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Sometimes It's Good to be Short: The Serotonin Transporter Gene, Positive Parenting, and Adolescent Depression

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In threatening environments, the short (S) allele of 5-HTTLPR is proposed to augment risk for depression. However, it is unknown whether 5-HTTLPR variation increases risk for depression in environments of deprivation, lacking positive or nurturant features. Two independent longitudinal studies (n = 681 and 176, respectively) examined whether 5-HTTLPR moderated associations between low levels of positive parenting at 11–13 years and subsequent depression at 17–19 years. In both studies only LL homozygous adolescents were at greater risk for depression with decreasing levels of positive parenting. Thus, while the S allele has previously been identified as a susceptible genotype, these findings suggest that the L allele may also confer sensitivity to depression in the face of specific environmental challenges.

Depression is a common and debilitating disorder with a complex etiology that frequently has its initial onset during adolescence (Merikangas et al., 2010). The aggregation of depression within families has led to a focus on understanding how genetic contributions may interact with other factors to affect risk for the emergence of this disorder (Sullivan, Neale, & Kendler, 2000). One widely studied genetic risk factor for depression is a variable number tandem repeat located within the promoter of the serotonin transporter gene (5-HTTLPR), which has been shown to modify the effectiveness of the serotonin transporter enzyme in clearing the synaptic cleft (Heils et al., 1996).

The field is unclear, however, about the extent to which 5-HTTLPR modifies overall serotonin neurotransmission in vivo, and the extent to which this creates risk for, or protects against, depression. A seminal study by Caspi et al. (2003) found that individuals carrying the "low expression" short (S) 5-HTTLPR allele (associated with reduced transcriptional efficiency and lower serotonin uptake activity) were more vulnerable to the depressogenic

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effects of childhood maltreatment or multiple negative stressful life events than were individuals homozygous for the long (L) allele. Attempts to replicate Caspi and colleagues' seminal findings have yielded mixed results, with two large meta-analyses showing no support for this Gene × Environment (G × E) interaction (Culverhouse et al., 2017; Risch et al., 2009) and two providing support for the G × E effect (Karg, Burmeister, Shedden, & Sen, 2011; Sharpley, Palanisamy, Glyded, Dillingham, & Agnew, 2014).

The largest of these meta-analyses by Sharpley et al. (2014), however, also noted that while the majority of studies in their analysis (65%) supported an association between the S allele, adversity, and depression, nearly 26% of the included studies failed to show a significant interaction, and approximately 10% found opposite results to those expected, implicating the L allele as conferring risk for depression in the presence of adversity. The authors suggested that these mixed findings do not necessarily deny a moderating role for this polymorphism; rather, they suggest that interactive effects may be more complex than originally conceptualized. Interestingly, a similar conclusion was reached in a recent meta-analysis by Weeland, Overbeek, de Castro, and Mattys (2015) that included 12 studies examining the interaction between the serotonin transporter gene, family adversity, and externalizing behaviors. Four studies found S carriers to be more vulnerable to the deleterious effect of family adversity, whereas four studies found L-allele homozygous individuals to be more at risk as a result of adverse family environments, and a further four studies obtained null results. Both Sharpley et al. (2014) and Weeland et al. (2015) raised the possibility that the L allele may too be associated with psychopathology in certain environmental contexts.

The interplay between allelic variation in the serotonin transporter gene and the environment in predicting outcomes such as depression has most commonly been discussed from a diathesis–stress, or vulnerability, perspective. This framework has often designated the S allele as a "risk" allele that confers greater sensitivity to stress, which in turn increases susceptibility to disorder in contexts of high adversity (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). However, an alternative conceptualization has been suggested that proposes that the S allele may be a "plasticity" allele that exhibits differing levels of adaptive fitness depending on the environmental context (Belsky & Pluess, 2009; Belsky et al., 2009). In this "differential susceptibility hypothesis," S carrier status is not simply a risk factor for hypersensitivity to adversity, and hence psychiatric disorder, but is rather associated with a greater sensitivity to environmental influences more generally. In propitious environments, this sensitivity may promote well-being or competence, while in adverse environments it may increase risk for negative outcomes.

The differential susceptibility hypothesis thus encompasses the notion of diathesis–stress, as well as the notion of *vantage sensitivity*, the term that has been used to describe the potential for some individuals to derive more benefit from positive environmental experiences than others (Pluess & Belsky, 2013). Importantly, capturing the vantage sensitivity component of differential susceptibility phenomenon involves a consideration of the adaptive spectrum rather than simply the maladaptive spectrum, as the *absence* of negative outcomes (i.e., no psychopathology) may not be the same as the *presence* of positive outcomes that would characterize thriving or optimal functioning. A smaller body of research has focused on the influence of positive environments, and a recent meta-analysis has suggested that S carriers show a greater ability to capitalize on positive, supportive contexts to achieve positive developmental outcomes (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012), a finding consistent with the notion that the S allele may confer differential susceptibility.

The research focusing on the interaction between 5-HTTLPR and adversity, where significant variation in findings has been noted, has considered a broad set of exposures including physical or sexual abuse, institutional rearing, natural disasters, bullying victimization experiences, marital conflict, divorce, chronic poverty, and unresponsive or punitive parenting (Sharpley et al., 2014). Emerging evidence suggests that experiences of *threat*, involving the presence of experiences characterized by actual or threatened harm, versus *deprivation*, involving impoverished expressive environments or the absence of expected environmental inputs and learning opportunities in cognitive, social, or emotional domains, may have distinct influences on neurodevelopment and associated psychological outcomes (McLaughlin, Sheridan, & Lambert, 2014). In particular, McLaughlin (2016) and McLaughlin et al. (2014) have argued that experiences of threat may alter the development of emotional processing by serving as potent learning experiences that may ultimately bias attention toward potential danger, increase reactivity to negative emotional information, and decrease automatic downmodulation of

emotional responses. In contrast, the authors have proposed that more deprived environments may adversely influence the development of other aspects of emotional processing, such as emotion recognition and discrimination as well as hamper development of executive functioning.

It is plausible that the serotonin transporter gene might be a marker of characteristics such as emotion processing and executive functioning that interact with these two forms of environmental experience in different ways. Interestingly, the strongest evidence for an interaction between the serotonin transporter gene and adversity appears to come from studies that have considered a single, specific exposure, such as childhood abuse or medical illness (Caspi et al., 2010). Although these studies may have considered different types of exposures, they are arguably united by their focus on threatening events, involving either the experience or anticipation of significant harm. In contrast, findings appear to be more mixed among the group of studies that have employed composite or count measures of adverse experiences, particularly based on checklists. This approach, which often includes experiences of both threat and deprivation, possibly obscures the distinct ways that the serotonin transporter gene interacts with particular environmental experiences to influence development.

Importantly, a component of the relationship between the serotonin transporter gene and environmental factors that has received relatively little systematic attention is whether 5-HTTLPR genotypes might interact with environments of deprivation to influence subsequent maladaptive psychological outcomes. It is well established that parenting and parent–child interactions have an impact on young people's risk of developing depressive disorders during adolescence (Yap, Pilkington, Ryan, & Jorm, 2014). While negative, harsh, or aggressive parenting behavior and positive, warm, or nurturing behavior could be conceived as falling on opposite ends of a single spectrum, research suggests that they represent distinct, albeit correlated, dimensions that make opposite and independent contributions to depression (Barrera, Chassin, & Rogosch, 1993; Dallaire et al., 2006). Indeed, although most parents are likely to be aware that critical or hostile parenting behaviors can be detrimental for children, there is some indication that failure to engage in positive, nurturing, and affirming interactions with children may also have adverse effects (Schwartz et al., 2017).

Parents low in positivity may be offering their children fewer opportunities to learn about the nature of different positive emotions, the ways in which these emotions might be elicited by various stimuli, and the contextual appropriateness of emotional expression (Eisenberg et al., 2005; Morris, Silk, Steinberg, Myers, & Robinson, 2007). They may also be modeling poor emotion regulation strategies or a lack of emotion regulation strategies to their children. Reduced positive caregiving behaviors and less secure child attachment have been linked to less developed child executive function and related constructs such as self-regulation and effortful control (Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Eisenberg et al., 2005), which have been associated with greater risk of psychological disorders such as depression. Intriguingly the limited available literature suggests that in these more deprived environments, the *L allele* might be associated with a range of poor outcomes. For example, Sulik et al. (2012) reported a relationship between low levels of supportive parenting and noncompliance in young children that was evident only in the group of children with an LL genotype. Davies and Cicchetti (2014) found that maternal unresponsiveness predicted greater externalizing problems, such as aggression and defiance, in children with the homozygous L genotype.

It is less clear whether this pattern of findings extends to internalizing disorders. Two studies provide evidence of an interaction between the serotonin transporter gene and the broader family climate that suggests L homozygous individuals may be vulnerable to depression in less positive environments. Laucht et al. (2009) found that adolescents homozygous for the L allele, but not adolescents with an S allele, showed increased vulnerability to depression and anxiety when they belonged to families that experienced a number of chronic adversities, such as early parenthood, low parental education, sole parenting, or parental psychiatric disorder. Lavigne et al. (2013) found that LL homozygous 4-year-old children showed greater increases in depressive and anxiety symptoms in the context of greater caretaker depression and family conflict and lower socioeconomic status (SES), as well as greater increases in symptoms of oppositional defiant disorder in the context of increases in family stress. Although these factors are known to impact on parenting behaviors (e.g., Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Rao & Chen, 2009), and indeed, were correlated with measures of parental support/engagement and parental hostility in this study of much younger participants in early childhood, parental support/engagement and hostility did not interact significantly with 5-HTTLPR

genotype. Moreover, Li, Berk, and Lee (2013) found a marginally significant interaction in girls, such that reduced family support predicted greater depression symptoms only among girls with the LL genotype. In contrast, they obtained a significant interaction for boys that conformed to a differential susceptibility model.

There is therefore some indication in the literature to suggest that possession of an L allele may confer increased vulnerability to adverse effects of more deprived family environments characterized by low support and nurturance. However, a systematic consideration of the differential effects of different genotypes in interaction with deprivation or threat has not been conducted within the same gene–environment study. Studies focusing on specific types of experiences (e.g., parenting lacking in warmth and nurturance) without adjusting for relevant co-occurring exposures (e.g., more punitive parenting) are limited in their conclusions regarding specific mechanisms that might underpin gene–environment interactions involving these different dimensions of adverse experiences to psychopathology. Rather, studies able to measure and model both of these dimensions of experience are required to identify whether such specificity exists.

Toward a More Nuanced Perspective on Moderation by the Serotonin Transporter Gene

One potential explanation for findings suggesting that carriage of either an S allele or an L allele might confer vulnerability to psychopathology depending on the environmental context might be related to potential psychological and behavioral characteristics associated with these different genotypes. While these characteristics have not been conclusively identified, a number of reviews of the neuropsychological, psychophysiological, hormonal, and brain imaging correlates of 5-HTTLPR genotype have posited that the S allele may confer greater emotional reactivity and stress-responsivity (Canli & Lesch, 2007; Caspi et al., 2010; Hariri & Holmes, 2006; Homberg & Lesch, 2011), which may be associated with negative *or* positive outcomes, contingent on the environment. However, until relatively recently there has been little consideration of what these same studies might suggest about traits associated with an L allele, and whether these characteristics might also affect vulnerability to psychopathology. Two reviews of the literature from this alternative perspective have argued that L allele may be linked to reduced emotionality (including shallow affect, lower levels of fearfulness, and reduced empathy, guilt, and shame) and lower stress sensitivity which may potentially increase risk for higher levels of callous–unemotional traits or psychopathy in the context of additional genetic and environmental factors (Glenn, 2011; Yildirim & Derksen, 2013). For example, compared to those with the LS or SS genotype, women with an LL genotype self-reported significantly greater difficulties with identifying feelings on a subscale measuring Alexithymia, a personality construct that captures problems with recognizing, expressing emotions, and understanding others' emotions (Kano et al., 2012). The L allele may also be associated with a bias toward positive emotional stimuli and/or a bias away from negative stimuli (Fox, Ridgewell, & Ashwin, 2009), a pattern of attention that may be consistent with the reward-dominant response style or punishment insensitivity that is seen in individuals with psychopathy or who are high in callous–unemotional traits (Dadds & Salmon, 2003). L homozygous individuals have also been found to display less emotionally expressive behaviors and reported less amusement, shame, and anger when watching themselves in embarrassing situations (Gyurak et al., 2013). They also demonstrated reduced levels of prosocial emotional empathy and exhibited lower cardiovascular and electrodermal activity when watching others in serious distress (Gyurak et al., 2013). Individuals homozygous for the L allele have been found to display higher levels of callous–unemotional traits compared to S carriers (Brammer, Jezior, & Lee, 2016), though one study found this effect to be limited to the group of individuals brought up in socioeconomically disadvantaged environments, which can be a marker of deprived circumstances more broadly (Sadeh et al., 2010).

The potential link between the L allele and higher callous–unemotional traits is perhaps particularly noteworthy given research suggesting that individuals high in callous–unemotional traits who receive low levels of parental warmth may be at particular risk of behavior symptoms (Pasalich, Dadds, Hawes, & Brennan, 2011) and that greater parental warmth/involvement predicts a decline in levels of callous–unemotional traits (Pardini, Lochman, & Powell, 2007). Furthermore, while callous–unemotional traits have typically been thought to be associated with low levels of anxiety and mood difficulties (Lykken, 1995), a number of studies have found that higher levels of callous–unemotional traits can in fact predict higher levels of internalizing problems (e.g., Hawes et al., 2014; Waller et al., 2015). One possible explanation for these

findings is that restricted affect and reduced empathy may pose increased risk for depression via greater social withdrawal, isolation, and anhedonia (Waller et al., 2015).

A number of genetic association studies have additionally suggested possible links between the 5-HTTLPR L allele and various aspects of executive functioning, including reduced cognitive flexibility (Borg et al., 2009; Tükel et al., 2016) and poorer sustained attention (Strobel et al., 2007). In addition, two studies provide some indication that the development of executive function of LL homozygous individuals may be impeded by adverse family environments potentially high in deprivation, involving higher levels of maternal depressive symptomatology (Weikum et al., 2013) or lower levels of parental supervision (Li et al., 2015). Interestingly, LL homozygous individuals also performed better than their S-allele counterparts on executive function tasks when their mothers endorsed few depression symptoms (Weikum et al., 2013).

In environments involving a high degree of threat, S-allele carriers, who are thought to be more emotionally reactive and especially sensitive to their context, may be at greater risk of stress-related psychopathologies, such as depression, than their less affectively responsive L homozygotes. Moreover, in certain positive environments, these particular traits associated with S-allele carriage may promote certain aspects of well-being, particularly those associated with socioemotional functioning. By contrast, in deprived environments that lack important nurturing features, the primary affective task may be to engage and extract nurturance and support from others in the interpersonal environment, a task for which S carriers might be better suited than L homozygous individuals, due to their greater capacity for affective engagement and social cognition. In such interpersonal environments where the primary challenge is to elicit care and support that is lacking, S carriers' greater capacity for emotional responding and engagement with others may offer a buffer against psychopathology. In these contexts, it may therefore be the emotionally hyporesponsive L homozygous individuals who are less adaptive, placing them at greater risk of psychopathology. Importantly, deficient emotional experiences, in the form of reduced emotional reactivity or low emotional responsiveness to changing contexts, have been associated with depressive disorders (Bylsma, Morris, & Rottenberg, 2008). Deficits in executive function have also been linked with depression (Snyder, 2013).

Thus, consideration of the L allele as simply insulating individuals from all environments (both positive and negative), as per the differential susceptibility hypothesis, may present an incomplete picture. Instead, it may be that *both* S-allele and L-allele individuals possess specific characteristics that may be advantageous or detrimental, depending on their environment. In other words, it is the *fit* (or lack thereof) between genetic or biological predispositions and environmental challenges that determines functioning and well-being. Importantly, this perspective does not suggest, for example, that S carriers do not require positive parenting or that L homozygous individuals are not hurt by aggressive, critical parenting, but rather that there may be combinations of genotypes and environments that are particularly adaptive or unfavorable relative to other combinations. This paradigm has some parallels with Thomas, Chess, and Birch's (1968) "goodness-of-fit" theory, which suggests that the degree of match or mismatch between a child's characteristics (temperament, capacities, and motivations) and the demands and expectations of the caregiving environment in which he or she functions is an important determinant of behavioral adjustment.

Our aim in this study was to examine whether allelic variations in the 5-HTTLPR moderate risk for depression in the context of low levels of positive parenting (a form of deprivation), while controlling for the effect of high levels of negative, hostile parenting (a form of threat), in two longitudinal studies. This approach enabled us to test the same conceptual model of the relationship between positive parenting and depression in independent samples using different methods of measurement. There is a particular need for such replications given the inconsistencies in findings to date regarding $G \times E$ interactions involving the serotonin transporter gene. Based on previous studies indicating poor outcomes in LL genotype children and adolescents exposed to low nurturant environments, we predicted L-allele homozygous individuals would show greater vulnerability to depression in these contexts, relative to S-allele carriers.

Study 1

Method

Participants and Procedures

Participants were from the Australian Temperament Project (ATP). The original ATP cohort comprised 2,443 four- to eight-month-old infants and

their families, recruited through maternal and child health centers in 1983. Families have been surveyed by mail generally every 1–2 years. Full descriptions of the background, sampling, and design of the ATP can be found in Prior, Sanson, Smart, and Oberklaid (2000). The subsample used for the current analysis consisted of the 681 participants (355 male) who had provided a DNA sample for genotyping purposes. Genetic samples were collected from participants who could conveniently be visited at home. These participants therefore tended to be located in more urban areas and were of higher SES than participants who did not provide genetic samples, but the two groups did not differ on the variables of interest (parenting measures at 13–14 years and depressive symptoms at 17–18 years). Participants were identified as of either Anglo/European Australian (96.8%) or non-Anglo/European Australian (3.2%) descent, based on parental country of birth. The analysis also draws on survey data collected when participants were 13–14 years and 17–18 years old.

Measures

Depressive symptomatology at 13–14 years and 17–18 years. Depressive symptomatology was measured by the self-report version of the Short Mood and Feelings Questionnaire (Angold et al., 1995), which has high reliability ($\alpha = .87$) in the overall ATP sample.

Parenting. Positive parenting, in the form of parental warmth (e.g., I enjoy listening to and doing things with my child), and harsh, aversive parenting, in the form of physical punishment (e.g., how often do you hit, slap or spank your child?), at age 13–14 years were measured according to the ATP-devised Parenting Practices Questionnaire (Letcher et al., 2004), which is based on parent report. The parental warmth scale and the physical punishment scale have shown adequate reliability ($\alpha = .74$ and .66, respectively) in the overall sample and have demonstrated good criterion validity (e.g., lower warmth and higher physical punishment have predicted higher levels of child internalizing and externalizing problems (Letcher et al., 2004)).

Genotyping. Buccal epithelial cells were collected via cotton swabs when participants were between 15 and 18 years old. Genomic DNA was isolated from the cells using QIA ampblood DNA kits (Qiagen, Hilden, Germany). Polymerase chain reaction (PCR) primers and conditions were as described by Heils et al. (1996). The method used for visualization of the PCR products in the ATP study has been described previously (Jorm et al., 2000). The genotype distribution for 5-HTTLPR ($n = 222$, LL; $n = 346$, SL; $n = 113$, SS) was in Hardy–Weinberg equilibrium, $\chi^2(1, N = 681) = 1.25$, $p = .263$.

Analysis Plan

Primary analysis. As the majority of studies have converged on dominance of the S allele over the L allele (e.g., Canli & Lesch, 2007; Heils et al., 1996), we focused our analyses on a dominant genetic model (LL = 0, SL + SS [i.e., S carriers] = 1).

Path models were specified to investigate the moderating effect of 5-HTTLPR genotype on the relationship between parental warmth and depressive symptoms, with adolescent gender, ethnicity, and physical punishment as covariates. The hypothesized model outlining the tests for moderating effects, which also includes potential evocative gene–environment correlations (*r*GE) between genotype and parenting, is presented in Figure 1. A covarying path between gender and ethnicity was not specified in the model as gender and ethnicity would not be expected to be related. Path models were calculated using the maximum likelihood estimator in Mplus (Muthén & Muthén, 1998–2012) and were based on 5,000 bias-corrected bootstrapped samples.

Prior to estimating the models, all continuous predictor variables and covariates were centered to reduce problems with multicollinearity. The interaction term was created by multiplying genotype and parental warmth. Significant interactions were clarified through post hoc analyses assessing whether the simple slopes representing associations between parental warmth and depressive symptomatology were significantly different from zero for the different genotypes (Preacher, Curran, & Bauer, 2006).

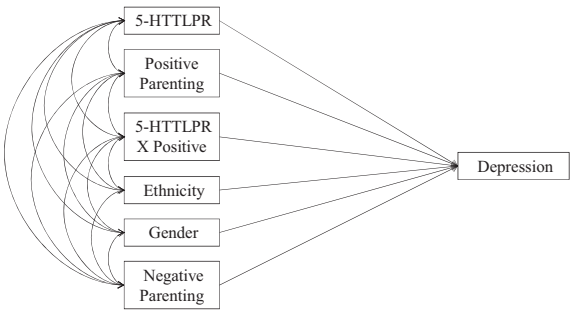

Figure 1. Hypothesized conceptual model outlining pathways examined in testing Gene × Parenting Effects on adolescent depression.

In addition, to assess the possibility of differential susceptibility, Roisman et al. (2012) have recommended that investigators conduct regions of significance (RoS) tests to determine the full range of values of the predictor X (i.e., parenting) for which the association between the moderator Z (i.e., 5-HTTLPR genotype) and Y (i.e., depressive symptoms) is significant. Roisman et al. (2012) recommend that results consistent with differential susceptibility predictions would require a significant moderator–outcome association at both the low end of X and the high end of X. Roisman et al. (2012) suggested a guideline of bounding the range of X by ± 2 *SD* for the RoS tests to reduce the likelihood that values of X are not represented in the sample, however, they also note that this approach is sensitive to sample size, and that it is not uncommon for plots that look highly consistent with a pattern of differential susceptibility to be incorrectly classified as providing evidence for diathesis–stress as a result of low statistical power. The authors therefore additionally recommend the use of a metric named the proportion of interaction (PoI) index, a measurement of the proportion of the total area between the two lines for each genotype group that comprise the interaction plot bounded by +2 *SD* on X, that is, above the crossover point. In a prototypical interaction plot for differential susceptibility (i.e., a cross-over or disordinal interaction), the lines would be expected to cross-over at the mean of X, resulting in 50% of the area bounded by the regression lines representing the "for better" region. In a prototypical plot for diathesis–stress (i.e., an ordinal interaction), the crossover point will occur on the far right side of the plot, such that 0% of the total area would represent the "for better" region. Roisman et al. (2012) initially specified that, as an approximate marker, interactions with values on the PoI metric between about 0.40 and 0.60 could be considered highly consistent with differential susceptibility. More recently, Del Giudice (2017) has proposed a revision based on a 0.20–0.80 range of PoI values given concerns that the narrower window of 0.40–0.60 may be associated with a high likelihood of false negatives, while the 0.20–0.80 window improves detection with little elevation in the rate of false positives. As noted by both Del Giudice (2017) and Salvatore and Dick (2015), there can however be difficulties with classifying variants as differential susceptibility loci by such methods, given measures of the environments typically do not have true zeros. As such, the range of environments captured for any given sample (i.e., high or low risk) will affect the shape of the observed interaction. To generate RoS on Z and PoI, we used a web-based program available at http://www.yourpersonality.net/interaction/ that is a supplement to the article by Roisman et al. (2012) developed by the author Fraley.

Follow-up analyses. The primary interest of this study was whether the lack of a positive environment (i.e., reduced warmth, or positive behaviors displayed by parents) would alter risk for depression differently in S carriers versus L homozygous individuals. A large literature however suggests that S carriers are more susceptible to the presence of harsh, negative environments (such as those involving significant child maltreatment or stressful life events) compared to L homozygous individuals. We therefore also examined whether 5-HTTLPR interacted with parental use of physical punishment, controlling for gender, ethnicity, and parental warmth.

To further clarify the nature of the interactions, some additional exploratory analyses were conducted. First, due to possible variation in allelic frequencies among different racial groups, analyses evaluating the interaction between 5-HTTLPR genotype and parenting were tested separately in the group of participants of Anglo-European background ($n = 656$). Second, we completed a set of analyses that additionally controlled for baseline depressive symptoms at 13–14 years. Inclusion of baseline depressive symptomatology as a covariate allowed an examination of whether the interaction predicted prospective *change/growth* in depressive symptomatology over adolescence rather than *absolute* depressive symptomatology at the end of adolescence. The addition of this covariate introduces seven new paths into analyses. The reductions in power associated with this inclusion also means that these analyses should be interpreted with some caution.

Given that "dose-related" additive effects of the S allele in addition to dominance effects have been documented by some studies (e.g., Caspi et al., 2003), with recessive effects being observed far less frequently (e.g., Williams et al., 2003), all of these analyses were rerun based on an additive genetic model (LL = 0, SL = 1, SS = 2).

Missing data. Missing data averaged 12.1% (range = 0%–16.9%). Analyses presented in Supporting Information suggested that data were missing at random (MAR). Missing data were therefore accounted for by the full information maximum likelihood (FIML) method to increase statistical power and to make optimal use of the data. FIML is recommended in situations where data are MAR, including when a large proportion of participants are missing data (Schlomer, Bauman, & Card, 2010)

and has been found to be less biased and more efficient than deletion and single-imputation methods (Enders & Bandalos, 2001).

Results

Descriptive statistics, including intercorrelations between depression, variation in the serotonin transporter polymorphism, ethnicity, gender, parental warmth, and physical punishment are shown in Table 1.

The bivariate correlation between 5-HTTLPR genotype and parental warmth was not significant, suggesting that any G × E effects are not a function of an evocative *r*GE.

Primary Analysis

Model fit indices showed that model provided an acceptable fit to the data (see Table S1). Path model results are displayed in Table 2. For parsimony, only key relations of interest between the independent variables (5-HTTLPR, parental warmth, and the 5-HTTLPR × Parenting interaction term), covariates (gender, ethnicity, and physical punishment) with the dependent variable (depressive symptomatology), and the covarying association between 5-HTTLPR and positive parenting are shown. Results of the complete models, including other covarying paths between independent and covariate variables, are provided in Table S2.

The model explained 12% of the variance in depressive symptoms, as indicated by the R^2 value (.12). Results indicated a significant path from lower parental warmth at 13–14 years to higher levels of depressive symptomatology at age 17–18 years. There was no main effect of physical punishment or 5-HTTLPR genotype on adolescent depression, nor was genotype related to parental warmth, physical punishment, or to participant ethnic background. Female gender was significantly related to higher depressive symptomatology and parental warmth, and to lower levels of physical punishment. Lower parental warmth was significantly associated with higher physical punishment. There was a significant 5-HTTLPR × Parental Warmth interaction effect on depressive symptomatology, which is shown in Figure 2.

The interaction indicated that parental warmth significantly predicted depressive symptoms for the L homozygous group ($b = -0.29$ [95% CI: −0.43, −0.15], $SE = 0.07$, $\beta = -.29$, $p = .0001$), but not the S carrier group ($b = -0.08$ [95% CI: −0.19, 0.02], $SE = 0.05$, $\beta = -.08$, $p = .126$). S carriers showed a stable risk for depressive symptoms that was independent of parental warmth, whereas L homozygous individuals showed increasing risk for depressive symptoms as a function of decreasing levels of parental warmth.

For the RoS on X test, the regression of depressive symptoms on serotonin transporter genotype is statistically significant for all values of positive parenting that fall outside of the range of −0.30 to 2.53. As the upper bound exceeds 2 *SD*, this finding suggests the association between genotype and depression is predominantly significant when positive parenting is lower, and the interaction is considered to be more consistent with diathesis–stress

Table 1
Descriptive Statistics and Intercorrelations for Variables From the Australian Temperament Project in Study 1

Variables	1	2	3	4	5	6	7
1. Depressive symptoms at 17–18 years	—	.33***	.11	−.02	−.12**	.06	.46***
2. Gender (0 = male, 1 = female)		—	−.08	−.03	.15**	−.14**	.137**
3. Ethnicity (0 = Australian-European descent, 1 = non-Australian-European descent)			—	−.08	−.10	−.12	.191
4. Dominant serotonin transporter genotype (0 = LL, 1 = SS or SL)				—	.00	−.02	−.103*
5. Parental warmth					—	−.12***	−.151***
6. Parental physical punishment						—	.118**
7. Depressive symptoms at 13–14 years							—
Percentage of sample or *M* (*SD*)	2.10 (0.60)	Males = 52.2%	Australian-European descent = 96.8%	LL = 32.6%	4.21 (0.60)	1.25 (0.47)	4.30 (3.35)

*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Table 2
Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Warmth at 13–14 Years on Depressive Symptomatology at 17–18 Years in Study 1

Pathway	*b*	*SE*	95% CI [lower, upper]	β	*p*
5-HTTLPR → Depressive symptoms	−0.06	0.05	[−0.16, 0.04]	−.05	.245
Parental warmth → Depressive symptoms	−0.29	0.07	[−0.43, −0.14]	−.29	.000
Physical punishment → Depressive symptoms	0.10	0.06	[−0.01, 0.21]	.08	.080
Ethnicity → Depressive symptoms	0.16	0.15	[−0.11, 0.47]	.05	.268
Gender → Depressive symptoms	0.34	0.05	[0.25, 0.44]	.29	.000
5-HTTLPR × Parental Warmth → Depressive symptoms	0.20	0.09	[0.02, 0.39]	.16	.028
5-HTTLPR ↔ Parental warmth	0.00	0.01	[−0.02, 0.03]	.01	.777

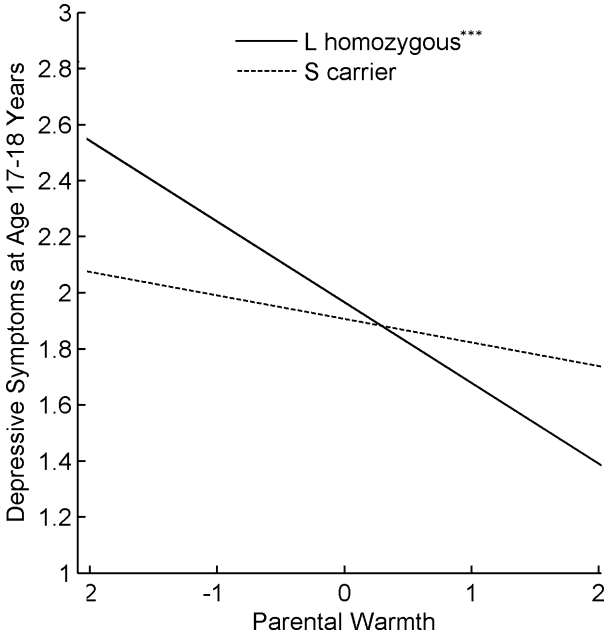

Figure 2. Influence of parental warmth at age 13–14 years on depressive symptoms at 17–18 years for L homozygous individuals and S carriers in Study 1.
***$p < .001$.

rather than differential susceptibility. However, the PoI = 0.36 may be interpreted as providing moderate support for a differential susceptibility model, given it is within the range of 0.20–0.80 that is considered as consistent with differential susceptibility, and only just outside of the range of 0.40–0.60, specified as providing strong support for differential susceptibility model.

Follow-Up Analyses

There was no evidence of a significant interaction between 5-HTTLPR and negative parenting (parental use of physical punishment), as shown in Table S3. The finding of an interaction between 5-HTTLPR and parental warmth predicting depression cannot be accounted for by an association between parental warmth and physical punishment.

The same patterns of findings involving a significant interaction between 5-HTTLPR (analyzed according to an S-allele dominant model) and parental warmth were observed when models were rerun for the largest ethnic subsample ($n = 656$) of participants of Anglo-European background (Table S4). The interaction involving physical punishment remained nonsignificant (Table S5). The interaction between 5-HTTLPR and parental warmth was no longer significant when baseline depressive symptoms were included in the model (Table S6). The interaction between 5-HTTLPR and physical punishment controlling for baseline depressive symptoms also failed to predict depressive symptoms at 17–18 years (Table S7).

None of the interactions between 5-HTTLPR × Parenting was significant when an additive genetic model was used, as shown in Tables S2–S7.

Study 2

Method

Participants and Procedures

The analyses in Study 2 are based on an initial subsample of 176 participants from the longitudinal Orygen Adolescent Development Study (ADS), conducted in Melbourne, Australia, who had provided a genetic sample during the course of their participation. Of the 176 participants, 1 participant was diagnosed with major depressive disorder (MDD) at the diagnostic assessment during the first wave of the study (W1) and another was diagnosed with major depressive episode within the context of a bipolar I disorder during the course of the study.

These 2 participants were excluded from this research to enable the study to be prospective in relation to MDD onset specifically (rather than affective disorders more broadly), leaving a total sample of 174 participants (71% of the total sample of 245 participants; 83 male).

The broad recruitment and screening of ADS participants has been fully reported previously (Yap et al., 2008). Briefly, the sample, drawn from the general community of final year primary school students in metropolitan Melbourne, was risk enriched based on the scores on the temperament dimensions of negative emotionality and effortful control, measured according to the Early Adolescent Temperament Questionnaire–Revised (Ellis & Rothbart, 2001) given their hypothesized role as vulnerability factors for emotional and behavioral disorders. Participants in the current analyses were identified as of either Anglo-European (87.7%) or non-Anglo-European (12.3%) background, based on their grandparents' country of birth.

The ADS involved four waves of data collection: W1 (M_{age} = 12.7 years, range = 11.4–13.7 years) included a diagnostic interview that assessed for current and lifetime episodes of MDD to exclude participants with a history of the disorder, and a family interaction assessment, which allowed observation and coding of parenting behavior. Study 2 examines depressive symptoms at age 18–19 years collected via questionnaire at the fourth and final wave of the study (W4) as the outcome of interest, to closely replicate Study 1.

Measures

Depressive symptomatology at 11–13 years and 18–19 years. Depressive symptomatology was measured according to the Center for Epidemiological Symptoms Depression Scale (CES–D; Radloff, 1977). The CES–D consists of 20 items, rated on a 4-point scale from 0 (*rarely or none of the time*) to 3 (*most or all of the time*).

Parenting. The frequency of positive and aversive parenting behaviors displayed by mothers was assessed during two 20-min parent–child interaction tasks at W1, which were videotaped for coding. An event-planning task was completed first, followed by a problem-solving task. The tasks were intended to differentially elicit positive and negative behaviors, respectively, thereby enabling an explicit examination of the effect of the interactional context on affective processes. Our previous work has indicated that negative parental behavior displayed during the positive event-planning interaction (EPI) task and positive parental behavior during the negative problem-solving interaction (PSI) task may be particularly salient predictors of adolescent depression (Schwartz et al., 2017). The ordering of tasks was fixed because of concern that negative affective states elicited by the problem-solving task had the potential to persist into the positive, event-planning task if the latter were conducted second.

For the EPI, mothers and adolescents were instructed to plan one or more pleasant events to do together, with up to five events chosen based on items that both the mother and adolescent rated as being *very pleasant* on the Pleasant Events Schedule (MacPhillamy & Lewinsohn, 1976). For the PSI, up to five issues for discussion were selected that both the mother and adolescent endorsed as occurring the most frequently and generating the highest intensity of anger on the issues checklist (Prinz, Foster, Kent, & O'Leary, 1979). Parenting behavior from the tasks was coded according to the Living in Family Environments (LIFE) coding system. The LIFE (Hops, Biglan, Tolman, Arthur, & Longoria, 1995) is an observational, microsocial coding system that enables a detailed analysis of individual family members' behaviors and interactive family behaviors. In this study, the constructs of interest were the frequency of positive behaviors and aversive behaviors displayed by mothers on both the EPI and the PSI. Positive behavior included displays of happy, pleasant, and caring affect as well as approving, validating, affectionate, or humorous comments made with neutral affect. Aversive behavior included all events with contemptuous, angry, and belligerent affect, as well as disapproving, threatening, or argumentative verbal content with neutral affect. Approximately 20% of the interactions were coded by a second observer to provide an estimate of observer agreement. Kappa coefficients (a conservative index of interobserver reliability based on point-by-point agreement and corrected for chance) for the positive and aversive behavior constructs were .86 and .70, respectively. The validity of the LIFE system as a measure of family processes has been established in numerous studies (e.g., Sheeber, Davis, Leve, Hops, & Tildesley, 2007).

Genotyping. Saliva was collected from participants for genetic analysis using Oragene DNA saliva collection kits (www.dnagenotek.com). Methods used for PCR amplification and visualization by gel electrophoresis were as described by Edenberg and Reynolds (1998). The genotype distribution for 5-HTTLPR (n = 54, LL; n = 83, SL; n = 37, SS) was in Hardy–Weinberg equilibrium, $\chi^2(1, N = 174) = 0.24$, $p = .627$.

Analysis Plan

The same analytic strategy employed in Study 1 was used to predict continuous depressive symptoms in Study 2, except that two separate path models were estimated to document effects of positive parenting in the EPI task and the PSI task.

Treatment of missing data. Levels of missing data averaged 13.3% (range = 0%–28.6%). Little's (1988) MCAR test was nonsignificant, $\chi^2(163) = 179.54$, $p = .178$, therefore FIML was used to account for missing data.

Results

Correlations between variables in Study 2, namely depressive symptoms, serotonin transporter polymorphism variation, ethnic background, gender, positive parenting, and aversive parenting in the two interaction tasks, are shown in Table 3. 5-HTTLPR genotype and positive maternal behavior in the PSI (though not in the EPI) task were significantly correlated ($r = .22$, $p < .05$), indicating that a G × E effect between these two variables could be a function of evocative *r*GE. Aversive maternal behavior in the EPI and the PSI were not significantly correlated with 5-HTTLPR genotype.

Primary Analyses

Model fit indices showed that all models in Study 2 provided an acceptable fit to the data (see Table S1). Results for the paths from independent variables (5-HTTLPR, positive parenting, and the 5-HTTLPR × Positive Parenting interaction term) and covariates (gender, ethnicity, and aversive parenting) predicting depressive symptoms, as well as the covarying association between 5-HTTLPR and positive parenting are presented in Table 4. Results of the complete models are provided in Table S8. The model for the EPI task explained 12% of the variance in risk for depressive symptomatology ($R^2 = .12$), while the model for the PSI task explained 9% of the variance in risk for depressive symptomatology ($R^2 = .09$). In the EPI, both lower frequencies of positive maternal behavior and higher frequencies of aversive maternal behavior at age 12–13 years were associated with higher levels of depressive symptomatology at 18–19 years. Lower positive maternal behavior was also related to higher aversive maternal behavior. Gender and ethnicity did not show significant associations with depressive symptoms, parenting, or genotype. Neither 5-HTTLPR genotype nor the interaction

Table 3
Descriptive Statistics and Intercorrelations for Variables From the Adolescent Development Study in Study 2

Variables	1	2	3	4	5	6	7	8	9
1. Depressive symptoms at 18–19 years	—	.15	.11	.03	−.19*	−.18	.27**	.13	.33***
2. Gender (male = 0, female = 1)		—	−.004	.13	−.08	−.05	.07	−.07	−.12
3. Ethnicity (0 = Australian-European descent, 1 = non-Australian-European descent)			—	.22	−.26	−.21	.05	.12	−.12
4. Dominant serotonin transporter genotype (0 = LL, 1 = SS or SL)				—	.12	.24*	−.12	−.11	−.04
5. Positive parent behavior event-planning interaction					—	.41***	−.31***	−.26**	.08
6. Positive parent behavior problem-solving interaction						—	−.43***	−.44***	−.14
7. Aversive parent behavior event-planning interaction							—	.52***	.18*
8. Aversive parent behavior problem-solving interaction								—	.11
9. Depressive symptoms at 11–13 years									—
Percentage of sample or *M* (*SD*)	30.92 (9.29)	Male = 47.70%	Australian-European descent = 87.70%	LL = 31%	2.368 (0.64)	1.752 (0.68)	.57 (0.41)	1.26 (0.61)	31.21 (9.50)

*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Table 4
Path Model Testing the Interaction Between 5-HTTLPR Genotype × Positive Maternal Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years

	EPI task					PSI task				
	b	*SE*	95% CI [lower, upper]	β	*p*	*b*	*SE*	95% CI [lower, upper]	β	*p*
5-HTTLPR → Depressive symptoms	1.04	1.61	[−2.18, 4.19]	.05	.520	1.02	1.58	[−2.04, 4.16]	.05	.517
Positive parenting → Depressive symptoms	−5.19	2.39	[−10.20, −0.68]	−.27	.030	−6.28	2.32	[−11.36, −2.19]	−.46	.007
Aversive parenting → Depressive symptoms	5.31	2.14	[1.09, 9.52]	.23	.013	0.80	1.88	[−2.96, 4.41]	.05	.672
Ethnicity → Depressive symptoms	1.28	2.36	[−3.33, 5.92]	.05	.587	1.19	2.35	[−3.62, 5.67]	.04	.614
Gender → Depressive symptoms	1.82	1.54	[−1.05, 5.01]	.10	.238	1.81	1.57	[−1.15, 5.00]	.10	.248
5-HTTLPR × Positive parenting → Depressive symptoms	5.86	3.50	[−0.93, 12.79]	.23	.094	6.18	2.87	[0.58, 11.94]	.37	.031
5-HTTLPR ↔ Positive parenting	0.02	.02	[−0.03, 0.06]	.09	.375	0.05	0.03	[0.00, 0.11]	.17	.054

Note. EPI = event-planning interaction; PSI = problem-solving interaction.

between 5-HTTLPR genotype and positive maternal behavior were significant predictors of depressive symptomatology.

In the PSI, low frequencies of positive maternal behavior were associated with more frequent aversive maternal behavior as well as with higher levels of depressive symptomatology in late adolescence. Aversive maternal behavior however was not associated with later depressive symptoms. Gender and ethnicity were also unrelated to depressive symptoms, genotype, and parenting. 5-HTTLPR genotype was associated with positive maternal behavior at trend level (p = .054), but not with aversive maternal behavior. Critically, the interaction between 5-HTTLPR genotype and positive maternal behavior was significant.

The interaction, graphed in Figure 3, indicated that the frequency of positive maternal behavior was predictive of depressive symptoms for L homozygous individuals (b = −6.28 [95% CI: −11.26, −1.30], SE = 2.54, β = −.46, p = .014), but not S carriers (b = −0.10 [95% CI: −3.42, 3.22], SE = 1.70, β = −.09, p = .953). S carriers' risk for depressive symptoms was observed to remain stable, independent of the frequency of positive maternal behavior experienced, while L homozygous individuals' risk increased as a function of decreased frequencies of positive maternal behavior. RoS analysis indicated that the association between serotonin transporter genotype and depressive symptoms was significant for all values of positive maternal behavior outside of the values of [−2.21, .72]. As the lower bound exceeds 2 *SD*, this finding suggests the association between genotype and depression is predominantly significant when positive parenting is higher (indicative of a buffering effect of positive parenting on depression risk for L homozygyous individuals relative to S carriers). However, the PoI = 0.58, which may be interpreted as providing high support for a differential susceptibility model resembling a cross-over interaction with a cross-over close to the mean.

Follow-Up Analyses

As in Study 1, we did not find evidence that 5-HTTLPR interacted with aversive parenting to predict depressive symptomatology (see Table S9). The

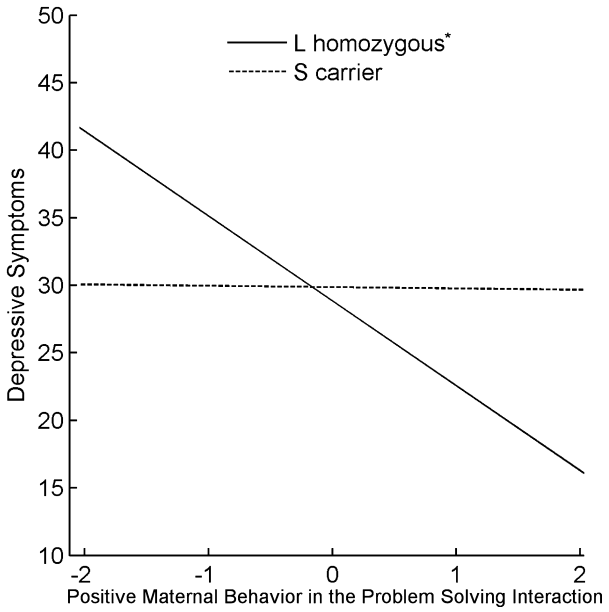

Figure 3. Influence of positive maternal behavior experienced at 11–13 years on depressive symptoms at 18–19 years for L homozygous individuals and S carriers in Study 2.
*p < .05.

finding of an interaction between 5-HTTLPR and positive parenting predicting depression therefore cannot be accounted for by an association between positive parenting and aversive parenting. Interactions were also nonsignificant when analyses were rerun according to an additive model (see Tables S8 and S9).

We additionally ran path models separately for the largest ethnic subsample of participants of Anglo-European background (n = 150), which are displayed in Tables S10 and S11. When the S allele was treated as dominant, the size of the standardized coefficient of the interaction between Positive Maternal Behavior × 5-HTTLPR (β = .31) was very similar to that obtained for the overall sample, though this finding was no longer significant (p = .089), presumably reflecting the decrease in power associated with a smaller sample size.

As shown in Tables S12 and S13, analyses were also rerun with the inclusion of baseline depressive symptomatology as a covariate to allow an examination of whether the interaction predicted prospective *change/growth* in depressive symptomatology over adolescence. The interaction between 5-HTTLPR and positive parenting in the PSI remained significant when an S-allele dominant genetic model was assumed, and nonsignificant when an additive genetic model was assumed. In addition, significant interactions between 5-HTTLPR and positive parenting in the EPI emerged for both S dominant and additive genotype models. Specifically, lower frequencies of positive maternal behavior significantly predicted depressive symptoms for the L homozygous group, but not for S carriers.

Discussion

The current results provide evidence of an interaction between 5-HTTLPR and low levels of positive parenting in predicting depression. In two independent cohorts, findings indicated that when the S allele of the serotonin transporter gene was coded as dominant, adolescents carrying at least one copy of the S allele showed little change in their risk of depression as a function of the positive parenting they received, while adolescents in the L homozygous group were at greater risk for depression with decreasing levels of positive parenting. Overall, the findings conflict somewhat with the more traditional view of the differential susceptibility hypothesis, which has suggested that the S allele is a "plasticity" allele that increases general sensitivity to environmental effects while the homozygous L disposition is associated with more fixed outcomes across environments (Belsky et al., 2009). This pattern of results is consistent with findings by other studies demonstrating that L homozygous individuals who experience low maternal responsiveness or lack of supportive parenting may be more vulnerable to externalizing difficulties (e.g., Davies & Cicchetti, 2014; Lavigne et al., 2013), and with one previous study finding a trend suggesting that L homozygous girls may exhibit higher depressive symptoms than S carriers in family environments involving low levels of support (Li et al., 2013). Taken together, these studies constitute an emerging body of research that suggests that in certain contexts L homozygous individuals may also be vulnerable to maladaptive outcomes.

It is noteworthy that the current findings were obtained in two longitudinal cohorts, based on independent samples, with different measures of depression (i.e., depressive symptomatology using a self-report scales at 17–18 years in Study 1 and at 18–19 years in Study 2) and different methods of measuring positive parenting (i.e., parental warmth according to parent report vs. an observational measure of positive parental behavior).

Somewhat surprisingly, the association between positive parenting and depression was nonsignificant for S carriers in both Study 1 and Study 2, suggesting that S carriers were neither at increased risk for depression in more deprived environments of lower positive parenting, but they also did not appear to be buffered from depression in arguably more, supportive environments of higher positive parenting. While the former finding was in line with the hypotheses of the current study, the latter finding might be interpreted by some as a contradiction of the hypothesis that S carriers demonstrate vantage sensitivity—a proclivity to benefit from enriched environments. We would contend however, in line with positive development/adjustment research which views positive functioning and well-being as distinct from (albeit partly related to) the absence of mental ill health (Tolan, Ross, Arkin, Godine, & Clark, 2016), that the lack of a protective effect of high positive parenting on depression risk for S carriers relative to LL homozygous individuals does not necessarily mean that enhancing effects of positive parenting on component behaviors, capabilities, and experiences of more positive functioning would not be present.

There was also evidence that S carrier status was correlated with higher levels of observed positive parenting behaviors during the PSI in Study 2 (though a similar association was not detected in Study 1, which was based on parent report). This

finding could indicate an evocative *r*GE that would be consistent with the possibility that S carriers are better able to elicit warmth or nurturance from their parents. However, as parent genotype was not available in the current study, the possibility that genetic relatedness between the parent and the adolescent accounts for the observed correlation between adolescent genotype and positive parenting, such that parent genotype may in fact be predicting the levels of their own positive behavior (a passive *r*GE; Plomin, DeFries, & Loehlin, 1977) cannot be ruled out. It is noteworthy that a different study that also relied on observational methods of parenting found the S allele of the serotonin transporter gene in boys predicted higher levels of mothers' positive parenting, with this effect being mediated by greater self-control exhibited by the child (Pener-Tessler et al., 2013). Interestingly, while there was also an association between mothers' serotonin transporter genotype and positive parenting, the effect of boys' 5-HTTLPR genotype on parenting remained significant following the inclusion of mothers' genotype in the model, suggesting that the association between the child's genotype and parenting could not be solely attributed to a passive *r*GE and supporting a hypothesis for the role of an evocative *r*GE.

Contrary to expectations, the interaction between the serotonin transporter gene was not found to moderate risk for depression in family environments involving more hostile and punitive parenting in both samples. However, null findings in the broader serotonin transporter Gene × Environment literature are certainly not uncommon (Sharpley et al., 2014). Moreover, several studies have failed to identify an interaction between the serotonin transporter gene and negative parenting specifically in predicting depression (Fergusson, Horwood, Miller, & Kennedy, 2011; Lavigne et al., 2013). Recent reviews suggest that the interaction implicating S carriers may be most readily detected when relatively extreme forms of adverse, threatening environments, such as those involving significant child maltreatment are considered (Caspi et al., 2010). It is possible that the degree of threat or adversity captured by the negative parenting measures in both the current and some other studies with null findings were not severe enough to reveal the interaction. We have identified, however, in the ADS sample that inclusion of hippocampal volume as an intermediate phenotype in a pathway from the serotonin transporter gene to MDD onset during the adolescent period reveals potential S carrier vulnerability to depression in the context of negative parenting (Little et al., 2015). Specifically, possession of a greater number of S alleles was associated with smaller hippocampal volume, and the specific variance in hippocampal volume accounted for by genotype was in turn associated with increased risk for MDD onset, but only in the context of more negative, punitive maternal behavior. This imaging gene–environment study suggests that inclusion of intermediate phenotypes such as brain structure in analyses may assist in the detection of otherwise unapparent relations between genes, the environment, and behavioral outcomes.

A strength of the current G × E study involving the serotonin transporter gene is the systematic investigation of the impact of an environment involving a form of *deprivation* on the maladaptive outcome of depression. This study is in contrast with the vast majority of research investigating G × E effects, which to date has tended to focus on the relationship between positive environments and positive outcomes, or threatening environments and negative outcomes. We believe that this study makes a valuable contribution to current theoretical understanding of associations involving the serotonin transporter gene, environments, and psychological outcomes by differentiating between interactions of deprivation versus threat. It may also offer a potential explanation for the sizable group of G × E studies that have identified null findings, some of which may have examined environments involving both deprivation and threat, and hence were not able to identify the effects of one allele over the other on risk for psychological difficulties. Future research would benefit from replicating the current findings in additional cohorts and extending them by considering other theoretically grounded environmental contexts that might be expected to show differential effects for S carriers and L homozygous individuals.

There are several limitations in the current study that should be noted. First, as noted earlier, although there is a body of a priori theoretical and empirical research supporting an association between 5-HTTLPR, stress sensitivity, emotional reactivity, and social cognition (Canli & Lesch, 2007; Caspi et al., 2010; Glenn, 2011), which we have speculated may underlie the specific G × E interaction investigated here, this putative mechanism was not explicitly tested. A second limitation is our consideration of only one gene in the current research design, despite general acknowledgment that depression represents a highly complex polygenetic condition (Sullivan et al., 2000). We purposely selected 5-HTTLPR because the evidence

supporting its involvement in G × E interactions is relatively advanced compared to other genes (Caspi et al., 2010), while noting emerging evidence supporting its role in multilocus polygenetic profiles, gene–gene interactions, and gene–gene–environment interactions in conferring risk for psychopathology (e.g., Ressler et al., 2010; Vrshek-Schallhorn et al., 2015). In addition, we did not analyze the minor allele rs25531, which comprises a single-nucleotide variant (A → G) within the L polymorphism that renders an L_g allele functionally similar to the S variant (Hu et al., 2006). Thus, it is possible that some LL or LS genotypes would have been better classified with the S allele in the current study. However, the current classification would be expected to be associated with an attenuated effect or false negative rather than a false positive result.

Furthermore, while prior research has strongly implicated parenting factors in the development of child/adolescent depression, the exact degree to which parenting factors measured in the current study represent causal influences remains somewhat unclear due to issues regarding the direction of effects. It is conceivable that child depression could evoke, reinforce, or shape particular parenting behaviors, and therefore that the parenting constructs in the current study may reflect a response to their adolescents' depressive behaviors to some extent. As we did not have information about parent genotype, we were also not able to rule out the possibility of a passive *r*GE. At least one previous study has noted the possibility of passive *r*GE processes in the association between parenting and children's depression, which may be underpinned by parental depressive symptomatology (Rice, Lewis, Harold, & Thapar, 2013). Finally, the samples in the current analyses are quite small for genetic analyses, and the number of participants in the analyses in Study 2 in particular might be considered preliminary. It is possible that our sample sizes may have limited power to detect smaller effects. Equally, there may be results that are "false positives." These results (perhaps particularly the nonsignificant findings of small effect size) should be interpreted with caution until they are replicated by studies with larger samples.

In summary, results from two independent studies suggest that L homozygous individuals may be more sensitive than S-allele carriers to the depressogenic effects of low positive parenting. This finding suggests that it is not only the S allele that determines environmental sensitivity. Rather, consistent with a differential *capability* framework, both alleles can confer sensitivity to a maladaptive outcome such as depression (as well as potentially positive outcomes), dependent on the match or mismatch of the phenotypic characteristics of the individual and the challenges posed by the environment in which they are developing.

References

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, *5*, 237–249.

Barrera, M., Chassin, L., & Rogosch, F. (1993). Effects of social support and conflict on adolescent children of alcoholic and nonalcoholic fathers. *Journal of Personality and Social Psychology*, *64*, 602–612. http://dx.doi.org/10.1037/0022-3514.64.4.602

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*, 746–754. https://doi.org/10.1038/mp.2009.44

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885–908. https://doi.org/10.1037/a0017376

Bernier, A., Carlson, S. M., Deschenes, M., & Matte-Gagne, C. (2012). Social factors in the development of early executive functioning: A closer look at the caregiving environment. *Developmental Science*, *15*, 12–24. https://doi.org/10.1111/j.1467-7687.2011.01093.x

Borg, J., Henningsson, S., Saijo, T., Inoue, M., Bah, J., Westberg, L., . . . Farde, L. (2009). Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *International Journal of Neuropsychopharmacology*, *12*, 783–792. https://doi.org/10.1017/s1461145708009759

Brammer, W. A., Jezior, K. L., & Lee, S. S. (2016). Psychopathic traits mediate the association of serotonin transporter genotype and child externalizing behavior. *Aggressive Behavior*, *42*, 455–470. https://doi.org/10.1002/ab.21642

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review*, *28*, 676–691. https://doi.org/10.1016/j.cpr.2007.10.001

Canli, T., & Lesch, K.-P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience*, *10*, 1103–1109. https://doi.org/10.1038/mp.2008.37

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*, 509–527. https://doi.org/10.1176/appi.ajp.2010.09101452

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of

life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386–389. https://doi.org/10.1126/science.1083968

Culverhouse, R. C., Saccone, N. L., Horton, A. C., Ma, Y., Anstey, K. J., Banaschewski, T., . . . Bierut, L. J. (2017). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2017.44

Dadds, M. R., & Salmon, K. (2003). Punishment insensitivity and parenting: Temperament and learning as interacting risks for antisocial behavior. *Clinical Child and Family Psychology Review*, *6*, 69–86. https://doi.org/10.1023/A:1023762009877

Dallaire, D. H., Pineda, A. Q., Cole, D. A., Ciesla, J. A., Jacquez, F., LaGrange, B., & Bruce, A. E. (2006). Relation of positive and negative parenting to children's depressive symptoms. *Journal of Clinical Child and Adolescent Psychology*, *35*, 313–322. https://doi.org/10.1207/s15374424jccp3502_15

Davies, P. T., & Cicchetti, D. (2014). How and why does the 5-HTTLPR gene moderate associations between maternal unresponsiveness and children's disruptive problems? *Child Development*, *85*, 484–500. https://doi.org/10.1111/cdev.12148

Del Giudice, M. (2017). Statistical tests of differential susceptibility: Performance, limitations, and improvements. *Development and Psychopathology*, *29*, 1267–1278. https://doi.org/10.1017/S0954579416001292

Edenberg, H. J., & Reynolds, J. (1998). Improved method for detecting the long and short promoter alleles of the serotonin transporter gene HTT (SLC6A4). *Psychiatric Genetics*, *8*, 193–195

Eisenberg, N., Zhou, Q., Spinrad, T. L., Valiente, C., Fabes, R. A., & Liew, J. (2005). Relations among positive parenting, children's effortful control, and externalizing problems: A three-wave longitudinal study. *Child Development*, *76*, 1055–1071. https://doi.org/10.1111/j.1467-8624.2005.00897.x

Ellis, L. K., & Rothbart, M. K. (2001). *Revision of the Early Adolescent Temperament Questionnaire*. Paper presented at the Biennial Meeting of the Society for Research in Child Development, Minneapolis, MN.

Enders, C., & Bandalos, D. (2001). The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Structural Equation Modeling*, *8*, 430–457. https://doi.org/10.1207/S15328007SEM0803_5

Fergusson, D. M., Horwood, L. J., Miller, A. L., & Kennedy, M. A. (2011). Life stress, 5-HTTLPR and mental disorder: Findings from a 30-year longitudinal study. *The British Journal of Psychiatry*, *198*, 129–135. https://doi.org/10.1192/bjp.bp.110.085993

Fox, E., Ridgewell, A., & Ashwin, C. (2009). Looking on the bright side: Biased attention and the human serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences*, *276*, 1747–1751. https://doi.org/10.1098/rspb.2008.1788

Glenn, A. L. (2011). The other allele: Exploring the long allele of the serotonin transporter gene as a potential risk factor for psychopathy: A review of the parallels in findings. *Neuroscience Biobehavioral Reviews*, *35*, 612–620. https://doi.org/10.1016/j.neubiorev.2010.07.005

Gyurak, A., Haase, C. M., Sze, J., Goodkind, M. S., Coppola, G., Lane, J., . . . Levenson, R. W. (2013). The effect of the serotonin transporter (5-HTTLPR) polymorphism on empathic and self-conscious emotional reactivity. *Emotion*, *13*, 25–35. https://doi.org/10.1037/a0029616

Hariri, A. R., & Holmes, A. (2006). Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Sciences*, *10*, 182–191. http://dx.doi.org/10.1016/j.tics.2006.02.011

Hawes, S. W., Byrd, A. L., Henderson, C. E., Gazda, R. L., Burke, J. D., Loeber, R., & Pardini, D. A. (2014). Refining the parent-reported inventory of callous-unemotional traits in boys with conduct problems. *Psychological Assessment*, *26*, 256–266. https://doi.org/10.1037/a0034718

Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., & Lesch, K. P. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*, *66*, 2621–2624. https://doi.org/10.1046/j.1471-4159.1996.66062621.x

Homberg, J. R., & Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*, *69*, 513–519. http://dx.doi.org/10.1016/j.biopsych.2010.09.024

Hops, H., Biglan, A., Tolman, A., Arthur, J., & Longoria, N. (1995). *LIFE: Living In Family Environments coding system manual*. Eugene, OR: Oregon Research Institute.

Hu, X. Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., . . . Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics*, *78*, 815–826. https://doi.org/10.1086/503850

Jorm, A., Prior, M., Sanson, A., Smart, D., Zhang, Y., & Easteal, S. (2000). Association of a functional polymorphism of the serotonin transporter gene with anxiety related temperament and behavior problems in children: A longitudinal study from infancy to the mid teens. *Molecular Psychiatry*, *5*, 542–547. https://doi.org/10.1038/sj.mp.4000782

Kano, M., Mizuno, T., Kawano, Y., Aoki, M., Kanazawa, M., & Fukudo, S. (2012). Serotonin transporter gene promoter polymorphism and alexithymia. *Neuropsychobiology*, *65*, 76–82. https://doi.org/10.1159/000329554

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry*, *68*, 444–454. https://doi.org/10.1001/archgenpsychiatry.2010.189

Laucht, M., Treutlein, J., Blomeyer, D., Buchmann, A. F., Schmid, B., Becker, K., . . . Banaschewski, T. (2009).

Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: Evidence from a high-risk community sample of young adults. *International Journal of Neuropsychopharmacology*, *12*, 737–747. https://doi.org/10.1017/S1461145708009875

Lavigne, J. V., Herzing, L. B. K., Cook, E. H., LeBailly, S. A., Gouze, K. R., Hopkins, J., & Bryant, F. B. (2013). Gene × Environment effects of serotonin transporter, dopamine receptor D4, and monoamine oxidase A genes with contextual and parenting risk factors on symptoms of oppositional defiant disorder, anxiety, and depression in a community sample of 4-year-old children. *Development and Psychopathology*, *25*, 555–575. https://doi.org/10.1017/S0954579412001241

Letcher, P., Toumbourou, J., Sanson, A., Prior, M., Smart, D., & Oberklaid, F. (2004). Parenting style as a moderator of the effect of temperament on adolescent externalising and internalising behaviour problems. *Australian Educational and Developmental Psychologist*, *19*, 5–34. https://doi.org/10.1017/S0816512200029278

Li, J. J., Berk, M. S., & Lee, S. S. (2013). Differential susceptibility in longitudinal models of gene-environment interaction for adolescent depression. *Development & Psychopathology*, *25*, 991–1003. https://doi.org/10.1017/S0954579413000321

Li, J. J., Chung, T. A., Vanyukov, M. M., Scott Wood, D., Ferrell, R., & Clark, D. B. (2015). A hierarchical factor model of executive functions in adolescents: Evidence of gene-environment interplay. *Journal of the International Neuropsychological Society*, *21*, 62–73. https://doi.org/10.1017/S1355617714001039

Little, R. J. A. (1988). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association*, *83*, 1198–1202. https://doi.org/10.1080/01621459.1988.10478722

Little, K., Olsson, C. A., Youssef, G. J., Whittle, S., Simmons, J. G., Yucel, M., . . . Allen, N. B. (2015). Linking the serotonin transporter gene, family environments, hippocampal volume and depression onset: A prospective imaging Gene × Environment analysis. *Journal of Abnormal Psychology*, *124*, 834–849. https://doi.org/10.1037/abn0000101

Lovejoy, M. C., Graczyk, P. A., O'Hare, E., & Neuman, G. (2000). Maternal depression and parenting behavior: A meta-analytic review. *Clinical Psychology Review*, *20*, 561–592. https://doi.org/10.1016/S0272-7358(98)00100-7

Lykken, D. T. (1995). *The antisocial personalities*. Hillsdale, NJ: Erlbaum.

MacPhillamy, D. J., & Lewinsohn, P. M. (1976). *Manual for the pleasant events schedule*. Eugene, OR: University of Oregon.

McLaughlin, K. A. (2016). Future directions in childhood adversity and youth psychopathology. *Journal of Clinical Child and Adolescent Psychology*, *45*, 361–382. https://doi.org/10.1080/15374416.2015.1110823

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*, 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., . . . Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*, 980–989. https://doi.org/10.1016/j.jaac.2010.05.017

Morris, A. S., Silk, J. S., Steinberg, L., Myers, S. S., & Robinson, L. R. (2007). The role of the family context in the development of emotion regulation. *Social Development*, *16*, 361–388. https://doi.org/10.1111/j.1467-9507.2007.00389.x

Muthén, L. K., & Muthén, B. O. (1998–2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Author.

Pardini, D. A., Lochman, J. E., & Powell, N. (2007). The development of callous-unemotional traits and antisocial behavior in children: Are there shared and/or unique predictors? *Journal of Clinical Child and Adolescent Psychology*, *36*, 319–333. https://doi.org/10.1080/15374410701444215

Pasalich, D. S., Dadds, M. R., Hawes, D. J., & Brennan, J. (2011). Do callous-unemotional traits moderate the relative importance of parental coercion versus warmth in child conduct problems? An observational study. *Journal of Child Psychology and Psychiatry*, *52*, 1308–1315. https://doi.org/10.1111/j.1469-7610.2011.02435.x

Pener-Tessler, R., Avinun, R., Uzefovsky, F., Edelman, S., Ebstein, R. P., & Knafo, A. (2013). Boys' serotonin transporter genotype affects maternal behavior through self-control: A case of evocative gene–environment correlation. *Development and Psychopathology*, *25*, 151–162. https://doi.org/10.1017/S095457941200096X

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, *84*, 309–322. http://dx.doi.org/10.1037/0033-2909.84.2.309

Pluess, M., & Belsky, J. (2013). Vantage sensitivity: Individual differences in response to positive experiences. *Psychological Bulletin*, *139*, 901–916. https://doi.org/10.1037/a0030196

Preacher, K. J., Curran, P. J., & Bauer, D. J. (2006). Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *Journal of Educational and Behavioral Statistics*, *31*, 437–448. https://doi.org/10.3102/10769986031004437

Prinz, R. J., Foster, S., Kent, R. N., & O'Leary, K. D. (1979). Multivariate assessment of conflict in distressed and non-distressed mother-adolescent dyads. *Journal of Applied Behavioural Analysis*, *12*, 691–700. https://doi.org/10.1901/jaba.1979.12-691

Prior, M., Sanson, A., Smart, D., & Oberklaid, F. (2000). *Pathways from infancy to adolescence: Australian Temperament Project 1983–2000*. Melbourne, Vic: Australian Institute of Family Studies.

Radloff, L. S. (1977). A CES-D scale: A self-report depression scale for research in the general population.

Applied Psychological Measurement, *1*, 385–401. https://doi.org/10.1177/014662167700100306

Rao, U., & Chen, L. A. (2009). Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders. *Dialogues in Clinical Neuroscience*, *11*, 45–62.

Ressler, K. J., Bradley, B., Mercer, K. B., Deveau, T. C., Smith, A. K., Gillespie, C. F., . . . Binder, E. B. (2010). Polymorphisms in CRHR1 and the serotonin transporter loci: Gene × Gene × Environment interactions on depressive symptoms. *American Journal of Medical Genetics Part B*, *153B*, 812–824. https://doi.org/10.1002/ajmg.b.31052

Rice, F., Lewis, G., Harold, G. T., & Thapar, A. (2013). Examining the role of passive gene–environment correlation in childhood depression using a novel genetically sensitive design. *Development and Psychopathology*, *25*, 37–50. https://doi.org/10.1017/S0954579412000880

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., . . . Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *The Journal of the American Medical Association*, *301*, 2462–2471. https://doi.org/10.1001/jama.2009.878

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and Psychopathology*, *24*, 389–409. https://doi.org/10.1017/S0954579412000065

Sadeh, N., Javdani, S., Jackson, J. J., Reynolds, E. K., Potenza, M. N., Gelernter, J., . . . Verona, E. (2010). Serotonin transporter gene associations with psychopathic traits in youth vary as a function of socioeconomic resources. *Journal of Abnormal Psychology*, *119*, 604–609. https://doi.org/10.1037/a0019709

Salvatore, J. E., & Dick, D. M. (2015). Gene–environment interplay: Where we are, where we are going. *Journal of Marriage and Family*, *77*, 344–350. https://doi.org/10.1111/jomf.12164

Schlomer, G. L., Bauman, S., & Card, N. A. (2010). Best practices for missing data management in counseling psychology. *Journal of Counseling Psychology*, *57*, 1–10. https://doi.org/10.1037/a0018082

Schwartz, O. S., Simmons, J. G., Whittle, S., Byrne, M. L., Yap, M. B. H., Sheeber, L. B., & Allen, N. B. (2017). Affective parenting behaviors, adolescent depression, and brain development: A review of findings from the Orygen Adolescent Development Study. *Child Development Perspectives*, *11*, 90–96. https://doi.org/10.1111/cdep.12215

Sharpley, C. F., Palanisamy, S. K. A., Glyded, N. S., Dillingham, P. W., & Agnew, L. L. (2014). An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings. *Behavioural Brain Research*, *273*, 89–105. https://doi.org/10.1016/j.bbr.2014.07.030

Sheeber, L., Davis, B., Leve, C., Hops, H., & Tildesley, E. (2007). Adolescents' relationships with their mothers and fathers: Associations with depressive disorder and subdiagnostic symptomatology. *Journal of Abnormal Psychology*, *116*, 114–154. https://doi.org/10.1037/0021-843X.116.1.144

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, *139*, 81–132. https://doi.org/10.1037/a0028727

Strobel, A., Dreisbach, G., Müller, J., Goschke, T., Brocke, B., & Lesch, K.-P. (2007). Genetic variation of serotonin function and cognitive control. *Journal of Cognitive Neuroscience*, *19*, 1923–1931. https://doi.org/10.1162/jocn.2007.19.12.1923

Sulik, M. J., Eisenberg, N., Lemery-Chalfant, K., Spinrad, T. L., Silva, K. M., Eggum, N. D., . . . Verrelli, B. C. (2012). Interactions between serotonin transporter gene haplotypes and quality of mothers' parenting predict the development of children's noncompliance. *Developmental Psychology*, *48*, 740–754. https://doi.org/10.1037/a0025938

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, *157*. https://doi.org/10.1176/appi.ajp.157.10.1552

Thomas, A., Chess, S., & Birch, H. G. (1968). *Temperament and behaviour disorders in children*. New York, NY: New York University Press.

Tolan, P., Ross, K., Arkin, N., Godine, N., & Clark, E. (2016). Toward an integrated approach to positive development: Implications for intervention. *Applied Developmental Science*, *20*, 214–236. https://doi.org/10.1080/10888691.2016.1146080

Tükel, R., Alkaş, E., Gürvit, H., Aslantaş Ertekin, B., Ertekin, E., Baran, B., . . . Saruhan Direskeneli, G. (2016). Serotonin transporter promoter polymorphism is associated with executive function impairments in patients with obsessive compulsive disorder. *The Clinical Neuropsychologist*, *30*, 536–546. https://doi.org/10.1080/13854046.2016.1162329

van Ijzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Translational Psychiatry*, e147. https://doi.org/10.1038/tp.2012.73

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Zinbarg, R. E., Adam, E. K., Redei, E. E., . . . Craske, M. G. (2015). Additive genetic risk from five serotonin system polymorphisms interacts with interpersonal stress to predict depression. *Journal of Abnormal Psychology*, *124*, 776–790. https://doi.org/10.1037/abn0000098

Waller, R., Wright, A. G., Shaw, D. S., Gardner, F., Dishion, T. J., Wilson, M. N., & Hyde, L. W. (2015). Factor structure and construct validity of the Parent-Reported Inventory of Callous-Unemotional Traits among high-risk 9-year-olds. *Assessment*, *22*, 561–580. https://doi.org/10.1177/1073191114556101

Weeland, J., Overbeek, G., de Castro, B. O., & Mattys, W. (2015). Underlying mechanisms of gene-environment interactions in externalizing behavior: A systematic review and search for theoretical mechanisms. *Clinical Child & Family Psychology Review*, *18*, 413–442. https://doi.org/10.1007/s10567-015-0196-4

Weikum, W. M., Brain, U., Chau, C. M. Y., Grunau, R. E., Boyce, W. T., Diamond, A., & Oberlander, T. F. (2013). Prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and serotonin transporter promoter genotype (SLC6A4) influence executive functions at 6 years of age. *Frontiers in Cellular Neuroscience*, *7*, 180. https://doi.org/10.3389/fncel.2013.00180

Williams, R. B., Marchuk, D. A., Gadde, K. M., Barefoot, J. C., Grichnik, K., Helms, M. J., . . . Siegler, I. C. (2003). Serotonin-related gene polymorphisms and central nervous system serotonin function. *Neuropsychopharmacology*, *28*, 533–541. https://doi.org/10.1038/sj.npp.1300054

Yap, M. B. H., Pilkington, P. D., Ryan, S. M., & Jorm, A. F. (2014). Parental factors associated with depression and anxiety in young people: A systematic review and meta-analysis. *Journal of Affective Disorders*, *156*, 8–23. http://dx.doi.org/10.1016/j.jad.2013.11.007

Yap, M. B. H., Whittle, S., Yucel, M., Sheeber, L., Pantelis, C., Simmons, J. G., & Allen, N. B. (2008). Interaction of parenting experiences and brain structure in the prediction of depressive symptoms in adolescents. *Archives of General Psychiatry*, *65*, 1377–1385. https://doi.org/10.1001/archpsyc.65.12.1377

Yildirim, B. O., & Derksen, J. J. L. (2013). Systematic review, structural analysis, and new theoretical perspectives on the role of serotonin and associated genes in the etiology of psychopathy and sociopathy. *Neuroscience and Biobehavioral Reviews*, *37*, 1254–1296. https://doi.org/10.1016/j.neubiorev.2013.04.009

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Fit Statistics of Path Models for Study 1 and Study 2 Primary Analyses

Table S2. Complete Findings for the Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Warmth at 13–14 Years on Depressive Symptomatology at 17–18 Years in Study 1

Table S3. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Use of Physical Punishment at 13–14 Years on Depressive Symptomatology at 17–18 Years in Study 1

Table S4. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Warmth at 13–14 Years on Depressive Symptomatology at 17–18 Years in Individuals of Anglo-European Background Only (n = 656) in Study 1

Table S5. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Physical Punishment at 13–14 Years on Depressive Symptomatology at 17–18 Years in Individuals of Anglo-European Background Only (n = 656) in Study 1

Table S6. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Warmth at 13–14 Years on Depressive Symptomatology at 17–18 Years, Controlling for Gender, Ethnicity, Physical Punishment, and Baseline Depressive Symptomatology at 13–14 Years in Study 1

Table S7. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Parental Physical Punishment at 13–14 Years on Depressive Symptomatology at 17–18 Years, Controlling for Gender, Ethnicity, Physical Warmth, and Baseline Depressive Symptomatology at 13–14 Years

Table S8. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Positive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years in Study 2

Table S9. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Aversive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years in Study 2

Table S10. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Positive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years in Individuals of Anglo-European Backgrounds (n = 150) in Study 2

Table S11. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Aversive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years in Individuals of Anglo-European Backgrounds (n = 150) in Study 2

Table S12. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Positive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years, Controlling for Gender, Ethnicity, Aversive Parenting Behavior, and Baseline Depressive Symptomatology at 11–13 Years in Study 2

Table S13. Path Model Testing the Interaction Between 5-HTTLPR Genotype × Aversive Parenting Behavior at 11–13 Years on Depressive Symptomatology at 18–19 Years (T4), Controlling for Gender, Ethnicity, Positive Parenting Behavior, and Baseline Depressive Symptomatology at 11–13 Years (T1) in Study 2