmeister, Shedden, & Sen, 2011), anxiety-related personality traits (Lesch et al., 1996; Sen, Burmeister, & Ghosh, 2004), and attention biases to negative emotion among psychologically healthy individuals (Pergamin-Hight et al., 2012). The serotonin transporter (5-HTT) is a protein critical to the regulation of serotonin function in the brain because it terminates the action of serotonin in the synapse via reuptake. This is a well-studied gene that has a functional number of tandem repeats (VNTR) polymorphism (5-HTTLPR) in the promoter region. The most common variants of 5-HTTLPR are the long allele (L), consisting of 16 copies of an approximately 22 base pair (bp) repeat unit, and a short allele (S), composed of 14 copies (for a review, see Hariri & Holmes, 2006). The decreased transcriptional efficiency associated with the S allele results in approximately 50% less serotonin being recaptured in the presynaptic neuron when compared with the L allele (Lesch et al., 1996).

Research with adults has suggested that 5-HTTLPR may be a biological marker for the biased processing of emotional stimuli (Beevers et al., 2009; Beevers, Gibb, McGeary, & Miller, 2007). For example, variations in 5-HTTLPR expression appear to affect neural circuits associated with the processing of negatively valenced

emotional stimuli with adults (Canli et al., 2005; Hariri et al., 2002; Hariri et al., 2005; Heinz et al., 2004; Heinz et al., 2007; Pezawas et al., 2005). These studies demonstrated that S carriers have greater amygdala activation and reduced functional communication between the prefrontal cortex (PFC) and limbic system when viewing negatively valenced pictures (Heinz et al., 2004), processing negative words (Canli et al., 2005) or undefined task conditions (Heinz et al., 2007) and matching fearful and angry faces (Hariri et al., 2002; Hariri et al., 2005; Pezawas et al., 2005). In sum, 5-HTTLPR has been linked with dysfunctional neural processing of negative emotional information when utilizing diverse measurement types, suggesting that it could serve as a promising candidate gene of interest related to the biased attention to negative emotional stimuli.

More recently, researchers have begun to investigate how variants of 5-HTTLPR impact attention to emotional cues behaviorally with adults. However, findings have been mixed. Some studies show that both psychiatric inpatients (Beevers et al., 2007) and healthy adults (Beevers et al., 2011; Beevers, Pacheco, Clasen, McGeary, & Schnyer, 2010; Beevers et al., 2009) possessing one or two copies of the S allele allocated more attentional resources broadly to any type of emotional face (e.g., happy, sad, or fearful vs. neutral) as compared to those homozygous for the L allele. In contrast, a recent meta-analysis found that those homozygous for the S allele showed an attention bias specifically to negative stimuli (e.g., sad, fearful, or threatening valenced faces, words, or pictures; Pergamin-Hight et al., 2012). Although, this meta-analysis suggests that 5-HTTLPR is a biological marker specifically for biased processing of negative emotional stimuli, questions remain regarding the finding from several studies showing a broader bias to both positive and negative emotional stimuli.

COMT. In addition to 5-HTTLPR, the present study sought to provide an examination of the associations between attention biases to emotional stimuli and the *COMT* gene, which is associated with dopamine and norepinephrine neurotransmission (Opmeer, Kortekaas, & Aleman, 2010). Depression and anxiety are associated with disturbances in monoamine (serotonin, dopamine, norepinephrine) neurotransmission (Ressler & Nemeroff, 2000; Ruhé, Mason, & Schene, 2007). Dopamine has also been shown to play a role in neural functioning associated with reward processing (Wise, 2002), and dysfunctions in reward neural circuitry have been indicated in adolescent depression (Forbes & Dahl, 2012). However, there have been mixed findings when directly examining the relationship between depression and anxiety and *COMT* with some studies finding no association and others finding a relationship between *COMT* and depression (see Antypa, Drago, & Serretti, 2013, for a review) and anxiety (e.g., Ohara, Nagai, Suzuki, Ochiai, & Ohara, 1998; Olsson et al., 2005). Therefore, similar to 5-HTTLPR, it has been suggested that *COMT* may be more closely associated with basic and homogenous processes related to depression and anxiety, such as attention and other cognitive processes (e.g., Mier, Kirsch, & Meyer-Lindenberg, 2009).

The majority of studies examining the influence of *COMT* have focused on the Val108/158Met polymorphism, which is involved in catabolizing dopamine and norepinephrine. Val homozygotes catabolize dopamine at up to four times the rate of *COMT* Met carriers, which leads to Val homozygotes performing worse on tasks that involve PFC function (Camara et al., 2010; Egan et al., 2001). However, a meta-analysis examining brain imaging data found differential neural activation across *COMT* variants with Val allele carriers showing impaired performance in cognitive paradigms (i.e., encoding and memory), whereas Met allele carriers had less efficient processing during emotionally valenced tasks (i.e., viewing valenced pictures; Mier et al., 2009). As proposed by Mier and colleagues (2009), these findings suggest that *COMT* variants' relationship with PFC functioning may demonstrate an inverted U-shaped curve with either extreme in dopamine and norepinephrine levels conferring risk for inefficient neural processing of information. Although important for our overall understanding of how *COMT* function impacts neural processing of information, none of the studies included in this meta-analysis examined the association between *COMT* variants and tasks measuring attention biases to emotional faces, which is a task that involves cognitive, or attentional, control within the context of viewing emotional stimuli. Given previously established research demonstrating the relationship between attention biases and depression and anxiety, it is important to examine whether *COMT* variants are related to biased attention to emotional information to better understand the possible genetic contribution to this risk factor.

Interaction of* COMT *and 5-HTTLPR. Given the complex nature of stress-reactive emotional disorders, investigators have begun to examine how additional genes may moderate G×E associations (i.e., G×G×E) to predict onset of and risk factors associated with stress-reactive disorders. Specifically, a G×G×E was found to predict depression in older adolescents whereby the 5-HTTLPR G×E occurred only among *COMT* Val homozygotes who had experienced greater stress (Conway, Hammen, Brennan, Lind, & Najman, 2010). Furthermore, structural and functional imagining studies among psychiatrically healthy adults have found *COMT*x5-HTTLPR predicting smaller gray matter volume across a variety of

brain regions involved in emotion processing (Radua et al., 2013), neural response across similar regions when viewing negatively valenced stimuli (Smolka et al., 2007), as well as reduced connectivity within an emotion processing circuit while viewing emotional faces (Surguladze et al., 2012). However, a recent behavioral study examining the effects of *COMT* and 5-HTTLPR genotype status on emotion identification biases among healthy adults found only direct effects of each gene when processing anger and happiness and no G×G effect (Gohier et al., 2014). Of note, *COMT*x5-HTTLPR studies to date have occurred primarily within adult samples and have not examined attention bias to emotion, so it remains unclear whether a G×G effect would be associated with attention bias among youth.

Attention bias to emotion as an intermediate trait among youth

Very few studies have investigated how 5-HTTLPR is related to processing of affective cues in youth samples, and no study has examined whether *COMT* is associated with attention biases to emotion among either adults or youth. Of the limited research examining 5-HTTLPR and attention biases among youth, findings have been mixed: Two studies found 5-HTTLPR variants to be associated with attention biases toward negative emotional faces (angry faces in Perez-Edgar et al., 2010; fearful faces in Thomason et al., 2010), whereas others showed biases away from sad (Gibb et al., 2009) and angry (Gibb et al., 2011) faces. Discrepancies within the child literature may be accounted for by methodological and participant differences. For example, neither Perez-Edgar et al. (2010; examined angry and happy faces) nor Thomason et al. (2010; examined angry and fearful faces) included sad faces within their stimuli set. In addition, both studies finding 5-HTTLPR to be associated with preferential attention toward negative emotional faces (Perez-Edgar et al., 2010; Thomason et al., 2010) utilized healthy community samples of youth that were not preselected for depression or anxiety risk. However, Gibb and colleagues examined 5-HTTLPR and attention biases for sad, angry, and happy faces among children at-risk for depression (i.e., children of depressed mothers), and examined mothers' depressive symptoms (Gibb et al., 2009) and mothers' expressed criticism about their child (Gibb et al., 2011) as moderators of the association between 5-HTTLPR and attentional avoidance of negative emotion. Overall, it appears that sample characteristics, including risk for psychopathology and the type of stimuli used, may have an influence over the types of biases observed within the context of genetic risk.

Examining attention biases as an intermediate trait related to stress-reactive disorders, including anxiety and depression, is of particular importance among children and adolescents. Most individuals experience their first onset of depression and anxiety during adolescence (Costello, Egger, & Angold, 2004; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Hankin et al., 1998) and adolescent-onset depression and anxiety has been shown to substantially increase the risk for recurrence of internalizing disorders in adulthood (Rutter, Kim-Cohen, & Maughan, 2006). Given that biases in attention to emotional stimuli have been theorized (Gotlib & Krasnoperova, 1998; Mogg & Bradley, 2005) and studied (Beevers et al., 2007; Beevers et al., 2009) as a possible intermediate trait primarily among adults, it is necessary to clarify the genetic correlates to attention biases among youth as well as the specific biases observed.

Examining stressful life events as a moderator

Research shows that SLEs are associated with increased risk for depression and anxiety (Grant et al., 2003). Specifically, investigators have theorized that recent, discrete SLEs (within approximately 3–6 months) are more closely related to risk for depression compared with chronic stress (see Monroe & Reid, 2008, for a review). Given that 5-HTTLPR variants have been shown to predict a broad bias to any emotion as well as attention toward and away from negative emotional stimuli, it is possible that other, yet unstudied, factors influence the types of attention biases observed within the context of genetic risk. As cognitive models of psychopathology posit that SLEs trigger cognitive biases, such as preferential attention toward negative emotion (Gotlib & Krasnoperova, 1998), SLEs could function as a potential moderator of the relationship between genetic risk and attention biases to emotion.

Within the animal literature, it has been well established that stress alters serotonin synthesis and release in the brain (Amat, Matus-Amat, Watkins, & Maier, 1998; Chaouloff et al., 1999; Keeney et al., 2006). Among humans, a recent meta-analysis demonstrated that individuals homozygous for the S allele of 5-HTTLPR show increased cortisol secretion in response to a laboratory stressor (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012). In addition, there is initial evidence showing that S/S carriers demonstrate decreased inhibition when processing negatively valenced pictures after an acute laboratory stressor in a small sample of adults (Markus & De Raedt, 2010). These findings are suggestive that acute stress affects attentional processes differentially based on 5-HTTLPR genotype status.

Stress has also been shown to affect dopaminergic function in animals (Arnsten & Goldman-Rakic, 1998; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996), and a

study in mice found variations in *COMT* enzyme activity to be related to differential stress responses (Papaleo et al., 2008). There are also initial findings suggesting that *COMT* gene variants are associated with cortisol release during a laboratory stressor among children (Armbruster et al., 2012). Although, to our knowledge, there is no research examining the relationship among *COMT*, attention biases to emotion, and stress, these findings indicate stress may also play a critical role in how *COMT* genotype relates to attentional biases. Therefore, the current study sought to examine whether recent, discrete SLEs (events within the last 3 months) functioned as a moderator of 5-HTTLPR and *COMT* genetic risk to predict attention biases among youth.

Current study

The current study sought to uniquely contribute to research on attentional bias to emotion (sad, happy, and angry) as a potential intermediate trait influenced by theoretically motivated candidate genes (5-HTTLPR and *COMT*) among youth. Given the mixed findings in the extant literature, particularly among studies examining the relationship between 5-HTTLPR and attention bias to emotion, SLEs within the past 3 months were investigated as a possible moderator of the relationship between genes and attention bias. As a recent meta-analysis (Pergamin-Hight et al., 2012) showed 5-HTTLPR to be associated with biased attention toward negative stimuli, it was hypothesized that there will be a G×E whereby youth who are homozygous for the S allele (S/S) and who have experienced a greater amount of recent SLEs will show biased attention toward negative emotional faces (i.e., sad and angry faces). In addition, due to the lack of research investigating the relationship between *COMT* and attention biases to emotion, analyses were conducted to examine the association between *COMT* and *COMT*x5-HTTLPR and attention biases to emotion, along with whether SLEs moderate these relationships. To mirror previous studies examining genetic associations with attention bias to emotion among healthy community samples (i.e., Beevers et al., 2009; Perez-Edgar et al., 2010) and to control for the effects of current internalizing symptoms on attention bias to emotion, symptoms of anxiety and depression were included as covariates in all analyses.

Method

Participants

Participants included 467 children and adolescents who were recruited from suburban and urban school districts in Colorado and New Jersey. A brief screening was conducted with parents to determine eligibility of their child. Youth had to currently be in third, sixth, or ninth grade. They were excluded if they had a severe learning or psychiatric problem (e.g., autism, psychosis) that was likely to interfere with completion of an extensive laboratory protocol. The sample was approximately evenly divided by sex (59% girls), was of mixed ethnic origin representative of their geographic region (68% White, 11% African American, 8% Hispanic, 6% Asian, and 7% Mixed Race or Other), and ranged in age from 7 to 16 years old (M = 11.91, SD = 2.30). Parents of youth were primarily mothers (91%). Median annual parental income was $90,000, and 18% of the youth received free/reduced-price lunch at school.

Procedures

Each eligible parent and youth visited the laboratory to complete the dot-probe task, DNA collection via saliva, and questionnaire data with youth and parents about their child, in that order. Parents provided informed written consent for their participation and for their child and youth provided written assent. Trained and supervised graduate students, staff, and undergraduate research assistants administered the measures. All procedures were approved by the Institutional Review Board at the University of Denver and Rutgers University and were carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Youth and parents were reimbursed for their participation. All youth and parents were given referral forms with lists of various affordable psychological services and community mental health centers in the area.

Measures

Attentional biases. Youths' attentional biases for facial displays of emotion were assessed using a modified dot-probe task (MacLeod, Mathews, & Tata, 1986) administered using E-Prime. Stimuli for the dot-probe task consisted of pairs of facial expressions that contained one affective (angry, sad, or happy) and one neutral photograph from the same actor taken from a standardized stimulus set (Tottenham et al., 2009). Photographs from each actor (16 men and 16 women) were used to create sad–neutral, happy–neutral, and angry–neutral stimulus pairs (96 pairs).

Each stimulus pair was presented in random order over the course of two blocks, with a rest in between blocks, for a total of 192 trials. Each trial began with a blank computer display with only a white fixation cross in the middle of the screen for 1,000 ms. Then, a pair of pictures was presented for 1,000 ms, followed by a dot where one of the prior pictures had been (either the

Table 1. Correlations Among Attention Biases, Genes, SLEs, Psychopathology, and Age

Variable	1	2	3	4	5	6	7	8
1. Negative bias	—							
2. Positive bias	.04	—						
3. 5-HTTLPR	−.14*	−.09	—					
4. *COMT*	−.02	.13*	.15*	—				
5. ALEQ	.06	−.05	−.08	−.01	—			
6. CDI	.09	.002	−.02	−.02	.33**	—		
7. MASC	.02	−.02	−.001	−.05	.14*	.29**	—	
8. Age	.003	−.01	.06	−.02	.37**	.13*	−.08	—

Note: ALEQ = Adolescent Life Events Questionnaire combined parent and child report; CDI = Children's Depression Inventory; MASC = Multidimensional Anxiety Scale for Children. ALEQ scores were computed by averaging the number of parent- and child-reported life events in the previous 3 months and ranged from 1.50 to 31. Negative bias combined sad and angry attention bias scores, and positive bias score included happy attention bias scores.
*$p < .01$. **$p < .001$.

affective or neutral picture) that was presented for 1,000 ms. Youth were instructed to indicate as quickly as possible the location of the dot (left vs. right side of the screen) using the computer keyboard ("z" labeled "left"; "/" labeled "right"). The computer recorded the accuracy and response time for each response. Consistent with prior research (Gotlib et al., 2004), trials with response errors were excluded as were trials with response times less than 150 ms or greater than 1,500 ms. Error rates were quite low (less than 1.5%), and a small portion (1.8%) were excluded for being out of response time range. Of the 467 children who completed the dot-probe task, 416 had completed genotype data for 5-HTTLPR and 456 had completed genotype data for *COMT*. The final samples within each gene did not differ from the total sample on age, gender, or ethnicity/race (*p*s > .13).

Mean attention bias scores (Mogg, Bradley, & Williams, 1995) were then calculated separately for each affective stimulus type (angry, sad, or happy face) by subtracting the mean response time for cases in which the probe replaced the affective face from mean response times for cases in which the probe replaced the neutral face. Bias scores greater than zero represent preferential attention toward the affective face, whereas bias scores less than zero indicate attentional avoidance of the affective face.

As meta-analytic findings show 5-HTTLPR to be associated with a broad range of negative stimuli (i.e., sad, fearful, threatening stimuli; Pergamin-Hight et al., 2012), a composite negative emotion bias variable was created by summing bias scores for both sad and angry faces to represent attention biases to negative emotion; positive emotion bias refers to bias scores calculated for happy facial emotion trials.

Stressful life events. The Adolescent Life Events Questionnaire (ALEQ; Hankin & Abramson, 2002) consists of 37 items that assess the number of SLEs occurring within the past 3 months. The ALEQ assesses a broad range of negative life events that typically occur among youth, including school, friendship, romantic, and family events. Respondents indicated whether or not the event occurred within the past 3 months and is scored by summing the number of events endorsed. Both the child (ALEQ-C) and parent (ALEQ-P) reported on the child's exposure to stressors by indicating whether or not a stressor occurred within the last 3 months. ALEQ-C and ALEQ-P were given at the baseline assessment. ALEQ-C and ALEQ-P scores were moderately correlated, $r(466) = .23$, $p < .001$, so they were standardized and averaged together to form an overall score. Scores for ALEQ-C ranged from 0 to 37 ($M = 16.46$, $SD = 7.83$), and ALEQ-P scores ranged from 0 to 37 ($M = 15.53$, $SD = 7.41$). The ALEQ demonstrated good validity in past research (Hankin, 2008a, 2008b; Hankin, Stone, & Ann Wright, 2010). In addition, validity of the ALEQ is supported by significant correlations with objective ratings of episodic stressors ($r = .44$, $p < .001$) from a contextual stress interview (Rudolph & Flynn, 2007). In sum, the ALEQ possesses strong psychometric properties and provides reasonably objective, reliable, valid assessment of stressors among youth.

Genotyping. Saliva samples were obtained from all study participants with Oragene™ (DNA Genotek, Kanata, Ontario, Canada) collection kits, and DNA was extracted using standard salting-out and solvent precipitation methods. The method for 5-HTTLPR and SNP rs25531 ($N = 416$) is detailed in (Haberstick et al., 2014).

Based on findings from the Pergamin-Hight et al. (2012) meta-analysis showing that those homozygous for the S allele showed an attention bias to negative material compared with L allele carriers, two groups of participants were formed based on their 5-HTTLPR genotyping:

youth homozygous for the lower expressing S or L_G alleles (i.e., S/S, n = 96) and those heterozygous or homozygous for the higher expressing L_A allele (i.e., SL/LL, n = 320).

Genotyping of Val158Met rs4680 in *COMT* (n = 456) is outlined in Haberstick and Smolen (2004). In contrast to 5-HTTLPR, three groups of participants were formed based on their *COMT* genotyping: youth homozygous for the higher expressing Val allele (i.e., Val/Val, n = 133), those heterozygous (i.e., Val/Met, n = 213), and those homozygous for the low expressing Met allele (i.e., Met/Met, n = 110) due to findings that both Met and Val homozygotes are related differentially to emotionally valenced and cognitive based tasks, respectively, and we hoped to examine whether there was an additive effect of either Met or Val allele on our findings. The successful call rate for the overall project was 97.5% for 5-HTTLPR and 96.3% for *COMT*. All of the genotypes were in Hardy–Weinberg equilibrium.

The distribution of genotype groupings across *COMT*x5-HTTLPR is as follows: Met/Met and SL/LL = 114, Val/Met and SL/LL = 221, Val/Val and SL/LL = 125, Met/Met and SS = 24, Val/Met and SS = 71, Val/Val and SS = 48.

Symptoms of anxiety and depression. The Multidimensional Anxiety Scale for Children (MASC; March, Parker, Sullivan, Stallings, & Conners, 1997) assessed youths' self-reported recent symptoms of anxiety. The MASC has good reliability and validity (Silverman & Ollendick, 2005). The Children's Depression Inventory (CDI; Kovacs, 1984) assessed youths' self-reported symptoms of depression occurring in the last week. The CDI has good reliability and validity (Klein, Dougherty, & Olino, 2005). Internal consistency (α) was .89 for CDI and .90 for MASC. Means and standard deviation of CDI and MASC scores are presented in Table 2 and are comparable to published norms (Kovacs, 1984; March et al., 1997) and prior research with general community samples (Baldwin & Dadds, 2007; Petersen et al., 1993). Using recommended clinical cutoff for the MASC and CDI (T-scores > 65), 3% of youth were above CDI clinical cutoff and 6% above MASC clinical cutoff, which are consistent with point prevalence rates for depression and anxiety disorders among community samples of youth (see review by Merikangas, Nakamura, & Kessler, 2009)

Results

Preliminary analyses

Table 1 provides the zero-order correlations among all primary and control variables. Means and standard deviations for all primary variables (Table 2) overall and separated by genotype for 5-HTTLPR and *COMT* are presented. There were no significant differences among genotypes for age (ps > .28), race (ps > .17), or gender (ps > .09).

Data analytic plan

Multiple regression analyses were used to test G (5-HTTLPR or *COMT*) × E (SLEs) as well as a G (5-HTTLPR) × G (*COMT*) × E (SLEs) as a predictor of attention bias to positive (happy) and negative (angry, sad) emotional faces using the SPSS macro PROCESS (Hayes, 2013). Attention bias scores, SLEs (i.e., ALEQ scores), anxiety symptoms (i.e., MASC scores), and depression symptoms (i.e., CDI scores) were centered prior to analyses. Youths' MASC and CDI scores were entered to control for covariance between symptoms of depression and anxiety and attention bias to emotion. Although neither age (ps > .09) nor grade (ps > .1) were found to be significant moderators among all analyses, age was also controlled for due to the wide age range of the sample. All main effects and interactions were entered simultaneously and unstandardized regression coefficients are reported (Hayes, 2013) for each set of analyses.

Post hoc analyses of significant interactions were conducted (Aiken & West, 1991; Holmbeck, 2002). New product terms were computed at different levels (i.e., genotype groups) of the moderator variable. Separate regressions were conducted that included each of these product terms. This enables examination of the significance of simple slopes at different levels of genotype.

5-HTTLPR. There was no significant gene–environment correlation (rGE) between 5-HTTLPR and SLEs, $r(415) = -.09$, $p = .07$. Multiple regression analyses revealed no significant main effect of SLEs or covariates (i.e., age and symptoms of depression or anxiety) and a trend level main effect of gene, such that youth homozygous for the S allele were more likely to avoid negative emotion (Tables 2 and 3). This main effect should be interpreted in light of a significant interaction between SLEs and 5-HTTLPR,[1] predicting attention bias to negative emotion (Table 3).[2] This G×E effect is shown in the top portion of Figure 1 with SLEs depicted at 1 *SD* above and below the mean. Post hoc analyses showed a significant slope for those with the S/S (b = 3.91, SE = 1.30, t = 3.01, p = .003) genotype, indicating that youth homozygous for the S allele exhibited biases toward negative emotion when experiencing high as compared with low levels of SLEs. The slope for the LL/SL genotype group was not significant (b = –0.14, SE = 0.69, t = –0.20, p = .84). No significant main effects, including covariates (i.e., age and symptoms of depression or anxiety) or interactions, were found when examining attention bias to positive emotion (Table 3).

Table 2. Descriptive Statistics Overall and by 5-HTTLPR and *COMT* Genotypes

		5-HTTLPR		*COMT*		
	Full sample (n = 467)	LL/SL (n = 320)	S/S (n = 96)	Met/Met (n = 110)	Val/Met (n = 213)	Val/Val n = 133)
Variable	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Negative bias	–13.19 (74.18)	–6.50 (74.46)	–29.58 (72.87)	–9.89 (63.59)	–12.51 (79.68)	–16.24 (74.56)
Positive bias	–12.52 (52.59)	–8.97 (53.90)	–19.15 (48.09)	–18.23 (46.60)	–15.29 (51.67)	0.55 (55.74)
ALEQ	16.00 (5.98)	15.66 (5.99)	14.65 (6.22)	15.72 (5.98)	15.44 (6.04)	15.47 (6.28)
MASC	42.15 (15.96)	42.33 (15.97)	41.60 (16.23)	42.25 (16.61)	43.02 (15.83)	40.93 (15.85)
CDI	7.02 (5.93)	7.04 (6.04)	6.55 (5.87)	7.02 (6.44)	7.04 (5.65)	6.66 (5.94)

Note: ALEQ = Adolescent Life Events Questionnaire combined parent and child report; CDI = Children's Depression Inventory; MASC = Multidimensional Anxiety Scale for Children. ALEQ scores were computed by averaging the number of parent- and child-reported life events in the previous 3 months and ranged from 1.50 to 31. Negative bias combined sad and angry attention bias scores, and positive bias score included happy attention bias scores.

COMT. There was no significant rGE between *COMT* and SLEs, $r(453) = -.009$, $p = .85$. Multiple regression analyses revealed no significant main effect of SLEs or covariates (i.e., age or symptoms of depression or anxiety) and a significant main effect of gene such that youth with more copies of the Met allele were more likely to avoid positive emotion (see Tables 2 and 4). However, this main effect should be interpreted in light of a significant interaction between SLEs and *COMT* predicting attention bias to positive emotion (Table 4). The G×E effect is shown in the bottom portion of Figure 1 with SLEs depicted at 1 *SD* above and below the mean. Post hoc analyses showed a significant slope for those with the Val/Val genotype ($b = -1.43$, $SE = 0.66$, $t = -2.16$, $p = .03$) indicating that youth homozygous for the Val allele experienced greater avoidance of positive emotion when experiencing high as compared with low levels of SLEs. The slope for the Met/Met ($b = 0.82$, $SE = 0.73$, $t = 1.13$, $p = .26$) and Val/Met ($b = -0.31$, $SE = 0.41$, $t = -0.75$, $p = .45$) genotype groups were not significant. No significant main effects, including covariates (i.e., age and symptoms of depression or anxiety) or interactions, were found when examining attention bias to negative emotion (Table 4).

COMT*x5-HTTLPR*. Multiple regression analyses were run to examine whether there was a G×G×E effect predicting attention bias to positive and negative emotion. There continued to be a main effect of 5-HTTLPR predicting attention bias away from negative emotion

Table 3. Prediction of Attention Biases to Negative and Position Emotional Faces From 5-HTTLPR and Stressful Life Events (SLEs)

Predictor	β (*SE* β)	95% CI	*t*	*p*
Negative emotion (angry/sad)				
Intercept	4.27 (21.31)	–37.62, 46.16	0.20	.84
5-HTTLPR	–18.21 (9.07)	–36.04, –0.39	–2.01	.05
SLEs	–0.28 (0.79)	–1.83, 1.27	–0.36	.72
5-HTTLPR × SLEs	3.86 (1.47)	0.98, 6.74	2.64	.009
Age	0.08 (1.76)	–3.40, 3.55	0.04	.97
MASC	0.07 (0.24)	–0.40, 0.56	0.31	.76
CDI	0.72 (0.67)	–0.60, 2.05	1.07	.28
Positive emotion (happy)				
Intercept	–8.06 (15.42)	–38.38, 22.25	–0.52	.60
5-HTTLPR	–11.73 (6.56)	–24.63, 1.17	–1.79	.07
SLEs	–0.58 (0.57)	–1.70, 0.54	–1.02	.31
5-HTTLPR × SLEs	–0.04 (1.06)	–2.12, 2.04	–0.04	.97
Age	0.90 (1.28)	–1.61, 3.42	0.70	.48
MASC	–0.14 (0.18)	–0.49, 0.21	–0.80	.42
CDI	0.52 (0.49)	–0.44, 1.47	1.06	.29

Note: CDI = Children's Depression Inventory youth self-report; MASC = Multidimensional Anxiety Scale for Children youth self-report.

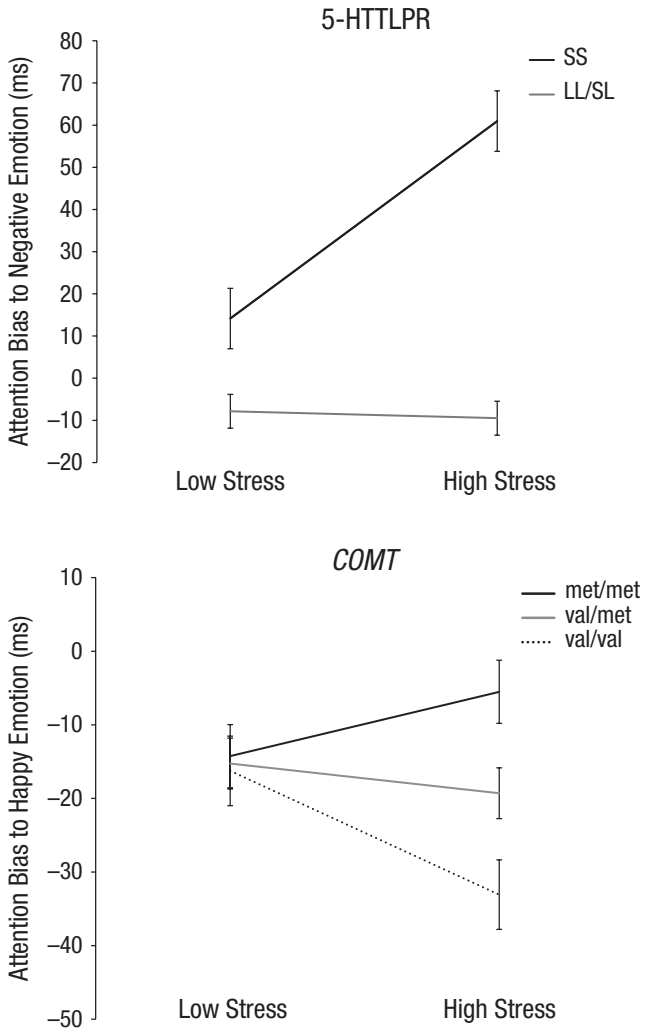

Fig. 1. Interaction between 5-HTTLPR (top) and *COMT* (bottom) and stressful life events (SLEs) with 5-HTTLPR predicting attention bias toward negative emotion (i.e., sad and angry emotional faces) and *COMT* predicting attention bias away from positive emotion (i.e., happy faces) with SLEs depicted at 1 *SD* above (high stress) and below (low stress) the mean.

(β = –137.78, *SE* = 48.17, *t* = –2.86, *p* = .005) as well as a 5-HTTLPR×SLE predicting attention bias toward negative emotion among S homozygotes who have experienced more recent SLEs (β = 7.43, *SE* = 3.22, *t* = 2.31, *p* = .02). Similarly, there continued to be a main effect of *COMT* predicting attention bias away from positive emotion among Met carriers (β = 33.31, *SE* = 11.41, *t* = 2.92, *p* = .004) as well as a trend for *COMT*×SLE predicting attention bias away from positive emotion among Val homozygotes who have experienced more recent SLEs (β = –1.22, *SE* = 0.66, *t* = –1.85, *p* = .07). Although the *COMT* × SLE finding no longer reached significance, the size of the effect was comparable to the previous analysis without the inclusion of other effects related to the G×G×E analyses (β = –1.12, *SE* = 0.57). There were no other significant findings among all other main effects, covariates, and two-way interactions, including the three-way interaction of interest (i.e., 5-HTTLPRx*COMT*×SLE; *p*s > .19) predicting attention bias to either positive or negative emotion.

Discussion

The primary aim of this study was to investigate the role of theoretically specified and biologically plausible candidate genes, specifically 5-HTTLPR and *COMT* genotype, in youths' attention to emotion as well as whether the relationship between genotype and attention bias was moderated by recent SLEs. Results supported the hypothesized interaction for 5-HTTLPR, demonstrating that youth at high genetic risk (S/S genotype) who also experienced higher levels of recent SLEs showed attentional biases toward negative emotional faces. In addition, this study sought to explore whether *COMT* genotype was associated with biased attention to emotion within the context of experiencing recent SLEs. This study provides support for a G×E effect with *COMT* Val/Val carriers showing attentional avoidance of positive emotion in those with recent high levels of SLE exposure. No G×G or G×G×E was found when examining *COMT*x5-HTTLPR to predict attention bias to emotion. Overall, findings supported the previously untested notion that stress plays a critical role in understanding the relationship between genetic risk and attention biases to emotion.

The current study provided a unique perspective on the mixed findings seen within the 5-HTTLPR and attention bias literature. Although the majority of studies have found 5-HTTLPR to be associated with attention biases toward negatively valenced material, as evidenced by a recent meta-analysis (Pergamin-Hight et al., 2012), there have been several studies within both the child and adult literature that have found either attentional avoidance of negative emotion (Gibb et al., 2009; Gibb et al., 2011) or a broad attention bias toward any emotion (Beevers et al., 2007; Beevers et al., 2009). The current study demonstrated the importance of considering exposure to environmental stress, particularly recent SLEs, as a moderator of the 5-HTTLPR and attention bias relationship. Although little is known about the precise mechanisms behind this relationship, it is possible that exposure to recent SLEs for those at high genetic risk (S/S homozygotes) primes individuals to attend more to negative information within their environment. In addition, S/S carriers of 5-HTTLPR have been shown to experience greater cortisol reactivity in response to laboratory stressors (see Miller et al., 2012, for a meta-analysis) and increased risk for depression when exposed to greater environmental stress (see Karg et al., 2011, for a meta-analysis). Indeed, it has been theorized that S/S carriers of 5-HTTLPR are more sensitive to their environment and therefore more susceptible to negative outcomes, such as depression, when exposed to greater environmental

Table 4. Prediction of Attention Biases to Negative and Position Emotional Faces From *COMT* and Stressful Life Events (SLEs)

Predictor	β (*SE* β)	95% CI	*t*	*p*
Negative emotion (angry/sad)				
Intercept	10.68 (21.39)	–31.37, 52.73	0.50	.62
COMT	–2.72 (4.87)	–12.28, 6.90	–0.56	.58
SLEs	0.83 (1.11)	–1.36, 3.02	0.75	.45
COMT × SLEs	–0.01 (0.81)	–1.60, 1.58	–0.02	.99
Age	–0.75 (1.70)	–4.09, 2.59	–0.44	.66
MASC	0.05 (0.24)	–0.42, 0.51	0.20	.84
CDI	0.73 (0.66)	–0.57, 2.03	1.10	.27
Positive emotion (happy)				
Intercept	–2.97 (15.04)	–32.53, 26.58	–0.20	.84
COMT	9.07 (3.42)	2.35, 15.78	2.65	.008
SLEs	0.87 (0.78)	–0.67, 2.40	1.11	.27
COMT × SLEs	–1.12 (0.57)	–2.23, 0.0002	–1.97	.05
Age	–0.53 (1.20)	–2.88, 1.82	–0.45	.66
MASC	–0.11 (0.17)	–0.44, 0.21	–0.68	.50
CDI	0.38 (0.46)	–0.54, 1.29	0.81	.42

Note: CDI = Children's Depression Inventory youth self-report; MASC = Multidimensional Anxiety Scale for Children youth self-report.

stress as well as benefit more from a positive or nurturing environment (i.e., differential susceptibility; Belsky & Pluess, 2009; Caspi et al., 2010). Although the present study did not measure positive environmental exposure, it may be informative for future research to include measures that capture both positive and negative environmental factors to determine whether the relationship between genes and attention biases functions within a differential susceptibility framework. In addition, the present study's findings contribute to a body of literature that suggests attention bias to emotion may be a more proximal risk factor for stress-reactive psychopathology, potentially functioning as an intermediate trait between genetic risk and disorder. Future research incorporating symptom measures of anxiety and depression will be necessary to determine the specific relationship among attention, stress, 5-HTTLPR, and stress-reactive psychopathology.

This study also sought to examine whether *COMT* genotype interacted with recent SLEs as well as 5-HTTLPR (G×G×E) to predict attention biases among youth. It is interesting that findings show a differential effect between 5-HTTLPR and *COMT*, with *COMT* Val/Val carriers showing attentional avoidance of happy faces in youth with higher levels of recent SLEs, but no G×G effects. This is the first study to examine whether *COMT* genotype is related to attention biases to emotion, particularly within the context of SLEs, so it is important to interpret these findings cautiously within the context of the broader *COMT* literature. One possibility is that the specificity for avoidance of positive emotion reflects Val/Val carriers' sensitivity to rewarding stimuli, particularly when exposed to a greater number of SLEs. There is considerable evidence showing happy faces are socially rewarding starting in infancy (e.g., Tronick, Als, Adamson, Wise, & Brazelton, 1979) and activate reward neural circuitry (Phillips et al., 1998). The association between *COMT* and avoidance of rewarding stimuli could relate to dopamine's role in reward processing that has been linked to midbrain structures and the ventral striatum (Wise, 2002). Indeed, a neuroimaging study demonstrated abnormal reward processing among Val/Val participants as compared with Met/Met carriers (Camara et al., 2010). In addition, avoidance of rewarding stimuli (i.e., anhedonia) is a key diagnostic feature of depression and depressed adolescents show dysfunctions in reward neural circuitry (see Forbes & Dahl, 2012, for a review), which suggests that processing of happy faces may be a relevant factor to consider within the context of risk for depression.

Of note, the finding that Val/Val carriers are more prone to exhibit biased attention to positive emotion is somewhat contrary to a recent meta-analysis examining *COMT* and prefrontal neural activation during executive cognition and emotion-based tasks. This meta-analysis demonstrated Val allele carriers to have decreased neural efficiency (increased activation) during cognitive tasks whereas Met allele carriers showed this pattern of neural activation during emotion based tasks (Mier et al., 2009). Given that the dot-probe task involves both cognitive aspects (attentional control) along with emotion processing, it is unclear whether direct

comparisons can be drawn. In addition, previous studies have not examined the role of environmental context in the relationship between *COMT* and emotion or cognitive processing. It is important to note that our results demonstrated Met/Met carriers to show increased avoidance of positive emotion, yet this relationship reversed once SLEs were examined as a moderator. A similar pattern was found when comparing the direct and moderated effects of 5-HTTLPR: S/S carriers were more likely to avoid negative emotion as a main effect, but were more likely to attend to negative emotion when experiencing more recent SLEs. This underscores the need for future research to incorporate environmental context when investigating genetic associations with emotion processing constructs.

Furthermore, no interaction between 5-HTTLPR and *COMT* was found in the present study, but has been found in structural and functional neuroimaging studies examining passive viewing and emotion recognition tasks (Radua et al., 2013; Smolka et al., 2007; Surguladze et al., 2012). It is important to note that no previous studies have examined the direct or moderated role of *COMT* when examining attention bias to emotion and previous findings have generally been found within neuroimaging data as opposed to behavioral performance (Gohier et al., 2014; Mier et al., 2009). As the present study is the first to examine the direct and moderated relationship of *COMT* and attention bias to emotion, further investigation is necessary to better understand the lack of G×G found within our sample.

Overall, the differential findings between *COMT* and 5-HTTLPR variants predicting attention biases to emotion represent an intriguing step toward a better understanding of possible intermediate traits for stress-reactive internalizing psychopathology. It is possible that differential pathways exist to disorder within an equifinality framework or that each G×E may be part of a specific and separate pathway to disorder. Further research is needed to examine whether these associations predict future onset for disorder, and whether there is specificity to predict certain disorders depending on the risk factors observed.

There were several conceptual and methodological strengths of the present study. The majority of previous research has investigated genetic risk for attention bias to emotion among adult samples, with limited studies investigating these processes among youth. Given the majority of first onsets of anxiety and depression occur during adolescence (Merikangas et al., 2011), the lack of research within youth samples is a notable gap in the literature. In addition, none of the previous investigations among youth or adults considered SLEs as a possible moderator to the association between genetic risk and attention bias. Therefore, this is the first study to examine SLEs as a moderator to the relationship between 5-HTTLPR or *COMT* and biased attention to emotion. This is also the first study within either the adult or youth literature to investigate *COMT* genotype in association with attention biases to emotion. The differential findings between 5-HTTLPR and *COMT* provide an interesting avenue for future research on the developmental pathway to disorder. Methodological strengths include utilizing a large community sample of youth that allowed for greater ability to detect effects, controlling for age and symptoms of depression and anxiety, using a sample representative of the geographic area of recruitment, and employing a more objective measure of cognitive bias (dot-probe task). These strengths speak to the novel contribution this study provides to the broader literature on understanding intermediate traits for stress-reactive psychopathology.

Limitations of the study provide avenues for future research. Most notably, the current study did not examine whether the G×E predicted onset of psychological disorders or symptoms given the lack of diagnostic interviewing and cross-sectional nature of the study. Prospective studies utilizing diagnostic interviewing techniques will be an important next step to determine whether 5-HTTLPR, *COMT*, and attention biases contribute to the developmental pathway to stress-reactive psychopathology among youth. In addition, although participants' reported SLEs occurring in the 3 months prior to the laboratory visit, this study is still considered cross-sectional and causal inferences cannot be made. It is possible there is a transactional relationship between stress and attention biases, such that biased attention to emotion contributes to increased experience of SLEs (i.e., stress generation; Hammen, 1991). Future research utilizing multiple assessments of attention bias and SLEs is needed to examine this question.

Furthermore, although the current study's measure of attention bias is more objective compared with self-reported cognitive biases, there are limitations of the selected attention bias task. For example, we utilized a task that compared emotional (i.e., sad, angry, happy) to neutral faces; however, research has shown that youth perceive neutral or ambiguous facial expressions negatively (Tottenham, Phuong, Flannery, Gabard-Durnam, & Goff, 2013). Therefore, it is possible the *COMT*×SLE findings showing avoidance of positive emotion could be interpreted as preferential attention for negatively perceived neutral faces. Still, we did not find *COMT*×SLE to predict attention toward unambiguous negative emotional faces (i.e., sad and angry faces), which suggests our original interpretation of the findings is probable. In addition, given research showing patterns of attention bias may vary based on presentation time (e.g., 1,000 ms versus 500 ms) and diagnostic status (e.g., depression versus anxiety; Mathews & MacLeod, 2005), future

studies utilizing more precise measurement tools are needed to investigate information processing biases. For example, eye-tracking methodology provides real time assessment of attention biases at various interval lengths. This allows for examination of the time-course of attention biases when exposed to multiple stimuli or valence types as opposed to studying bias at one given point in time (i.e., 1,000 ms) with limited comparison stimuli (i.e., target emotion versus neutral emotion).

In sum, those who experienced high levels of recent SLEs and were at high genetic risk for 5-HTTLPR (S/S) and *COMT* (Val/Val) were found to exhibit biased attention to emotion. These G×E findings were differentiated by gene whereby 5-HTTLPR predicted attention toward negative facial expressions (sad and angry faces) whereas *COMT* predicted avoidance of positive facial expressions (happy faces), and no G×G effects were found. These findings suggest that the experience of stress plays a role in the relationship between genetic risk and attentional biases, which has implications for research examining intermediate traits for stress-reactive psychopathology among youth.

Author Contributions

J. L. Jenness developed the study concept. All authors contributed to the study design. Data collection was performed in part by J. L. Jenness, with A. Smolen contributing primarily to processing the genetic data and advising on genetic data collection. J. L. Jenness performed the data analysis and interpretation under the supervision of B. L. Hankin. J. L. Jenness drafted the manuscript, and B. L. Hankin, J. F. Young, and A. Smolen provided critical revisions. All authors approved the final version of the manuscript for submission.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Notes

1. Consistent with meta-analytic findings showing those homozygous for the S allele to demonstrate attention bias to negative stimuli (Pergamin-Hight et al., 2012), there was no significant interaction between 5-HTTLPR and SLEs predicting attention to negative emotion when utilizing a three genotype group (i.e., L/L, S/L, S/S) approach ($\beta = 1.11$, $p = .22$).

2. Regression coefficients were comparable when examining sad and angry attention bias scores separately (sad bias: $\beta = 2.00$, $SE = 1.04$; angry bias: $\beta = 1.80$, $SE = 1.05$) demonstrating similar processing of negative emotion overall, consistent with Pergamin-Hight et al. (2012).

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