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Children's Attentional Biases and *5-HTTLPR* Genotype: Potential Mechanisms Linking Mother and Child Depression

Brandon E. Gibb, Jessica S. Benas, and Marie Grassia
Department of Psychology, Binghamton University

John McGeary
Providence Veterans Affairs Medical Center and Center for Alcohol and Addiction Studies, Brown University

In this study, we examined the roles of specific cognitive (attentional bias) and genetic (*5-HTTLPR*) risk factors in the intergenerational transmission of depression. Focusing first on the link between maternal history of major depressive disorder (MDD) and children's attentional biases, we found that children of mothers with a history of MDD during their children's lives, compared to children of mothers with no depression history, exhibited greater attentional avoidance of sad faces. This attention bias was specific to sad, rather than happy or angry, faces. There was also preliminary evidence that this relation is stronger among children carrying the *5-HTTLPR* S or L_G allele than among those homozygous for the L_A allele. Next, conceptualizing mothers' levels of depressive symptoms during the multi-wave prospective follow-up within a vulnerability-stress framework, we found evidence for a three-way child *5-HTTLPR* × attentional bias × mother depressive symptom interaction predicting children's depressive symptoms. Specifically, the relation between mother and child depressive symptom levels over time was strongest among children carrying the 5-HTTLR S or L_G allele who also exhibited attentional avoidance of sad faces. These findings provide initial support for role of children's *5-HTTLPR* genotype and attentional biases for sad faces in the intergenerational transmission of depression.

The relation between maternal and child depression is well documented (for a review, see Goodman & Tully, 2008). What is less well understood are the mechanisms by which a depressed mother contributes vulnerability to her child. The genetic contribution to the intergenerational transmission of depression cannot be overlooked, with the heritability of major depressive disorder (MDD) estimated at approximately 37% (Sullivan, Neale, & Kendler, 2000). This estimate, however, suggests that there is substantial variance left to be explained by nongenetic factors. Also, little is known about which specific genes may increase risk among children of depressed mothers. The primary goal of this study was to test a model for the intergenerational transmission of depression that integrates specific genetic as well as cognitive risk factors.

According to cognitive theories of depression (e.g., Abramson, Metalsky, & Alloy, 1989; Clark, Beck, & Alford, 1999), individuals' characteristic ways of attending to, interpreting, and remembering negative events in their lives may contribute vulnerability to the development of depression. These theories present vulnerability-stress models of depression in that cognitive risk is hypothesized to contribute to the development of

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Correspondence should be addressed to Brandon E. Gibb, Department of Psychology, Binghamton University (SUNY), Binghamton, NY 13902-6000. E-mail: gibb@binghamton.edu

depression in the presence, but not absence, of environmental stressors. Depressive reactions to negative life events are hypothesized to be particularly likely when there is a match between the type of event and the specific form of cognitive vulnerability exhibited (Beck, 1987; Clark et al., 1999).

Although there is growing support for cognitive models of depression (for reviews, see Abela & Hankin, 2008; Clark et al., 1999; Gibb & Coles, 2005), the majority of studies utilize self-report assessments of cognitive vulnerability, which focus on cognitive content rather than cognitive processes and rely on participants' awareness of their depressive cognitions, many of which are hypothesized to operate outside the person's awareness (Gotlib & Neubauer, 2000). More recently, therefore, researchers have focused on computer-based measures of cognitive processes hypothesized to contribute vulnerability to depression. For example, a growing body of research has suggested that depression is associated with an attentional bias toward sad faces (e.g., Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007). These attentional biases appear to be specific to sad, rather than angry or happy, faces. There is also preliminary evidence that attentional biases moderate the link between negative life events and prospective changes in depressive symptoms (Beevers & Carver, 2003). These studies have focused almost exclusively on attention biases in adults; however, there is evidence from one study of attentional biases in children of depressed mothers. In this study, Joormann, Talbot, and Gotlib (2007) examined attentional biases among 9- to 14-year-old girls whose mothers either had a history of recurrent MDD during their daughters' lives or had no lifetime history of any *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM–IV*]; American Psychiatric Association, 1994) Axis I disorder. Girls in both groups had no lifetime history of any Axis I disorder. In this study, daughters of depressed mothers, compared to controls, exhibited preferential attention to sad but not happy faces, suggesting that children at risk for depression may exhibit attentional biases for sad faces even if they have never experienced clinical depression themselves.

Consistent with cognitive vulnerability-stress models, there is also preliminary evidence that mothers' depressive symptoms may serve as a stressor that interacts with children's cognitive vulnerability to predict changes in children's depressive symptoms. Specifically, one multiwave longitudinal study found that the relation between mother and child depressive symptoms over the course of the follow-up was stronger among children exhibiting negative inferential styles—a form of cognitive vulnerability to depression—than among children exhibiting positive inferential styles (Abela, Skitch, Adams, & Hankin, 2006). Based on Beck's (1987; Clark et al., 1999) vulnerability-event congruency hypothesis, we hypothesized that a mother's increases in depressive symptoms would be a particularly salient stressor for children exhibiting attentional biases for sad faces.

As noted earlier there is a clear genetic component to the intergenerational transmission of depression. Although cognitive theories acknowledge the role of genetic risk factors in the development of depression (e.g., Clark et al., 1999), relatively few studies have sought to integrate findings from psychiatric genetics with cognitive models of depression (see Beck, 2008). One way genetic risk factors may operate is via their influence on cognitive processing. That is, information-processing biases such as attention may serve as intermediate phenotypes for specific candidate polymorphisms. Genetic effects could also be observed in terms of gene–environment interactions ($G \times E$), gene–environment correlations (rGE), or a combination of both (see Jaffee & Price, 2007; Rutter, Moffitt, & Caspi, 2006). For example, certain genetic risk factors may increase reactivity to environmental stressors ($G \times E$), including the stress associated with having a depressed mother. Children with a genetic risk may also be exposed to more environmental stress (e.g., maternal depression or negative events more generally), which could be either independent of (passive rGE) or dependent on (active or evocative rGE) the child's influence. Indeed, research has suggested the presence of both rGE and $G \times E$ influences in risk for youth depression (e.g., Eaves, Silberg, & Erkanli, 2003; Lau & Eley, 2008). Supporting the promise of interactive models including specific cognitive and genetic vulnerabilities, findings from a recent twin study suggest that the link between cognitive risk and depression may be moderated by genetic and environmental factors (Eley et al., 2008; Lau, Rijsdijk, & Eley, 2006). However, it remains unclear which specific genes may increase risk among children of depressed mothers.

To date, the strongest support for a specific genetic risk factor for depression has been obtained for a putatively functional polymorphism in the serotonin transporter gene (*5-HTTLPR*). There are two common variants in *5-HTTLPR*, a short allele (S) and a long allele (L), with the short allele exhibiting less transcriptional efficiency than the long allele (Lesch et al., 1996). More recently, studies have suggested a triallelic variation (S, L_G, L_A; e.g., Hu et al., 2005), with the L_G allele exhibiting functional equivalence with the S allele. There is increasing evidence that carriers of these lower expressing alleles (S or L_G) are more likely to develop depression following negative events than are individuals with two copies of the long (or L_A) allele, an effect that has been observed in both adults and

children (e.g., for reviews, see Rutter et al., 2006; Uher & McGuffin, 2008). In contrast to the consistent G × E findings for *5-HTTLPR*, research examining potential gene-environment correlations has provided no evidence that *5-HTTLPR* genotype is correlated with levels of negative life events (e.g., Caspi et al., 2003; Kaufman et al., 2004; Kilpatrick et al., 2007), nor is there evidence for a main effect of *5-HTTLPR* on depression (for a review, see Anguelova, Benkelfat, & Turecki, 2003). Although the precise mechanisms by which *5-HTTLPR* genotype may confer risk in the context of environmental stressors are not well established, *5-HTTLPR* short allele carriers have been show to exhibit stronger amygdala reactivity to emotional stimuli (for a review, see Munafò, Brown, & Hariri, 2008) and greater cortisol reactivity to a laboratory stressor (Gotlib, Joormann, Minor, & Hallmayer, 2008). Therefore, the presence of the *5-HTTLPR* short allele appears to be related to stronger neurobiological reactivity to environmental stimuli. Most recently, researchers have begun to examine possible links between *5-HTTLPR* genotype and information-processing (attention and memory) biases. For example, one study of adult psychiatric inpatients found that carriers of the *5-HTTLPR* short allele, compared to those homozygous for the long allele, exhibited preferential attention for anxiety-relevant, but not depression-relevant, words (Beevers, Gibb, McGeary, & Miller, 2007). In another study, children homozygous for the *5-HTTLPR* short allele exhibited more negative self-referent memory biases following a negative mood induction than did children homozygous for the long allele (Hayden et al., 2008).

Children's *5-HTTLPR* genotype and attentional biases, therefore, may represent overlapping, independent, or interactive risk factors in the intergenerational transmission of depression. To the extent that they reflect overlapping risk factors, we would expect a significant relation between *5-HTTLPR* genotype and attentional biases, with neither uniquely moderating the link between maternal and child depression. To the extent that they are independent risk factors, we would expect both to predict significant *unique* variance, statistically controlling for their overlap. Finally, evidence for interactive risk would be obtained by a significant *5-HTTLPR* × Attentional Bias interaction, with attentional biases having a stronger effect among carriers of the *5-HTTLPR* S or L_G allele than among children homozygous for the L_A allele.

Our goal in the current study was to specifically examine the role of children's attentional biases and *5-HTTLPR* genotype in the intergenerational transmission of depression. First, we hypothesized that children of mothers with a history of MDD during the children's lives would exhibit attentional biases specifically for sad rather than happy or angry faces. We also examined potential links between children's *5-HTTLPR* genotype and their attentional biases, both as a main effect and interacting with mothers' MDD history. To the extent that *5-HTTLPR* genotype is related to stronger neurobiological reactivity to environmental stimuli (see Gotlib et al., 2008; Munafò et al., 2008), we predicted that maternal history of depression would be most strongly related to children's attentional biases for sad faces among carriers of the *5-HTTLPR* S or L_G alleles. Because children of mothers with a history of depression are likely to have a history of depression themselves (Goodman & Tully, 2008), we also examined whether the link between maternal MDD and children's attentional biases for sad faces would be maintained even after statistically controlling for the potential influence of children's current depressive symptoms and lifetime histories of MDD. Second, conceptualizing mothers' current depressive symptoms during the course of the follow-up within a vulnerability–stress framework, we predicted that children's attentional biases for sad faces would moderate the strength of the relation between mother and child depressive symptoms over the course of a 6-month multiwave prospective follow-up. Based on Beck's vulnerability–event congruency hypothesis (Beck 1987; Clark et al., 1999), we predicted that this vulnerability–stress relation would be specific to children's attentional biases for sad, rather than happy or angry, faces. Building from previous research suggesting that the link between cognitive risk and depression is moderated by both genetic and environmental factors (Eley et al., 2008; Lau et al., 2006), we also hypothesized that children's *5-HTTLPR* genotype would further heighten children's risk such that the strongest link between mother and child depressive symptoms over the follow-up would be found among children exhibiting both genetic risk (*5-HTTLPR* S and/or L_G alleles) and cognitive risk (attentional bias for sad faces).

METHOD

Participants

Participants in this study were 74 mother–child pairs drawn from the community. To qualify for inclusion in the "depressed" group ($n = 40$), mothers were required to meet criteria for at least one *DSM–IV* MDD during the child's lifetime. To qualify for inclusion in the control group ($n = 34$), mothers were required to have no lifetime diagnosis of any *DSM–IV* mood disorder. Exclusion criteria for both groups included symptoms of schizophrenia, organic mental disorder, alcohol or substance abuse within the last 6 months, or history of bipolar I disorder. Children's participation was limited such that no more than one child

per mother could participate. The only inclusion criterion for children was that they be between 8 and 12 years old. If more than one child was available within this age range, one child was chosen at random for participation. The average age of mothers in our sample was 39.04 years ($SD = 6.92$, range = 26–53). In terms of race, 89.2% of the mothers were Caucasian, 5.4% were African American, 4.1% were Asian American, and 1 mother (1.3%) was multiracial. The median annual family income was $50,000 to $55,000. For the children in our sample, the average age was 9.96 years ($SD = 1.27$, range = 8–12) and 51.4% were girls. In terms of race, 79.7% of the children were Caucasian, 6.8% were African American, 1.4% were Asian American, and 12.2% were multiracial.[1] Maternal history of MDD was not significantly related to children's age, sex, or race (Caucasian vs. non-Caucasian).

Measures

DSM–IV disorders. The Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS–L; Endicott & Spitzer, 1978) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K–SADS–PL; Kaufman et al., 1997) were used to assess for lifetime histories of *DSM–IV* Axis I disorders in mothers and their children, respectively. Both measures are widely used diagnostic interviews with well-established psychometric properties (Angold, 1989; Endicott & Spitzer, 1978; Kaufman et al., 1997). The SADS–L and K–SADS–PL were administered by separate interviewers. For the K–SADS–PL, mothers and children were interviewed separately. As previously noted, 40 mothers met criteria for at least one MDD during their child's lifetime. Of the children, 10 met lifetime criteria for MDD.[2] A subset of 20 SADS–L and 20 K–SADS–PL interviews from this project were coded by a second interviewer and kappa coefficients for lifetime diagnoses MDD in mothers and in children were excellent ($\kappa = 1.00$).

Depressive Symptoms. Mothers' and children's symptoms of depression were assessed at each time point using the Beck Depression Inventory–II (BDI–II; Beck, Steer, & Brown, 1996) and Children's Depression Inventory (CDI; Kovacs, 1981), respectively. Numerous studies have supported the reliability and validity of both measures (Beck et al., 1996; Kovacs, 1981, 1985; Smucker, Craighead, Craighead, & Green, 1986). In our study, both the BDI–II and the CDI exhibited good internal consistency (αs = .92–.93 and .76–.86, respectively, across all time points).

Attentional biases. Children's attentional biases for facial displays of emotion were assessed using a modified dot-probe task (cf. MacLeod, Mathews, & Tata, 1986) administered using E-Prime (Psychological Software Tools, 2002). Stimuli for the dot-probe task consisted of pairs of facial expressions that contained one emotional (sad, happy, or angry) and one neutral photograph from the same actor taken from a standardized stimulus set (Tottenham et al., in press).[3]

Photographs from each actor (16 male and 16 female) were used to create sad-neutral, happy-neutral, and angry-neutral stimulus pairs (96 pairs total). Each stimulus pair was presented in random order over the course of 2 blocks, with a rest in between blocks. Consistent with previous studies (Gotlib, Kasch, et al, 2004; Gotlib, Krasnoperova, et al., 2004), stimuli were presented for 1,000 msec and then both pictures disappeared and a dot replaced one of the pictures (either emotional or neutral). Participants were asked to indicate as quickly as possible using a response box the location of the dot (left vs. right side of the screen). In each pair, the emotional face was presented with equal frequency on the left and right side of the screen and the probe occurred with equal frequency in the location of the emotional and neutral faces. The intertrial interval was 1,000 msec. Trials with response errors were excluded (2.63%) as were trials with response times less than 150 msec or greater than 1,500 msec (2.38%). Mean bias scores (Mogg, Bradley, & Williams, 1995) were then calculated separately for each emotion type (sad, happy, angry) by subtracting the mean response time for trials in which the probe replaced the emotional face from mean response times for trials in which the probe replaced the neutral

[1]Given potential concerns regarding population stratification, analyses were also conducted limiting the sample to Caucasian children and all significant effects were maintained.

[2]Although not the focus of this study, we also assessed participants' histories of anxiety disorders. Of the mothers, 12 (10 from the depressed group and 2 from the control group) met criteria for an anxiety disorder during their child's life. Of the children, 13 met lifetime criteria for an anxiety disorder (1 of whom also met criteria for a lifetime MDD). We should note, however, that neither mothers' nor children's history of anxiety disorders were significantly related to children's 5-*HTTLPR* genotype, attentional biases, or levels of depressive symptoms over the follow-up and all significant results were maintained even after statistically controlling for the influence of anxiety diagnoses.

[3]We recognize that "neutral" faces may not be evaluated as truly neutral (see, e.g., Lee, Kang, Park, Kim, & An, 2008). However, in this task, we were primarily interested in differences in reaction time to probes following emotional versus neutral faces rather than in neutral faces per se. Also, because "neutral" faces were used as the comparison picture for all emotional face conditions (sad, happy, angry), lack of true neutrality among these faces should not have led to systematic differences in attentional bias scores for one emotion type versus another.

face. Positive bias scores represent preferential attention toward the emotional faces, whereas negative scores indicate attentional avoidance of the emotional faces.

DNA assays. Children provided buccal cells by rubbing swabs along their cheeks and gums and rinsing out their mouths with 10 ml of distilled water. DNA was collected and isolated using published procedures (Freeman et al., 1997; Lench, Stanier, & Williamson, 1988). The *5-HTTLPR* S alleles were assayed using previously reported methods (Pooley, Houston, Hawton, & Harrison, 2003) and the rs25531 SNP genotypes (L_A vs. L_G) were obtained using a combination of published methods. The primers used for PCR were those reported in Hu et al. (2005) and the MspI restriction site protocol follows Wendland et al. (2006). Samples were analyzed on an ABI PRISM® 3130xl Sequencer. Consistent with previous research (e.g., Zalsman et al., 2006), two groups of participants were formed based on their genotyping: children with either one or two copies of the lower expressing S or L_G alleles (S′; $n = 58$) and those homozygous for the higher expressing L_A allele (L′; $n = 16$).

Procedure

Potential participants were recruited from the community through a variety of means (e.g., newspaper and bus ads, flyers). Mothers responding to the recruitment advertisements were initially screened over the phone to determine potential eligibility. Those reporting either significant depressive symptoms during the child's life or no significant lifetime symptoms of depression were invited to participate in the study. Upon arrival at the laboratory, mothers were asked to provide informed consent and children were asked to provide assent to be in the study. Next, the mother was administered the K–SADS–PL interview by a research assistant. During this time, the child completed questionnaires, including the CDI, as well as the attentional bias and DNA assessments in a separate room. After completing the K–SADS–PL with the mother, the same interviewer then administered the K–SADS–PL to the child. While children were being administered the K–SADS–PL, mothers completed a series of questionnaires including the BDI–II and were then administered the SADS–L by a separate interviewer. Participation in this initial assessment took approximately 3 hr, which included frequent breaks for children to minimize fatigue effects. Follow-up assessments occurred 2, 4, and 6 months after the initial assessment, during which participants were administered the BDI–II and CDI over the phone. Of the 74 mother–child pairs, 67, 66, and 67 participated at the 2-, 4-, and 6-month follow-ups, respectively (9.5% attrition). The only significant difference between participants who completed all of the assessments and those with missing data was that participants with complete data were more likely to be Caucasian (85%) than were participants with missing data (54%), $\chi^2(1, N = 74) = 6.54$, $p = .01$, $r_{effect\ size} = .30$. Families were compensated $100 for their participation. This study was approved by the Binghamton University Human Subjects Research Review Committee.

RESULTS

Preliminary Analyses

Preliminary analyses were conducted to determine whether any of the study variables were significantly related to children's age or sex. There were no significant sex differences in any study variables, and none of these variables was significantly related to children's age. Although we also examined whether children's age or sex moderated any of the relations examined in this study, none of these analyses were significant. Next, replicating previous research, children's lifetime history of MDD was significantly related to mothers' history of MDD during the children's life, $\chi^2(1, N = 74) = 9.29$, $p = .002$, $r_{effect\ size} = .36$. Indeed, all 10 children with lifetime MDD in this sample had a mother with a history of MDD. Preliminary analyses were also conducted to examine the link between children's *5-HTTLPR* genotype and maternal and child history of MDD. Children's *5-HTTLPR* genotype was not significantly related to maternal history of MDD, $\chi^2(1, N = 74) = 0.01$, $p = .92$, $r_{effect\ size} = .01$ (54.4% of children carrying the S′ allele had a mother with a history of MDD, compared to 52.9% of L′ children). Children's *5-HTTLPR* genotype was also not significantly related to their own lifetime history of MDD, $\chi^2(1, N = 74) = 0.32$, $p = .57$, $r_{effect\ size} = -.07$ (12.3% of children carrying the S′ allele had a history of MDD, compared to 17.6% of L′ children).

Maternal MDD History, Child *5-HTTLPR*, and Children's Attentional Biases

Next, we examined the relations of mothers' MDD history and child *5-HTTLPR* genotype with children's attentional biases. Specifically, we conducted a 2 (Mother MDD history: Yes, No) × 2 (Child *5-HTTLPR* genotype: S′, L′) × 3 (Facial expression: angry, happy, sad) repeated measures analysis of variance with attentional bias scores serving as the dependent variable. The main effects for mothers' history of MDD, $F(1, 70) = 0.31$, $p = .58$; child *5-HTTLPR* genotype, $F(1, 70) = 2.10$, $p = .15$; and Facial Expression, $F(2, 140) = 0.86$, $p = .43$, were all nonsignificant. It is important to note, however, that there was a significant Mother MDD × Facial

Expression interaction, $F(2, 140) = 3.62$, $p = .03$. The Mother MDD × Child *5-HTTLPR* genotype × Facial Expression interaction was a nonsignificant trend, $F(2, 140) = 2.65$, $p = .07$.

The form of the Mother MDD × Facial Expression interaction is depicted in Figure 1. Contrary to previous research (Joormann et al., 2007), tests of simple main effects within each facial expression type revealed that children of mothers with a history of MDD exhibited greater attentional avoidance (rather than preferential attention) of sad faces than did children of control mothers, $t(72) = -2.60$, $p = .01$, $r_{effect\ size} = -.29$. In contrast, and consistent with previous research, there were no significant maternal MDD history differences for children's attentional biases for happy, $t(72) = 0.88$, $p = .38$, $r_{effect\ size} = .10$, or angry, $t(72) = 0.90$, $p = .37$, $r_{effect\ size} = .11$, faces.

Although not meeting formal criteria for statistical significance, we also explored the Mother MDD × Child *5-HTTLPR* genotype × Facial Expression interaction. Conclusions from these analyses, however, should remain tentative. Focusing on the Mother MDD × Facial Expression interaction within each *5-HTTLPR* genotype group separately, we found significant Mother MDD × Facial Expression interactions among children carrying the *5-HTTLPR* S′ allele, $F(2, 110) = 3.40$, $p = .04$, but not among children homozygous for the L′ allele, $F(2, 30) = 1.91$, $p = .16$. Among the *5-HTTLPR* S′ allele carriers, tests of simple main effects within each facial expression type revealed that children of mothers with a history of MDD exhibited greater attentional avoidance of sad faces than did children of control mothers, $t(55) = -2.10$, $p = .04$, $r_{effect\ size} = -.27$. There were no significant maternal MDD history differences among carriers of the *5-HTTLPR* S′ allele for children's attentional biases for happy, $t(55) = 1.72$, $p = .09$, $r_{effect\ size} = .23$, or angry, $t(55) = 0.12$, $p = .90$, $r_{effect\ size} = .02$, faces.

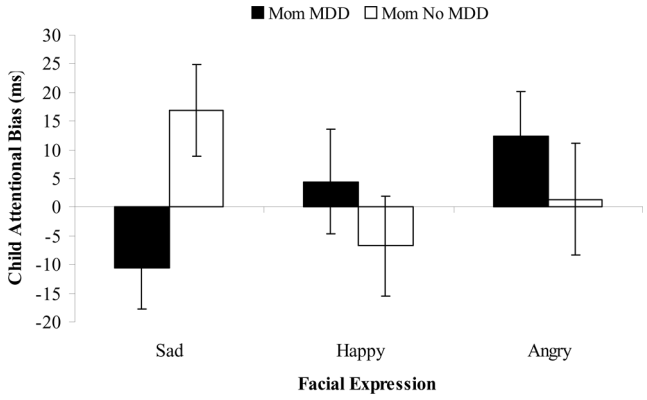

FIGURE 1 Children's mean attentional bias scores (in milliseconds) across the three facial expression types as a function of mother's major depressive disorder (MDD) history. *Note:* Error bars represent one standard error.

Although we also examined the link between children's history of MDD and their attentional biases, none of the main effects or interactions was significant (lowest $p = .19$).[4] However, children's attentional bias scores for sad faces were significantly related to their current depressive symptom levels, such that higher CDI scores were associated with greater attentional avoidance of sad faces ($r = -.25$, $p = .03$).

Additional analyses were then conducted to examine the robustness of the relation between maternal MDD history and children's attentional biases for sad faces. Children's attentional biases for sad faces remained significantly related to mothers' MDD history even when statistically controlling for the influence of mothers' current depressive symptoms (BDI-II scores), $F(1, 71) = 3.91$, $p = .05$, $r_{effect\ size} = -.23$, and even after excluding participant pairs in which the mother met criteria for current MDD ($n = 6$), $t(66) = -2.31$, $p = .02$, $r_{effect\ size} = -.27$, suggesting that children's attentional biases were not simply correlates of mothers' current depression. Also, the link between maternal MDD and children's attentional bias for sad faces remained significant even after statistically controlling for the influence of children's current depressive symptom levels (CDI scores), $F(1, 71) = 4.36$, $p = .04$, $r_{effect\ size} = -.24$, and when statistically controlling for children's lifetime history of MDD, $F(1, 71) = 3.82$, $p = .05$, $r_{effect\ size} = -.23$, suggesting that the biases were not simply a function of children's current depressive symptoms or lifetime history of MDD.

Although these findings are consistent with previous research suggesting that depression and depression risk are associated with attentional biases specifically for sad faces (e.g., Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Joorman et al., 2007), they contradict previous research in suggesting the presence of attentional avoidance, rather than preferential

[4]Children's attentional biases were associated with lifetime histories of depression more broadly defined (MDD, adjustment disorder with depressed mood, depressive disorder not otherwise specified). Specifically, conducting a 2 (child any depression history: yes, no) × 2 (Child *5-HTTLPR* genotype: S′, L′) × 3 (Facial expression: angry, happy, sad) repeated measures analysis of variance with attentional bias scores serving as the dependent variable, we found a significant Child Any Depression × Facial Expression interaction, $F(2, 140) = 5.27$, $p = .006$. Tests of simple main effects within each facial expression type revealed that children with a history of any depressive disorder ($n = 20$), compared to children with no depression history ($n = 54$), exhibited greater attentional avoidance of sad faces, $t(72) = -2.47$, $p = .02$, $r_{effect\ size} = -.28$. In contrast, there were no significant differences for children's attentional biases for happy, $t(72) = -0.03$, $p = .98$, $r_{effect\ size} = -.003$, or angry, $t(72) = 1.63$, $p = .11$, $r_{effect\ size} = .19$, faces. In these analyses, there were no significant main effects or interactions with children's *5-HTTLPR* genotype (lowest $p = .17$).

attention, for sad faces in at-risk children. Given this, exploratory analyses were conducted to determine whether any characteristics of mothers' MDD history were related to children's attentional biases for sad faces. Specifically, focusing only on children whose mother had a history of MDD ($n = 40$), we examined the potential impact of (a) whether the mother experienced recurrent MDD during her child's life ($n = 13$), (b) whether the mother was currently in an MDD episode ($n = 6$), (c) the child's age when his or her mother first experienced MDD during the child's life (range = 0–12 years), (d) the number of years since mother's MDD remitted (range = 0–12 years), and (e) the total proportion of the child's life that his/her mother met criteria for MDD (range = 0.003%–50%). The only significant relation was between children's age when their mother first experienced MDD and attentional biases for sad faces ($r = .34$, $p = .03$), indicating that the younger the child was when his or her mom first experienced MDD, the more attentional avoidance the child currently exhibited for sad faces.

Prospective Relation between Maternal and Child Depressive Symptoms

Next, we tested the hypothesis that children's attentional biases and *5-HTTLPR* genotype would moderate the link between mothers' and children's depressive symptoms during the follow-up period. We used Hierarchical Linear Modeling (HLM; Raudenbush & Bryk, 2002; Raudenbush, Bryk, Cheong, & Congdon, 2004) for these analyses, which allowed us to not only account for the nested structure of the data (repeated assessments of each mother–child pair) but also obtain maximum likelihood estimates of missing data, thereby allowing us to retain all participants for the analyses (cf. Schafer & Graham, 2002). In the HLM analyses, the dependent variable was children's CDI scores at each time point and the Level 1 predictor was mothers' BDI–II scores. The Level 2 predictors were children's attention bias scores for sad faces, *5-HTTLPR* genotype, and the *5-HTTLPR* × Attention Bias interaction. Mothers' history of MDD was also included in the Level 2 model to statistically control for its effects. In these analyses, none of the Level 2 variables were significantly related to the CDI intercept. Focusing next on the slope of the relation between BDI–II and CDI scores at each time point, we found that the relation was nonsignificant in the full sample, $t(69) = 1.08$, $p = .28$, $r_{effect\ size} = .13$. Of importance, however, the magnitude of the relation was significantly moderated by children's *5-HTTLPR* genotype, $t(69) = 1.98$, $p = .05$, $r_{effect\ size} = .23$; attention bias for sad faces, $t(69) = -2.74$, $p = .008$, $r_{effect\ size} = -.31$; and the *5-HTTLPR* × Attention Bias interaction, $t(69) = -2.87$, $p = .006$, $r_{effect\ size} = -.33$.

To determine the form of this interaction, we conducted analyses separately among children with at least one copy of the *5-HTTLPR* S′ allele versus those homozygous for the L′ allele. As with the previous analysis, the influence of mothers' history of MDD was statistically controlled in these subgroup analyses. Among carriers of the *5-HTTLPR* S′ alleles, although the slope of the relation between BDI–II and CDI scores at each time point was not significant, $t(54) = 1.46$, $p = .15$, $r_{effect\ size} = .19$, the relation was significantly moderated by children's attentional biases, $t(54) = -3.48$, $p = .001$, $r_{effect\ size} = -.43$, such that it was stronger among children exhibiting attentional avoidance of sad faces than among children exhibiting preferential attention. Among children homozygous for the L′ allele, the slope of the relation between BDI–II and CDI scores at each time point was not significant, $t(14) = -0.06$, $p = .95$, $r_{effect\ size} = .02$, nor was the effect significantly moderated by children's attentional biases, $t(14) = 1.10$, $p = .29$, $r_{effect\ size} = .28$. These results are depicted in Figure 2, for which we solved the HLM equations for values 1 *SD* below and above the attentional bias score mean (reflecting attentional avoidance and preferential attention, respectively; cf. Aiken & West, 1991) for specific levels of maternal depressive symptoms. To evaluate the robustness of these findings, the prospective analyses were repeated, statistically controlling for the influence of children's history of MDD. Each of the significant effects was maintained.

Finally, we tested our specificity hypothesis by examining whether children's attentional biases for happy or angry faces, alone or interacting with *5-HTTLPR* genotype, would moderate the link between mother and child depressive symptoms during the follow-up. None of these analyses was significant (lowest $p = .25$).

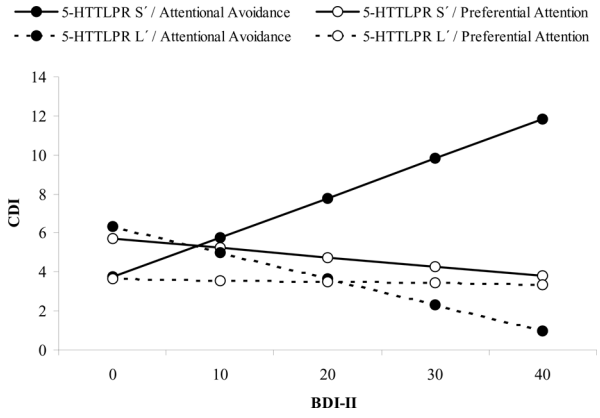

FIGURE 2 Relation between mothers' and children's depressive symptoms as a function of children's attentional biases for sad faces and 5-HTTLPR genotype. *Note:* BDI–II = Beck Depression Inventory–II; CDI = Children's Depression Inventory.

DISCUSSION

Our goal in this study was to test a model for the intergenerational transmission of depression integrating specific cognitive (attentional bias) and genetic (*5-HTTLPR*) risk factors. Supporting our hypotheses, children of mothers with a history of MDD during the children's lives, compared to children of mothers with no lifetime history of depressive disorders, exhibited attentional biases specifically for sad, rather than happy or angry, faces. However, in contrast to previous research (e.g., Joormann et al., 2007), we found evidence of attentional avoidance of sad faces rather than preferential attention. There was also some evidence that this attentional bias was stronger among children of depressed mothers carrying the *5-HTTLPR* S or L_G allele than among children homozygous for the L_A allele. Further, conceptualizing mothers' current depressive symptoms as an environmentally salient stressor with a vulnerability–stress framework, we found that mothers' and children's depressive symptoms covaried over the course of the follow-up, but only among children exhibiting both cognitive (attentional avoidance) and genetic (*5-HTTLPR* S or L_G allele) risk. Although previous research has supported the roles of attentional biases (e.g., Beevers & Carver, 2003) and *5-HTTLPR* genotype (Rutter et al., 2006; Uher & McGuffin, 2008) in risk for depression, this study is the first of which we are aware to support an interactive model of risk.

The current results are consistent with the hypothesis that the *5-HTTLPR* S and L_G alleles are associated with increased neurobiological reactivity to stress. Specifically, a number of studies have now documented the link between *5-HTTLPR* genotype and amygdala reactivity to emotional (facial) stimuli, with the *5-HTTLPR* short allele being associated with greater amygdala reactivity (for a review, see Munafò et al., 2008). There is also preliminary evidence that carriers of the *5-HTTLPR* S (or L_G) allele exhibit greater cortisol reactivity to a stressor (Gotlib et al., 2008). It is important to note, however, that current results suggest that *5-HTTLPR* genotype and attentional biases do not reflect purely overlapping risk factors for depression. Rather, our results are consistent with the hypothesis that *5-HTTLPR* genotype increases children's reactivity to their mothers' depression, which may not only contribute to the development of an attentional bias for sad faces but also interact with this attentional bias to increase children's depressive reactions to mothers' ongoing depressive symptoms.

Although our results are consistent with theory and previous research suggesting that attentional biases in depressed and depression-prone individuals are specific to sad faces (e.g., Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Joorman et al., 2007), they contradict previous research in suggesting the presence of attentional avoidance, rather than preferential attention, among children of mothers with a history of MDD during the children's lives. This discrepancy may have been due, in part, to the way in which attentional biases were assessed. Specifically, although the dot probe task used in this study was virtually identical to that used in previous research, previous studies have included a sad mood induction prior to assessing attentional biases. Some theorists (e.g., Clark et al., 1999; Persons & Miranda, 1992) have suggested that individuals' cognitive schema should be primed with a negative mood induction prior to assessing information-processing biases (e.g., attention biases). It is possible, therefore, that the direction of attentional biases for sad faces (preferential attention vs. attentional avoidance) may change depending on the child's current mood. In this light, it may be useful to draw upon findings from the infant literature. Specifically, there is evidence that infants of depressed mothers spend less time looking at their mothers than do infants of nondepressed mothers (Boyd, Zayas, & McKee, 2006). Similarly, infants look less at facial expressions of sadness than other emotions such as happiness or anger (Montague & Walker-Andrews, 2001). Researchers have suggested that infants avoid looking at sad faces as a mood regulation strategy and there is evidence that the extent to which this is unsuccessful (i.e., the extent to which infants do look at sad faces), the infants become sad themselves (Termine & Izard, 1988). It is difficult to draw any direct comparisons between findings from 3- to 9-month-old infants with those of 8- to 12-year-old children and there are likely developmental influences on attentional allocation to emotional stimuli. This said, it is possible that children of depressed mothers generally avoid looking at sad faces as a mood regulation strategy, but when dysphoric or under stress themselves, they may exhibit preferential attention for, or difficulty disengaging attention from, sad faces. We should note, however, that in our study, children's attentional bias scores for sad faces were negatively correlated with their concurrent depressive symptom levels as assessed with the CDI, such that higher CDI scores were associated with greater attentional avoidance of sad faces. It is possible that, because the CDI assesses levels of depressive symptoms over the past 2 weeks, scores on the questionnaire may not accurately reflect children's mood while actually completing the attention bias assessment. To more adequately test the mood-state dependent hypothesis, future research should seek to assess attentional biases in children of depressed mothers both before and after a mood induction. Finally, we should note that mixed findings have been observed in the direction of attentional biases with other disorders, such as anxiety. Specifically, although the

majority of research has supported the link between anxiety and preferential attention to threat in youth, there is evidence from some studies of attentional avoidance of threatening stimuli rather than preferential attention (for reviews, see Bar-Haim, Lamy, Pergamin, Bakersmans-Kranenburg, & van Ijzendoorn, 2007; Lau & Pine, 2008). Therefore, although we can have some confidence in the specificity of depression risk to attentional biases for sad rather than happy or angry faces, we must remain tentative regarding the direction of attentional biases among at-risk children, which may depend on current mood state, time course of attentional allocation, developmental influences, or unmeasured genetic effects. Future studies are needed to explore these possibilities.

We believe that the current results have a number of implications for models of the intergenerational transmission of depression. Specifically, they are the first of which we are aware to support the hypothesis that specific cognitive and genetic risk factors may interact to increase risk for depression in children of depressed mothers. As previously noted, these risk factors are typically examined independently, though both have been supported separately in vulnerability-stress models of depression (see Beevers & Carver, 2003; Rutter et al., 2006; Uher & McGuffin, 2008). Important for future research, children's attentional biases for sad faces moderated the link between mother and child depressive symptoms among children with at least one copy of the *5-HTTLPR* S or L_G allele but not among those homozygous for the L_A allele. An implication of this is that studies that do not take into account the potential moderating role of child genotype may miss meaningful effects based on cognitive risk. The current findings also provide support for Beck's cognitive vulnerability-event congruency hypothesis. Specifically, among children carrying the *5-HTTLPR* S or L_G allele, attentional biases for sad, but not happy or angry, faces interacted with mothers' depressive symptom increases to predict children's depressive symptom elevations. Therefore, maternal depression appears to be a particularly salient stressor for children who exhibit attentional biases for sad faces, especially when combined with the presence of the *5-HTTLPR* S or L_G allele. Future research should explore whether children's attentional biases for other facial expressions also interact with bias-specific negative life events. For example, given evidence that depressed mothers exhibit more criticism toward their children than do nondepressed mothers (for a review, see Goodman & Gotlib, 1999), it would be important to know whether attentional biases specifically for angry faces interact with levels of maternal criticism to predict child symptoms.

The current results also add to a growing body of research suggesting that the information-processing biases observed in children may be specific to the types of negative events they have experienced. Specifically, whereas in our study, mother history of MDD was associated with attention biases specifically to sad, rather than happy or angry, faces, other research has supported the specificity of children's histories of physical abuse to attention and interpretation biases for angry faces (Pine et al., 2005; Pollak & Kistler, 2002; Pollak & Tolley-Schell, 2003; see also Pollak, 2003). In our study, the link between mother history of MDD and children's attentional avoidance of sad faces was maintained even when mothers with current MDD were excluded from the analysis and when we statistically controlled for mothers' or children's current depressive symptoms or children's history of MDD, suggesting that the obtained results are not due simply to mothers' current depression or children's depression history. Although these results are consistent with the hypothesis that maternal depression may contribute to the development of children's attentional biases for sad faces, this conclusion must remain tentative pending future research examining whether maternal depression actually predicts prospective changes in children's attentional biases.

We should also highlight an interesting finding that emerged from our exploratory analyses of the characteristics of mothers' MDD history. Specifically, we found that children who were relatively younger when their mother first developed MDD exhibited greater attentional avoidance of sad faces than did children who were older at the time of their mothers' MDD onset. This result is consistent with the findings reviewed above from the infant literature in which infants of depressed mothers spend less time looking at their mothers than do infants of nondepressed mothers (Boyd et al., 2006). Although conclusions from these results must remain tentative pending replication, they suggest that the timing of developmental events (e.g., onset of maternal depression) may affect the development of children's attentional biases. Future studies are needed to further explore this intriguing possibility.

Despite the strengths of this study, there were limitations as well. First, although our use of the dot-probe task to assess attentional biases is consistent with previous research (e.g., Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Joormann et al., 2007), the dot-probe task only allows a determination of where children were allocating their attention at a specific point in time (e.g., 1,000 msec after stimulus onset). Future research would benefit from procedures that allow for a more fine-grained analysis of children's attentional patterns across an entire stimulus trial (e.g., eye-tracking). Second, our sample size was relatively small, which limited statistical power in this study. For example, it is possible that the Mother

MDD × Child *5-HTTLPR* genotype × Facial Expression interaction predicting children's attentional biases would have been statistically significant with a slightly larger sample size. This said, the fact that the significant relations were observed even with this relatively small sample speaks to the robustness of these findings. Nevertheless, future studies should seek to include larger samples, which will allow enough statistical power to define more precisely the role of children's *5-HTTLPR* genotype and attentional biases in the link between maternal and child depression. A third limitation was that the assessment of mothers' and children's depressive symptoms during the follow-up was based solely on their self-reports. Because each of the variables included in this study was based on a different method of assessment (e.g., child self-report, mother self-report, computer-based assessment of attention bias), it is unlikely that the observed results were due to shared method variance. This said, future studies should seek to include interviewer-administered, as well as self-report, measures of depressive symptoms across the follow-up. In addition to focusing on prospective changes in depressive symptom levels, research is also needed to determine whether children's attentional biases for sad faces predict the onset of depressive diagnoses. Fourth, as previously noted, because attentional biases were assessed only once, we could not examine whether mothers' depression contributed to prospective changes in children's attentional biases for sad faces. Prospective studies in which children's attentional biases are assessed repeatedly are needed to determine whether maternal depression actually contributes to the development of attentional biases for sad faces in children and whether these prospective effects are moderated by children's *5-HTTLPR* genotype. Fifth, there is always the possibility in any genetic association study of an unmeasured genetic or nongenetic third variable accounting for the associations reported (e.g., population stratification or linkage disequilibrium between measured variant and actual functional variant). Future studies, therefore, would benefit from the inclusion of a genomic control. Finally, we should note that we focused only on *5-HTTLPR* and a variety of genes likely contribute to the increased genetic risk for depression observed among children of depressed mothers. Indeed, other genes such as the brain-derived neurotrophic factor (*BDNF*) gene have been linked to cognitive vulnerability to depression (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007) and have been shown to interact with *5-HTTLPR* genotype to increase risk for depression in children (e.g., Kaufman et al., 2006). Future studies are needed to evaluate the potential role of *BDNF* and other genes in the intergenerational transmission of depression.

Implications for Research, Policy, and Practice

There is increasing evidence that providing effective treatment to depressed mothers reduces depression in their children (for a review, see Gunlicks & Weissman, 2008). Researchers are beginning to examine potential mechanisms of this effect (e.g., Foster et al., 2008) and studies are needed to determine the extent to which children's attentional biases for sad faces are also reduced with improvements in mothers' depression. It will also be important to identify potential moderators of this improvement (e.g., child age, chronicity of maternal depression, child genotype, etc.). To the extent that attentional biases serve as one mechanism in the intergenerational transmission of depression, particularly when combined with the presence of the *5-HTTLPR* S or L_G allele, it also becomes important to develop interventions specifically designed to reduce these attentional biases. There is increasing evidence for the efficacy of computer-based attentional modification programs in treating anxiety disorders (e.g., Amir, Beard, Burns, & Bomyea, 2009; MacLeod, Soong, Rutherford, & Campbell, 2007). Research is needed to determine whether similar approaches could be used for targeted prevention or early intervention programs among at-risk youth to reduce the likelihood that these attentional biases would contribute to the development of psychopathology later in life.

In summary, the current results suggest that specific cognitive (attentional biases for sad faces) and genetic (*5-HTTLPR* S or L_G allele) factors may interact to increase risk for the intergenerational transmission of depression. Although the exact nature of attentional biases for sad faces (vigilance vs. avoidance) among children of depressed mothers remains unclear, it does appear that these children exhibit altered attentional patterns to sad faces and that this attention bias is specific to sad faces rather than other types of emotion (happy or angry). There was also preliminary evidence that these effects may be stronger among carriers of the *5-HTTLPR* S or L_G allele than among children homozygous for the L_A allele. Most important, attentional biases for sad faces, in the presence of one or two *5-HTTLPR* S or L_G alleles, appear to heighten children's depressive reactions to their mothers' depressive symptom increases. We believe that the current findings represent an important initial step in integrating specific cognitive and genetic risk factors within models of the intergenerational transmission of depression.

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