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Abstract

Association studies of the serotonin transporter promoter polymorphism (5-HTTLPR) and negative emotionality (NE) are inconclusive. However, emerging evidence suggests that the association between this polymorphism and NE may be influenced by levels of another temperament trait, positive emotionality (PE). Therefore, this study examined whether the association between the 5-HTTLPR and NE was moderated by PE. A community sample of 413 three-year-old children completed a standardized battery of laboratory tasks designed to tap temperamental emotionality. Children were also genotyped for the 5-HTTLPR. No direct association between 5-HTTLPR genotype and NE was found. However, the interaction of child PE and NE predicted 5-HTTLPR genotype. Furthermore, children with a short allele who were also low in PE had significantly greater NE than children without a short allele or children with high PE. Our findings suggest that the short allele of the 5-HTTLPR is associated with NE only in the context of low PE. Inconsistent links between NE and this gene in previous research may stem from the failure to consider other temperament traits that moderate associations.

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Keywords

5-HTTLPR; temperament; personality

It is widely accepted that the monoamine neurotransmitter serotonin plays a key role in depression (Thase, 2009); accordingly, candidate studies of genetic polymorphisms that regulate its neurotransmission have been plentiful in the field of molecular genetics of mood disorders (Levinson, 2006). Many of these studies have focused on a functional variable number of tandem repeats polymorphism in the 5' promoter region of the serotonin transporter gene (5-HTTLPR, located on chromosome 17q) (Lesch, Bengel, Heils, & Sabol, 1996). Variants of this polymorphism are a long (L) allele, comprised of 16 copies of an approximately 22 bp repeat unit, and a short (S) allele, consisting of 14 copies (for a review, see Hariri & Holmes, 2006). The short allele conveys diminished transcription, lower transporter levels, and reduced serotonin uptake, with functional effects on neural circuits thought relevant to emotional processing and depression (Hariri & Holmes, 2006).

The literature examining direct associations between the 5-HTTLPR and depression is quite mixed, despite multiple candidate gene and linkage studies. Several related lines of research suggest reasons why this field has not produced a more cohesive pattern of findings. First, seminal work (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, et al., 2003) has been conducted examining gene-environment interactions (GXE) in predicting depression onset, focusing on the interaction between 5-HTTLPR genotype and stressful life events. This study indicated that individuals with at least one S allele of the 5-HTTLPR were at increased risk for depression in the context of stressful life events compared to those homozygous for the L allele (see Zammit & Owen, 2006, for a review). While controversial[1], this finding suggests that individuals with putative genetic vulnerability to depression, by virtue of having at least one S allele of the 5-HTTLPR, may develop depression more frequently in the context of stressful life events than those homozygous for the L allele.

To the extent that the 5-HTTLPR increases risk for depression in the context of negative life events, this suggests that the effect is mediated by the influence of this polymorphism on stress sensitivity (Beevers, Wells, Ellis, & McGeary, 2009; Hayden, Dougherty, Maloney, Olino, Durbin, Sheihk, et al., 2008). In turn, this indicates that the 5-HTTLPR may be more closely associated with phenotypes related to stress sensitivity than with depression per se. A second line of association studies focusing on the genetic basis of temperamental and biological markers of stress sensitivity is relevant to this possibility. Those interested in 5-HTTLPR and temperament/personality have focused largely on its associations with negative emotionality (NE)/neuroticism (e.g., Schinka, Busch, & Robichaux-Keene, 2004), a central aspect of which involves reacting to minor stressors with negative emotions such as sadness, anxiety, anger, and guilt (e.g., Tellegen, Bouchard, Wilcox, Segal, & Rich, 1988). In a complementary, emerging line of research, the 5-HTTLPR S allele has been linked to several biological indices of stress reactivity, including cortisol reactivity and amygdala activation (Gotlib, Joormann, Minor, & Hallmayer, 2008; Munafo, Brown, & Hariri, 2008).

However, research on the 5-HTTLPR and NE has also yielded mixed results (see Schinka et al., 2004, for a review), possibly due to the failure of these studies to incorporate measures of other factors that influence stress reactivity. In particular, recent work has emerged suggesting that positive emotionality (PE) may moderate physiological and emotional

[1]This finding has been controversial, with a number of replications and non-replications. A recent meta-analysis by Risch and colleagues (2009) reported negative results; however, the validity of the assessments of depression and life stress in many of the studies included in the meta-analysis has been questioned and Risch et al.'s conclusions have been challenged (Rutter, Thapar, & Pickles, 2009; Uher & McGuffin, 2010).

reactions to stress. For example, there is emerging evidence that PE moderates the rate of cardiovascular recovery from negative emotional arousal (Tugade & Frederickson, 2004), the association between momentary stress appraisals and NE (Wichers, Myin-Germeys, Jacobs, Peeters, Kenis, Derom, et al., 2007), and interpretation bias for threat in children with anxiety (Hughes & Kendall, 2008). If PE moderates the association between the 5-HTTLPR S allele and NE, this could help account for the findings linking this gene to the onset of depression in the context of stress, and could also explain why the literature linking this gene to NE has not provided more conclusive results. This would also be consistent with theoretical and empirical work implicating both low PE and high NE in depression risk (Clark & Watson, 1999), and with evidence that the two traits interact to predict subsequent depression (Gershuny & Sher, 1998; Joiner & Lonigan, 2000; Verkerk, Denollet, Van Heck, Van Son, & Pop, 2005).

To test these ideas, we examined the associations between 5-HTTLPR genotype and NE and PE. In particular, we sought to test the hypothesis that the association between the 5-HTTLPR genotype and NE is moderated by PE. We examined this question in a sample of young, community-dwelling children, as we wanted to minimize the likelihood that the temperament traits we measured were a consequence of prior or current depressive disorder, or were confounded by social desirability or other issues of self-presentation that are likely to emerge later in development. Most studies of temperament in young children use parent reports of child temperament. However, parent reports of child temperament and behavior can be influenced by parent characteristics, as well as child traits (Kagan, 1998; de Los Reyes & Kazdin, 2005), and some studies suggest that parent reports of preschoolers' behavior have relatively poor predictive validity for child internalizing symptoms (e.g., Mesman & Koot, 2000). Hence, we used standardized observer ratings of child temperament elicited during a structured set of laboratory tasks designed to evoke child emotional behavior.

Method

Participants

The sample was 413 children (218 males) from an original sample of 559 children and their parents from a suburban area[2]. The mean age of the children was 42.1 months (*SD* = 3.1). Potential participants were identified via a commercial mailing list. Eligible families had a child between three and four years of age, with no significant medical conditions or developmental disabilities, and at least one English-speaking biological parent. Most of the participants came from middle-class families, as measured by Hollingshead's Four Factor Index of Social Status (*M* = 45.0; *SD* = 10.8) (Hollingshead, 1975). The vast majority (96.6%) of children came from two-parent homes, and 51.1% of the mothers worked outside the home part- or full-time. Children were of average cognitive ability as indexed by the Peabody Picture Vocabulary Test (*M* = 103.4, *SD* = 13.5) (Dunn & Dunn, 1997).

When participants came to the laboratory for the behavioral assessments, buccal cells were collected for genetic analysis by rubbing the inside of each child participant's cheek with two swabs. The Qiagen DNA Micro Kit (Qiagen Valencia, CA, USA) was used to extract genomic DNA from buccal swab samples according to the manufacturer's instructions. Extracts were kept at 4 °C when being actively used for analysis, and were held at −80 °C

[2]To reduce the possibility of population stratification, all non-White children or those of unknown ethnicity in the original sample of 559 were excluded from the current study (N = 72). An additional 74 children from the original sample did not give a DNA sample. Other than ethnicity, these 146 children did not differ from the 413 participants in the genetic study on any demographic or study variables other than negative emotionality (NE); those in the present study had lower NE than those not participating at trend-level significance, t (557) = 1.93, p <.10.

for long-term storage. Genomic DNA was successfully extracted for 476 of the 478 children who provided buccal swabs for analysis.

The extracted DNA was used to genotype subjects for the 5-HTTLPR polymorphisms. Polymerase chain reaction (PCR) was carried out using the Applied Biosystems thermal cycler Gene Amp 9700, and PCR products were separated on polyacrylamide gels, stained with ethidium bromide, and visualized and documented by a UV imaging system (BioRad Labs, CA). Genomic DNA was purified from buccal swab cellular extracts and stored according to manufacturer instructions (Qiagen, Valencia, CA, USA). Following Chorbov et al. (2007), the primers used for amplification were 5′-GGCGTTGCCGCTCTGAATGC-3′ (forward) and 5′-GAGGGACTGAGCTGGACAAC CAC-3′ (reverse). The PCR conditions used were: 5 min of initial denaturation at 94 °C followed by 30 cycles of 30 s of denaturation at 94 °C, 20 s annealing at 58 °C and 20 s of extension at 72 °C, and a final extension of 5 min at 72 °C.

All genotyping was performed by research technicians blind to other study data. In our sample, 123 children (29.8%) were homozygous for the L allele, 208 (50.4%) were heterozygous, and 82 (19.9%) were homozygous for the S allele[3]. This distribution of genotypes is in Hardy-Weinberg equilibrium. Consistent with most investigations of the 5-HTTLPR, we contrasted children homozygous for the L alleles to all other children.

Laboratory Temperament Assessment

During the first laboratory visit, each child participated in a standardized set of 12 episodes drawn from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995). In support of the validity of the Lab-TAB as a measure of temperament, we have previously shown that Lab-TAB indices of preschool-aged child temperament show impressive convergence with observer ratings of child temperament made in a naturalistic setting, as well as moderate stability from ages 3 to 7 (Durbin, Hayden, Klein, & Olino, 2007). Additionally, we have reported theoretically meaningful associations between Lab-TAB temperament ratings and maternal depression (Durbin, Klein, Hayden, Buckley, & Moerk, 2005), child behavior problems (Hayden, Klein, & Durbin, 2005), EEG asymmetries (Shankman, Tenke, Bruder, Durbin, Hayden, & Klein, 2005), child cognitive styles (Hayden, Klein, Durbin, & Olino, 2006), subsequent child depressive symptoms (Dougherty, Klein, Durbin, Hayden, & Olino, in press) and child cortisol levels (Dougherty et al., 2009). The visit, which lasted approximately two and a half hours, was videorecorded through a one-way mirror for coding. A female experimenter led each child through the tasks. A parent was present in the main experimental area with their child for all episodes except Stranger Approach and Box Empty (see below). A description of each episode and the traits typically elicited is provided below.

Risk Room (NE, behavioral inhibition [BI], activity)—Before leaving the main experimental area, the experimenter invited the child to explore a set of novel and ambiguous stimuli (e.g. cloth tunnel, balance beam, Halloween mask, etc.). After several minutes, the experimenter returned and asked the child to touch each of the stimuli.

[3]A common single nucleotide polymorphism (SNP) occurs at the sixth nucleotide (adenine to guanine; A to G) within the first of two extra 20 to 23 bp repeats in the L allele (rs25531) of the 5-HTTLPR. Some evidence indicates that, of the L alleles, only the L allele containing the 'A' SNP (L_A) is high functioning with regard to promoter activity, whereas the L allele with the 'G' SNP (L_G) may exhibit the same transcriptional activity as the S allele (Hu, Oroszi, Chun, Smith, Goldman, & Schuckit, 2005; Hu et al., 2006). [0]Accordingly, all analyses were run contrasting children homozygous for the L_A alleles to those children with an L_G allele or an S allele; all findings were comparable to those presented here (data available from the first author).

Tower of Patience (NE, inhibitory control, interest)—The child and experimenter took turns building a tower with large blocks. During each of her turns, the experimenter adhered to a schedule of increasingly lengthy delays before placing her block on the tower.

Arc of Toys (NE, positive affect, interest)—The child was allowed to play freely by him or herself with toys for a few minutes. The experimenter then returned and asked the child to put the toys away.

Stranger Approach (NE, BI)—After leading the child into the main experimental area, the experimenter left the child alone under the pretense that she needed to get new toys for them to play with. After a brief delay, an unfamiliar male research assistant entered the room and spoke to the child in a neutral tone while gradually walking closer.

Car Go (positive affect, interest)—The child and experimenter played with two remote controlled cars.

Transparent Box (NE, persistence, interest)—The child selected a toy, which the experimenter locked in a transparent box. The child was then left to work to open the box with a set of keys that were, unbeknownst to the child, inoperable. After a few minutes, the experimenter returned with the correct key, and helped the child access the toy.

Exploring New Objects (NE, BI)—The child explored a set of novel and ambiguous stimuli, including a mechanical spider and bird, and sticky, soft gel balls.

Pop-up Snakes (positive affect)—The experimenter showed the child what appeared to be a can of potato chips, actually containing coiled spring snakes. The experimenter demonstrated the trick, and encouraged the child to surprise his or her mother with the snakes

Impossibly Perfect Green Circles (NE, persistence)—The child was repeatedly asked to draw a circle on a large piece of paper. After each drawing, the experimenter mildly criticized each circle.

Popping Bubbles (positive affect, interest)—The child and experimenter played with a bubble-shooting toy.

Snack Delay (inhibitory control)—The child was instructed to wait for the experimenter to ring a bell before eating a snack. The experimenter adhered to a schedule of varied delays before ringing the bell.

Box Empty (NE)—The child was given a gift-wrapped box, under the pretense that an appealing toy was inside. After a brief interval in which the child was left alone to discover that the box was empty, the experimenter returned with several small toys for the child to keep, explaining that she had forgotten to place the toys inside.

Coding—There were a total of 35 raters, including one full-time research assistant, four graduate students, and 30 undergraduate students. Before formal training in the coding methods, all raters watched five full Lab-TAB sessions to familiarize themselves with child behavior during the tasks. After watching the sessions, rater had an individual tutorial with the lead rater about the dimensions of temperament that were of interest to the study. Raters were then assigned to watch an additional 15 participants in one specific episode. The rater then worked with the lead rater on coding this episode jointly for five children. Raters then

coded five episodes independently. After coding the episodes, they were reviewed with the lead rater. Raters were permitted to begin coding independently if they had discrepancies on behavioral ratings of no more than 1 unit on no more than 2 codes per episode. After reaching this criterion, raters had every fifth episode reviewed by the lead rater. In order to calculate the interclass correlation coefficient (ICC), a two-way random, absolute agreement interrater ICC was used (Shrout & Fleiss, 1979). The intraclass correlations for interrater reliability for PE and NE (N = 35; 6%) were .89 and .82.

Sadness, anger, fear, positive affect, and interest were coded during each episode, regardless of the emotion a given episode was specifically designed to elicit. Previous reports from our group indicate that PE measured in negative tasks tends to correlate highly with PE measured in positive tasks (and vice-versa for NE), and ratings of affective behavior made across all Lab-TAB tasks have yielded scales with high internal consistency (Durbin, in press; Durbin et al., 2005). For sadness, fear, anger, and positive affect, each relevant display of facial, vocal, and bodily affect was coded on a three-point intensity scale. Ratings for the affective displays in each channel were summed within each episode, the totals for the 12 episodes were then standardized and summed, and the three channels were aggregated to create scores for sadness, fear, anger, and positive affect reflecting facial, vocal, and bodily indicators. Interest scores were coded on a four-point scale based on the frequency and intensity of relevant behaviors throughout the episode and the ratings were summed across the 12 episodes to form a total score. The NE scale was the composite of the total scores for sadness, fear, and anger across the 12 episodes (range = −.82–2.82). Children's scores on the final PE scale combining positive affect and interest ranged from −4.67 to 6.04. Coefficient alphas for the PE and NE scales were .82 and .74. Male and female children were not significantly different in NE, t (411) = −.84, p = .40, or PE, t (411) = −1.03, p = .30.

Results

Table 1 shows descriptive statistics for study and demographic variables for the two child 5-HTTLPR genotype groups. Groups based on genotype did not differ in NE and PE, indicating no direct association between this gene and these two dimensions of child temperament. We initially entered child sex as a factor in the model, but as no interaction term between child sex and temperament was significant, it was dropped.

We examined the associations between PE, NE, and the presence of a short allele of the 5-HTTLPR using logistic regression (Jaccard, 2001) after mean-centering to address multicollinearity (Aiken & West, 1991). Results are shown in Table 2. Although there were no significant main effects, the PE X NE interaction term significantly predicted child genotype. To better understand this relationship, we plotted estimated NE scores across estimated levels of PE for the two 5-HTTLPR genotypes (see Figure 1). The slopes for this figure were derived from separate multiple regressions predicting child NE from child PE for each genotype group. For children with an S allele, there was an inverse relationship between PE and NE, such that increasing levels of NE were associated with lower PE (B = −.05, SE = .02; p < .01). In contrast, for children homozygous for the L allele, PE and NE were essentially unassociated with each other, (B = .02, SE = .02; p = .43)[4].

[4]Separating children into s/s and s/l groups yielded similar findings: for children with one S allele, there was an inverse relationship between PE and NE, such that increasing levels of NE were associated with lower PE (B = −.05, SE = .02; p < .03). Children with two S alleles showed a generally similar, but slightly stronger pattern, with increasing levels of NE associated with lower PE (B = −.06, SE = .02; p < .03). Full results are available from the first author.

To better understand the relationship between these two temperament traits in children with different 5-HTTLPR genotypes, we next conducted post hoc tests using the least squares difference method to compare children's NE scores in the two genotype groups with low or high PE (indexed by having a score on PE below or above one standard deviation from the mean). Results are depicted in Figure 2. Children without the S allele of the 5-HTTLPR gene did not differ from one another significantly on NE, regardless of whether they had low or high PE (mean difference = .04, $p = .81$). Children with the S allele of the 5-HTTLPR with high PE were not significantly different on NE from those with no S allele, whether they had low (mean difference = −.09, $p = .56$) or high PE (mean difference = −.13, $p = .40$). However, children with at least one S allele and low PE displayed significantly greater NE than those with the same genotype with high PE (mean difference = .42, $p < .01$), the children with the L/L genotype and low PE (mean difference = .33, $p < .05$), and, at trend level, the children with the L/L genotype with high PE (mean difference = .29, $p = .07$).

Discussion

We examined the associations between PE, NE, and the presence of a short allele of the 5-HTTLPR. In particular, we were interested in whether the association of the 5-HTTLPR S allele with NE would be moderated by PE. Results were consistent with this hypothesis. As Figure 2 indicates, NE was highest among children with the S allele and low levels of PE. These results may suggest a mechanism for the associations found in some studies between the 5-HTTLPR S allele and depression in the context of negative life events, if this polymorphism influences individual differences in stress sensitivity, and suggests that accounting for individual differences in PE may help better delineate pathways between 5-HTTLPR genotype and vulnerability tied to negative emotional responses to stress. This possibility is consistent with recent findings from our group indicating that the S allele of this gene may interact with low PE to predict elevated early morning cortisol levels (Dougherty et al., 2009), which are, like NE, a putative index of maladaptive reactivity to stress. Considering the history of inconsistent findings in psychiatric genetics, these results need to be tested for replication in different samples; however, our hope is that the care with which our group has indexed emotion and stress sensitivity will yield a relatively robust pattern of findings.

Several theorists have argued that a key function of PE in protecting against depression risk is its capacity to buffer the effects of daily frustrations (Clark, 2005; Meehl, 1975). Empirical support for this notion was recently provided by Wichers and colleagues (2007), who used experience sampling methods to examine how appraisals of stress and positive and negative affect interacted over time. It is plausible that the 5-HTTLPR is associated with NE only in the context of insufficient PE to mitigate the effects of everyday disappointments. While our findings are consistent with such a process, this is speculative as our study was not designed to test the underlying mechanism and the children have not yet been followed into the age of risk for depression. In addition to longitudinal tests of this process, examining whether the obtained interaction is found with respect to adult personality and this genotype is another important future direction.

In analyses not reported, we tested whether a similar pattern of findings emerged using maternally-reported measures of child PE and NE, and found that mothers' reports of children's PE did not interact with child 5-HTTLPR genotype in predicting maternally-reported child NE (analyses available from the first author upon request). Previous reports from our group indicate that many, if not most, associations between early childhood temperament and an array of outcomes differ depending on whether laboratory observations or parent report methods are used (Dougherty et al., in press Hayden et al., 2005). This is not surprising given the modest correlations typically obtained between parent reports and other

measures of young children's emotional behavior (Durbin et al., 2007; Goldsmith & Campos, 1990; Kochanska, Coy Tjebkes, & Husarek, 1998; Rothbart, Derryberry, & Hershey, 2000; Seifer, Sameroff, Barrett, & Krafchuk, 1994), which suggest that various measures of child behavior are tapping largely unshared variance. In support of the use of laboratory measures of child emotionality, these measures converge well with ratings of temperament observed in the home and show high stability over time (Rothbart, Derryberry, & Hershey, 2000; Durbin, Hayden, Klein, & Olino, 2007). We again note previous reports from our group linking Lab-TAB temperament ratings to an array of meaningful correlates, including maternal depression (Durbin et al., 2005), child behavior problems (Hayden et al., 2005), EEG asymmetries (Shankman et al., 2005), child cognitive styles (Hayden et al., 2006), subsequent depressive symptoms (Dougherty et al., in press) and child cortisol levels (Dougherty et al., 2009). Further evidence for the value of laboratory measures of temperament comes from investigations linking such measures to child physiology (e.g., Fox, Henderson, Marshall, Nichols, & Ghera, 2005), moral development (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996), and the parent-child relationship (Kochanska, Aksan, & Carlson, 2005). We refer the interested reader to a more extensive review of the merits of laboratory measures of temperament (Durbin, in press).

Our use of laboratory measures of child temperament is a significant strength, given that very few investigations of the molecular genetics of personality/temperament have used phenotypes based on objective measures of observable behavior. However, our study had a number of limitations; first, experts disagree on the extent to which population stratification, which can produce false positive associations, is a concern in studies such as ours using an ethnically homogenous sample (Hutchison, Stallings, McGeary, & Bryan, 2004). Along similar lines, our findings may not generalize to non-White individuals, or to "high risk" samples, as our families were recruited from the community. Also, it is possible that the 5-HTTLPR is in linkage disequilibrium with another gene that accounts for the effects on child temperament. Finally, although our sample size was substantial compared to other genetic studies using lab-based phenotypes (e.g., Fakra et al., 2009), it is still relatively small for a genetic association study; thus, replication of our findings is especially important.

In conclusion, we found that the low PE modified the association between the S allele of the 5-HTTLPR and NE in a community sample of preschool-aged children. Considering that this combination of traits appears to be associated with especially high risk for depression, as well as an impaired ability to cope effectively with stressors, this association may suggest temperamental pathways that link this genotype to depressive outcomes.

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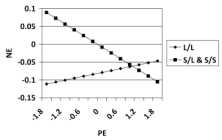

Figure 1.
Relationship between predicted child negative and positive emotionality by 5-HTTLPR genotype.
Note : L = long allele, S = short allele, PE = predicted positive emotionality values, NE = predicted negative emotionality values.

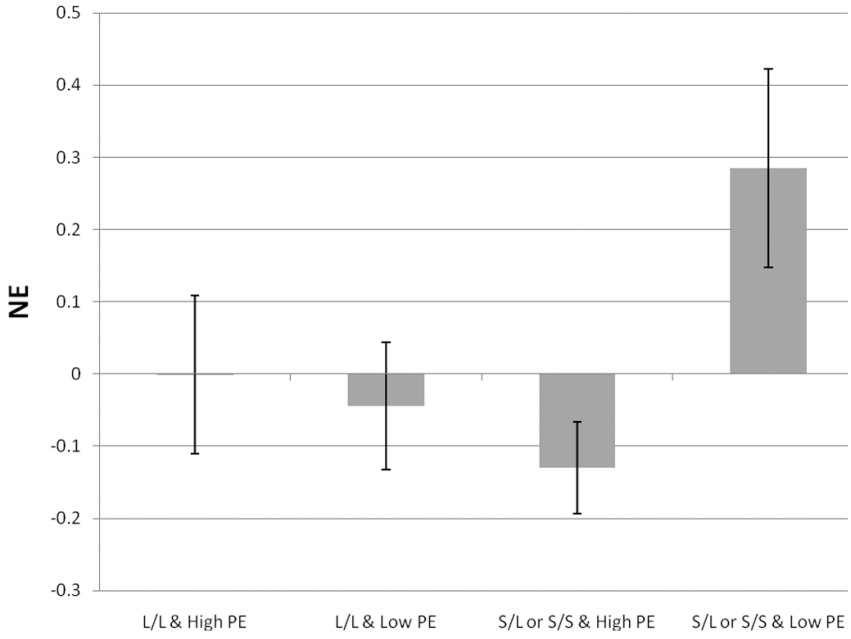

Figure 2.
Mean levels of child negative emotionality by 5-HTTLPR genotype and by low and high positive emotionality.
Note : L = long allele, S = short allele, PE = positive emotionality, NE = negative emotionality. High and low PE are indexed by having a score on PE below or above one standard deviation from the mean.

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Table 1

Demographic and study variables by child 5-HTTLPR genotype.

	Child 5-HTTLPR Genotype					
	L/L (N = 123)			L/S & S/S (N = 290)		
Variable	**M**	**SD**	**N**	**M**	**SD**	**N**
PE	.09	1.75		.13	1.71	
NE	−.08	.45		−.01	.52	
Child Sex (Male)			57 (46%)			161 (56%)
PPVT	103.20	13.50		103.51	13.55	
SES	44.59	11.08		45.12	10.67	

Note: L = long allele, S = short allele, PE = positive emotionality, NE = negative emotionality, PPVT = Peabody Picture Vocabulary Test, SES = socioeconomic status, as indexed by Hollingshead's Four Factor Index of Social Status (Hollingshead, 1975).

Table 2

Multiple logistic regression model predicting 5-HTTLPR genotype from child temperament.

	Child 5-HTTLPR genotype	
	Step 1	**Step 2**
	OR (95% CI)	**OR (95% CI)**
PE	1.02 (.90–1.16)	1.02 (.90–1.16)
NE	1.31 (.84–2.05)	1.31 (.82–2.10)
PE X NE		.73 (.54–.98)*

* $p < .05$

Note : PE = positive emotionality, NE = negative emotionality. 5-HTTLPR genotype coded as 0 = homozygous for the long allele, 1 = at least one short allele.