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Negative emotionality mediates the association of 5-HTTLPR genotype and depression in children with and without ADHD

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ABSTRACT

The 44-base-pair polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been implicated in the etiology of depression, but relatively little is known about potential mediators of this association. Although dimensions of temperament are likely to be proximal to the neurobiological and genetic factors underlying depression, studies have yet to formally evaluate temperament as a potential causal pathway. We examined individual differences in dimensions of temperament [negative emotionality (NE), prosociality (PRO), and daring (DA)] as potential mediators of 5-HTTLPR genotype and child depression. Using a multiple mediation framework, we tested the association of child 5-HTTLPR genotype and these dimensions of temperament with multi-informant ratings of child depression in a sample of 218 children with and without attention-deficit/hyperactivity disorder (ADHD). The long allele of 5-HTTLPR was associated with higher NE and lower PRO, but not DA. High NE mediated the association of 5-HTTLPR genotype and separate parent and teacher ratings of depression. ADHD status did not moderate the mediational role of NE for 5-HTTLPR and depression. Results suggest that NE may constitute a pathway between 5-HTTLPR and child depression. The role of genetic variation and temperament dimensions as intermediate traits in the development of depression is discussed.

1. Introduction

Childhood depression is a common, yet serious and persistent mental health problem that negatively affects the academic, social, and behavioral development of children (Ryan, 2005; Weisz et al., 2006). Lifetime estimates of major depression range from 4% to 24% in population-based samples of children and adolescents (Avenevoli et al., 2008). Childhood depression also frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD) (Biederman et al., 1998), with comorbid depression and ADHD predicting impaired work, social, and family functioning in adulthood relative to children with depression or ADHD only (Biederman et al., 1998; Weisz et al., 2006).

The precise etiology of childhood depression is poorly understood, particularly in children with ADHD (Sullivan et al., 2000). Genetic influences have been implicated through family aggregation, adoption, and twin studies (Rice et al., 2002). First-degree relatives of youth with ADHD had significantly higher rates of mood disorders than non-affected controls (Faraone and Biederman, 1997) and adopted children with ADHD had biological relatives with higher rates of major depression compared to adoptive relatives (Deutsch et al., 1982). A meta-analysis of family studies suggested that ADHD and depression also share familial risk factors, including parental psychopathology, family discord and low SES (Faraone and Biederman, 1997). Collectively, these studies converge to suggest that ADHD increases the risk of child depression (Chronis-Tuscano et al., 2010) and other mood disorders (Wozniak et al., 2004) with ADHD and depression sharing common risk factors, including familial (Faraone and Biederman, 1997) and genetic influences (Rowe et al., 1998).

The identification of replicated susceptibility loci for childhood depression has been elusive, with most studies having used candidate genes implicated in the etiology of depression, including variants affecting neurotransmission (Lesch, 2004). The serotonin transporter gene (5-HTTLPR) is a compelling candidate gene for depression because it affects the site of pharmacological action for the treatment of depression (Whittington et al., 2004). The human 5-HTTLPR gene consists of a 44 base-pair (bp) insertion/deletion polymorphism in the promoter region, resulting in short (S) and long (L) alleles (Heils et al., 1996). The S allele is associated with reduced transcriptional efficiency, expression, and function of the serotonin transporter (Lesch and Schmitt, 2002). In humans, 5-HTTLPR variation affects the amygdala, a subcortical structure rich in serotonin and critical to emotion regulation and fear processes (LeDoux, 2000). The S allele was associated with hyper-reactivity of the amygdala, which is associated with depleted serotonin transporter functionality (Munafò et al., 2008). Depressed children, adolescents and adults with the SL or

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SS genotype have significantly lower uptake of serotonin platelets compared to individuals with the LL genotype (Nobile et al., 1999). Children the SS genotype of 5-HTTLPR and the met allele of the brain-derived neurotropic factor (BDNF) gene had the highest levels of depression, but only if they experienced maltreatment (Kaufman et al., 2006). Although the literature suggests that the S allele increases the risk of youth depression by increasing vulnerability to environmental adversity (Zammit and Owen, 2006; Nobile et al., 2009), non-replications have also been reported (Munafò et al., 2003). Furthermore, meta-analytic evidence suggests a modest but significant association between the L allele and ADHD (Gizer et al., 2009), which diverges from the putative role of the S allele with respect to depression. Thus, the association between 5-HTTLPR and comorbid ADHD and depression requires further investigation.

Despite the increased precision afforded by the use of endophenotypes in candidate gene studies (Waldman, 2005), given their closer proximity to causal influences, few studies have considered temperament as a potential endophenotype (see Nederhof et al., 2010 for an exception). Individual differences in temperament are plausible endophenotypes for depression (and ADHD) because they reflect stable individual differences in socio-emotional behavior that are moderately heritable (Saudino, 2005), they reliably predict psychopathology (Kelvin et al., 1996), and they are sensitive to neurobiological factors that are implicated in depression (Auerbach et al., 2001). Hamer et al. (1999) found that 5-HTTLPR was associated with multiple temperament and personality traits, including negative emotionality, cooperativeness and harm avoidance. Emerging research has also shown that increased serotonin in normal healthy adults (through administration of an SSRI) may promote prosocial behavior by enhancing harm aversion, particularly among adults with high trait empathy (Crockett et al., 2010). Thus, there is established evidence of the association between 5-HTTLPR with temperament/personality, as well as depression and ADHD. However, models of temperament vary, as studies of temperament and psychopathology are often contaminated by common language that is likely to inflate associations.

To combat this limitation, three core dimensions of temperament were recently derived using exploratory factor analysis where items were explicitly created to avoid highly similar language to psychiatric symptoms: negative emotionality (NE), which is conceptually related to the Big Five personality trait of neuroticism, is defined as an individual's reaction to frustration, threat or loss (Lahey et al., 2008); prosociality (PRO), which is similar to (or a facet of) the construct of conscientiousness, reflects the extent to which an individual is concerned about others, is sociable, and their willingness to help and share with others (Compas et al., 2004); and, daring (DA), which approximates the personality trait of extraversion, refers to individual differences in the propensity for sensation seeking, risk taking, and enjoyment in rough or dangerous activities (Lahey et al., 2008). The combination of high NE and low PRO are well-established correlates of depression (Clark and Watson, 1991). Moreover, high NE may represent a dispositional trait underlying major depression and externalizing problems, including comorbid conduct disorder (Tackett et al. 2011). Given that conduct disorder and ADHD share common genetic and environmental risk factors (Thapar et al., 2001), these findings suggest a plausible role of high NE in comorbid depression and ADHD. Importantly, PRO, DA and NE share considerable variance (despite being factorially independent) and recent studies identified a general factor of personality from this shared variance (Van der Linden et al., 2012). Thus, future studies must rigorously discern the unique (and shared) association between PRO, DA, and NE with respect to psychopathology.

To our knowledge, there are no published molecular genetic studies of psychopathology where putative endophenotypes were evaluated using a multiple mediation model, which disentangles the relative effects of simultaneous mediators within the same model (see Preacher and Hayes (2008) for a thorough review). Furthermore, investigating temperament dimensions as mediators can potentially clarify reported discrepancies in the literature regarding the role of 5-HTTLPR with respect to youth depression and ADHD. The primary aim of this study was to examine the collective and unique meditational effects of NE, PRO and DA on the association between 5-HTTLPR genotype and childhood depression in a sample of children with and without ADHD using multiple informants (i.e., parents and teachers) and methods (i.e., structured interview and rating scales). Given the considerable diagnostic overlap between depression and ADHD (e.g., disrupted attention, motor activity), however, we also examined whether potential mediator effects were *independent* of child ADHD status by testing "moderated mediation" (Preacher et al., 2007). We proposed two hypotheses based on previous research and theory (Clark et al., 1994; Lahey et al., 2008): (1) the association between 5-HTTLPR and childhood depression would be at least partially mediated by NE, beyond the effects of PRO and DA; (2) we predicted that child ADHD diagnostic status would moderate this association (i.e., moderated mediation) such that the mediation effect of NE would only be evident in children with ADHD.

2. Methods

2.1. Participants

We recruited 218 ethnically diverse (56% Caucasian, 8% African America, 8% Hispanic or Latino, and 28% Mixed or Other) 6–9 year-old children with ($n=115$) and without ADHD ($n=103$). The mean age was 7.4 (S.D.=1.1) and 67% of the sample was male. Recruitment methods included mailings to local schools, flyers and advertisements, presentations to self-help groups, and referrals from mental health service providers. Study eligibility required all participants to have a Full Scale IQ above 70, to live with one biological parent at least half the time, and be fluent in English. Exclusion criteria included current or previous diagnosis of mental retardation, seizure, autism, or pervasive developmental disorders. ADHD diagnostic status was assessed using a fully structured diagnostic interview with child's parent (see below). ADHD probands met full diagnostic criteria for any of the three DSM-IV ADHD subtypes based on a structured diagnostic interview. Non-ADHD controls were allowed to meet diagnostic criteria for any disorder other than ADHD according to the same structured diagnostic interview. Teacher data were obtained but they were not used to make diagnostic designations.

2.2. Procedures

Eligibility was determined after parents completed an initial telephone screening. Eligible families who were interested in participating were mailed rating scales and then invited to our laboratory for in-person assessments. Following parent consent and child assent, parents completed a structured diagnostic interview of child psychopathology as well as measures of parenting, family functioning, and their own psychopathology. At the same time, children completed standardized tests of cognitive ability and academic achievement. Approximately 85% of children (mostly treated with stimulants) were assessed in the lab without medication. Similarly, parents and teachers were each asked to complete rating scales based on child's unmedicated behavior. We prioritized parent and teacher reports over child self-reports per expert recommendations (Jensen et al., 1999). All interviews were initially blind to child's diagnostic status. The IRB approved all study procedures. Prior to each interview, all interviewers were blind to the child's diagnostic status. The Institutional Review Board approved all study procedures.

2.3. Genotyping

DNA was extracted from saliva using DNA Genotek Oragene™ Self-Collection Kits (DNA Genotek, Inc., Ottawa, CA). The 5-HTTLPR 48-bp insertion/deletion polymorphism in the promoter region was genotyped using standard primers, which produced fragments of either 484 or 528 bp (Heils et al., 1996). The long variant (528 bp) has approximately three times the basal activity of the shorter promoter (484 bp) with the deletion (Lesch et al., 1996). We followed previous strategies (Auerbach et al., 2001) by comparing three genotypes with the following distributions: *SS* (24.3%, $n=53$), SL (45.0%, $n=98$), and LL (30.7%; $n=67$). The Lg allele was not genotyped. These frequencies did not deviate from Hardy–Weinberg equilibrium ($\chi^2=2.07$, d.f.=1, $p=0.15$).

2.4. Measures

2.4.1. Diagnostic Interview Schedule for Children, Version IV, Parent Version (DISC-IV-P; Shaffer et al., 2000)

The DISC-IV-P is a computer-assisted, fully structured diagnostic interview that was administered to parents about their child's DSM-IV psychopathology. The DISC-IV-P has good psychometric properties, including high test–retest reliability ($r=0.79$, 1 year) and internal consistency (ICC=0.84 for symptoms and ICC=0.77 for criterion) for parent ratings in a large community sample (Shaffer et al., 2000). We analyzed the total number of symptoms from the Major Depressive Disorder (past year) module of the DISC-IV-P, which exhibited adequate internal consistency (ICC=0.79).

2.4.2. Teacher Report Form (TRF; Achenbach and Rescorla, 2001)

Teachers rated 120 items querying competence and problem behavior. Each item is rated as 0 (not true), 1 (somewhat true), or 2 (very true or often true). Based on a nationally-representative sample of 6–18 year-olds, the TRF had good reliability (i.e., ICC=0.72–0.95) and short-term test–retest reliability ranged from 0.62 to 0.96 (Achenbach and Rescorla, 2001). We analyzed T-scores for the anxious/depressed (AD) (e.g., cries a lot, feels worthless, talks about suicide) and withdrawn/depressed (WD) (e.g., rather be alone, won't talk, sad, withdrawn) scales (ICC=0.82 and 0.84, respectively).

2.4.3. Child and Adolescent Dispositions Scale (CADS; Lahey and Waldman, 2005)

The CADS is a 50-item parent interview of youth negative emotionality (NE), prosociality (PRO), and daring (DA). Items included: "does [your child] react intensely when he/she gets upset?" (NE, 11 items), "does [your child] feel sorry for kids who get picked on?" (PRO, 13 items), and "does [your child] enjoy doing things that are risky or dangerous?" (DA, five items). Parents rated the frequency of these items over the past year as "not at all," "just a little," "pretty much," and "very much." We analyzed the total score for each dimension. The internal consistency was acceptable (ICC=0.87, 0.77 and 0.79 for PRO, NE, and DA, respectively).

2.5. Analyses

To evaluate multiple mediation, we used bootstrapping procedures recommended by Shrout and Bolger (2002) and Preacher and Hayes (2008). Bootstrapping is a nonparametric re-sampling procedure that repeatedly samples from a dataset k number of times, generating an empirical approximation of a sampling distribution of the indirect effect (Preacher and Hayes, 2008). We used the multiple mediator macro provided by Preacher and Hayes (2008), specifying 1000 bootstrap samples, and variables were entered as follows: 5-HTTLPR genotype was entered as the independent variable (SS=0, SL=1 and LL=2), dimensions of child temperament (i.e., NE, PRO, and DA) were entered simultaneously as mediators, and depression measures (i.e., TRF narrow band scales, DISC-IV depression symptom counts) were separately examined as dependent variables. We also entered child age, race–ethnicity and sex as covariates.

We also examined whether child ADHD diagnostic status (i.e., ADHD versus non-ADHD) moderated the mediation models. Although there are several types of moderated mediation (Preacher et al., 2007), we specifically examined whether the single ADHD diagnostic status variable concurrently moderated the association between 5-HTTLPR and the temperament variables *and* the association between each temperament variable and depression. Based on expert recommendations (Preacher et al., 2007), we used normal-theory based models (i.e., regression) to estimate coefficients and standard errors from the conditional indirect effects of each mediation model while controlling for child age, race–ethnicity and sex. Power was calculated using the *powerMediation* package in R version 2.9.0. A minimum of 108 participants were required to achieve 80% power to detect a "large" effect size.

3. Results

3.1. Demographics

Descriptive data from the sample are summarized in Table 1 and inter-correlations for depression and temperament variables are provided in Table 2. Given that 53% of the sample was diagnosed with DSM-IV ADHD, we examined whether parent- and teacher-ratings of depression differed between these two groups. As expected, children with ADHD had significantly more symptoms of major depression according to the DISC-IV ($t=-7.75$, $p<0.001$), anxious/depressed and withdrawn/depressed behavior from the TRF ($t=-4.21$, $p<0.001$ and $t=-5.79$, $p<0.001$, respectively) than children without ADHD. Given the robust association of ADHD and depression in our sample, as well as the potential overlap between symptoms of ADHD and depression, we covaried ADHD diagnostic status in all multiple mediation models. However, we also tested ADHD as a moderator in the moderated mediation analyses below.

Table 1
Means and percentages for demographic variables and parenting.

Variable	ADHD ($n=115$)	Non-ADHD ($n=103$)	p
Age (S.D.)	7.36 (1.17)	7.51 (1.12)	0.61
% Males	72.72	63.89	0.15
% Caucasian	55.96	55.56	0.84
% Household income < $70,000	47.27	46.15	0.66
WISC-IV FSIQ (*SD*)	104.03 (14.51)	108.85 (15.61)	0.01
% ODD diagnosis	46.77	12.96	< 0.01
% CD diagnosis	7.26	0	< 0.01
% Anxiety (not specific phobia)	18.18	8.08	0.03

Note: S.D.=standard deviation; WISC-IV FSIQ=Wechsler Intelligence Scale for Children, Fourth Edition, Full Scale IQ; ODD=oppositional defiant disorder; CD=conduct disorder

Table 2
Bivariate correlations of depression and temperament scales.

	1	2	3	4	5	6
1. TRF anxious/depressed	1.00					
2. TRF withdrawn/depressed	0.45**	1.00				
3. DISC-IV-P Depression	0.04	0.15	1.00			
4. CADS prosocial	0.09	0.01	−0.25**	1.00		
5. CADS negative emotionality	0.19*	0.14	0.47**	−0.32**	1.00	
6. CADS daring	0.06	0.02	0.11	−0.08	0.24**	1.00

Note: TRF=Teacher Report Form; DISC-IV-P=Diagnostic Interview Schedule for Children, 4th edition – parent version; CADS=Child and Adolescent Dispositions Scale.

* $p<0.05$.
** $p<0.01$.

3.2. Population stratification

We tested for potential population stratification because it can produce spurious results in genetic association studies. 5-HTTLPR genotypes were unrelated to age ($X^2=12.56$, d.f.=10, $p=0.25$), sex ($X^2=2.95$, d.f.=2, $p=0.23$) and ADHD diagnostic status ($X^2=1.11$, d.f.=2, $p=0.57$), thus minimizing the possibility of population stratification (Hutchison et al., 2004). However, 5-HTTLPR was expectedly related to race–ethnicity ($X^2=36.59$, d.f.=14, $p<0.01$), given that allele frequencies for 5-HTTLPR are known to vary by race–ethnicity (Gelernter et al., 1999; Mrazek et al., 2009). Thus, race–ethnicity was controlled in all statistical models.

3.3. Parent ratings of child depression

We first tested the association of 5-HTTLPR with depression and temperament dimensions using linear regression (Fig. 1). Excluding mediators from the model, there was no significant total effect of 5-HTTLPR on depression ($B=0.32$, SE=0.27, $p=0.22$) and DA ($B=0.43$, SE=0.30, $p=0.16$), although it was significantly associated with PRO and NE ($B=-1.14$, SE=0.52, $p<0.05$ and $B=1.39$, SE=0.46, $p<0.01$, respectively). Specifically, each additional copy of the L allele negatively predicted PRO, but positively predicted NE. Next, NE was significantly associated with higher depression ($B=0.18$, SE=0.04, $p<0.01$), but PRO and DA were unrelated to depression ($B=-0.04$, SE=0.03, $p=0.33$ and $B=-0.04$, SE=0.06, $p=0.52$, respectively). Finally, there was no

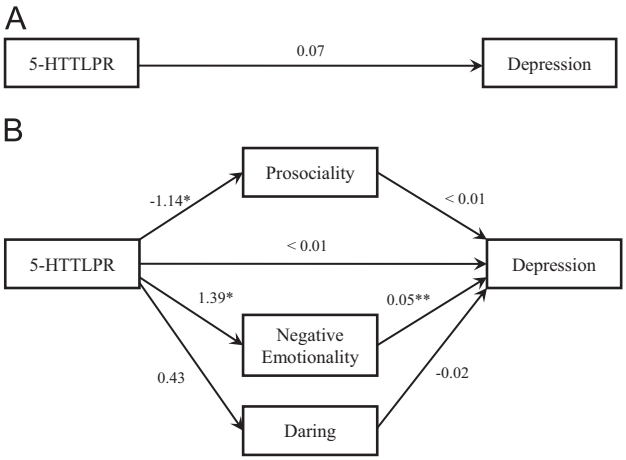

Fig. 1. Multiple mediator model of DISC-IV-P depression by temperament dimensions and 5-HTTLPR (beta coefficients). (A) Total effect and (B) indirect effects.

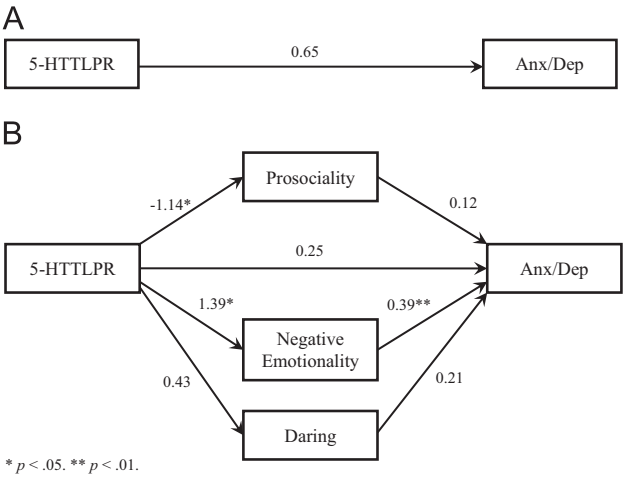

Fig. 2. Multiple mediator model of the anxious/depressed TRF scale by temperament dimensions and 5-HTTLPR (beta coefficients). (A) Total effect and (B) indirect effects.

Table 3
Mediation of 5-HTTLPR genotype and DISC-IV depression by prosociality, negative emotionality, and daring.

	Point est.	SE	95% BCa bootstrap CI	
			Lower	Upper
Indirect Effects				
Prosociality	0.04	0.05	−0.04	0.17
Negative Emotionality	**0.26**	**0.10**	**0.10**	**0.48**
Daring	−0.02	0.03	−0.12	0.02
TOTAL	0.28	0.11	0.08	0.54
Pair-Wise Contrasts				
Prosociality vs. Negative Emotionality	**−0.22**	**0.11**	**−0.48**	**−0.04**
Prosociality vs. Daring	0.05	0.06	−0.05	0.20
Negative Emotionality vs. Daring	**0.27**	**0.10**	**0.09**	**0.51**

Note: Point est.=point estimate of the indirect effect; SE=standard error; BCa bootstrap CI=Bias corrected and accelerated confidence intervals.

significant effect of 5-HTTLPR on depression through the mediators (i.e., direct effect) ($B=-0.04$, SE=0.03).

We calculated the total and specific indirect effects through NE, PRO and DA using a bootstrap analysis based on 1000 bootstrap simulation samples, yielding point estimates and the 95% bias corrected and accelerated (BCa) confidence intervals (CI) for each indirect effect (see Table 3). First, the point estimate of the difference between the total effect and direct effect through the three mediators (i.e., total indirect effect) was 0.28 (SE=0.11), with a 95% BCa bootstrap CI of 0.08–0.54., suggesting that the difference between the total and direct effects differed significantly from zero. Next, the specific indirect effects revealed that NE was a significant mediator, with a point estimate of 0.26 (SE=0.10) and a 95% BCa bootstrap CI of 0.10–0.48. However, the point estimates of the indirect effects of PRO and DA did not differ from zero (95% BCa bootstrap CI=[−0.04, 0.17] and [−0.12, 0.02], respectively). The pairwise contrasts between the specific indirect effects revealed that only the difference between DA and NE was significant, with a point estimate of 0.27 (SE=0.10) and a 95% BCa bootstrap CI of 0.09–0.51.

3.4. Teacher ratings of child depression

We conducted parallel multiple mediation analyses using the anxious/depressed (AD) and withdrawn/depressed (WD) narrowband scales of the TRF (see Fig. 2 for AD mediation model). There was no significant total effect of 5-HTTLPR genotype on AD and WD ($B=0.65$, SE=1.03, $p=0.53$ and $B=-0.40$, SE=34, $p=0.24$, respectively). The association between 5-HTTLPR and each dimension of temperament was identical to parent-rated depression, where each additional copy of the 5-HTTLPR L allele negatively predicted PRO and positively predicted NE (although there was no association with DA). Next, NE was significantly associated with AD ($B=0.39$, SE=0.15, $p<0.01$), but PRO and DA were not ($B=0.12$, SE=0.13, $p=0.32$ and $B=0.21$, SE=0.24, $p=0.38$, respectively). None of the dimensions of temperament was associated with WD (PRO: $B=<0.01$, SE=0.05, $p=0.93$; NE: $B=0.07$, SE=0.05, $p=0.20$; and DA: $B=0.08$, SE=0.08, $p=0.32$) nor was there a significant direct effect of 5-HTTLPR for AD ($B=0.25$, SE=1.04, $p=0.54$) or WD ($B=-0.55$, SE=0.36, $p=0.12$).

Once again, we conducted the bootstrap analysis for the total and specific indirect effects through NE, PRO and DA (Table 4). For AD, the point estimate of the total indirect effect was 0.19 (SE=0.22), with a 95% BCa bootstrap CI of −0.19 to 0.68. However, only NE significantly mediated 5-HTTLPR genotype and AD, with a point estimate of 0.26 (SE=0.10) and a 95% BCa bootstrap CI of 0.10–0.48. The point estimates of the indirect effects of PRO and DA did not significantly differ from zero (95% BCa bootstrap CI=[−0.50, 0.04] and [−0.10, 0.41], respectively). The pairwise contrasts between the specific indirect effects revealed that only the difference between PRO and NE was significant, with a point estimate of 0.36 (SE=0.21) and a 95% BCa bootstrap CI of 0.05–0.94. For WD, the point estimate of the total indirect effects was 0.15 (SE=0.13) with a 95% BCa bootstrap CI of −0.05 to 0.49. Point estimates for the specific indirect effects of PRO, NE, and DA did not significantly differ from zero (95% BCa bootstrap CI=[−0.12, 0.16], [−0.02, 0.33] and [−0.03, 0.35], respectively), suggesting that NE, PRO, and DA did not significantly mediate the association between 5-HTTLPR and WD.

3.5. Moderated mediation

Finally, we examined child ADHD status moderated the mediation effects of temperament dimensions for 5-HTTLPR and depression. ADHD status did not significantly moderate the association of 5-HTTLPR with PRO ($B=1.15$, SE=1.04, $p=0.26$), NE ($B=-0.97$, SE=0.92, $p=0.29$), and DA ($B=-0.17$, SE=0.61, $p=0.78$), respectively, in the mediation models for DISC-IV depression symptoms. Similarly, ADHD did not moderate the association between DISC-IV depression symptoms and PRO ($B=0.03$, SE=0.02, $p=0.06$), NE ($B=0.02$, SE=0.02, $p=0.20$), and DA ($B=0.02$, SE=0.03, $p=0.58$), respectively. Next, we examined moderated mediation with the AD narrow-band scale from the TRF. Once again, the interaction of ADHD and 5-HTTLPR was not significant for PRO ($B=1.34$, SE=1.32,

Table 4
Mediation of 5-HTTLPR genotype and anxious/depressed and withdrawn/depressed scales from the TRF by prosociality, negative emotionality and daring.

	Point est.	SE	95% BCa bootstrap CI	
			Lower	Upper
Anxious-Depressed Narrow-Band Scale				
Indirect Effects				
Prosociality	−0.16	0.20	−0.67	0.14
Negative Emotionality	**0.44**	**0.28**	**0.04**	**1.23**
Daring	0.10	0.20	−0.20	0.72
TOTAL	0.38	0.41	−0.34	1.33
Pair-Wise Contrasts				
Prosociality vs. Negative Emotionality	**−0.60**	**0.36**	**−1.58**	**−0.06**
Prosociality vs. Daring	−0.27	0.25	−0.92	0.14
Negative Emotionality vs. Daring	0.32	0.34	−0.19	1.17
Withdrawn-Depressed Narrow-Band Scale				
Indirect Effects				
Prosociality	0.04	0.17	−0.24	0.51
Negative Emotionality	0.22	0.22	−0.09	0.90
Daring	0.14	0.21	−0.12	0.81
TOTAL	0.40	0.34	−0.13	1.24
Pair-Wise Contrasts				
Prosociality vs. Negative Emotionality	−0.18	0.30	−0.93	0.34
Prosociality vs. Daring	−0.10	0.26	−0.79	0.31
Negative Emotionality vs. Daring	0.08	0.33	−0.57	0.76

Note: Point est.=point estimate of the indirect effect; SE=standard error; BCa bootstrap CI=Bias corrected and accelerated confidence intervals.

$p=0.31$), NE ($B=-0.80$, SE=1.13, $p=0.48$) and DA ($B=-0.52$, SE=0.76, $p=0.49$). ADHD did not interact with temperament in predicting AD (PRO: $B=0.20$, SE=0.24, $p=0.41$; NE: $B=-0.29$, SE=0.28, $p=0.31$; and DA: $B=0.18$, SE=0.43, $p=0.67$). Finally, we tested the moderated mediation effects on the TRF WD narrow-band scale. The interaction of ADHD and 5-HTTLPR was not significant for PRO ($B=1.62$, SE=1.33, $p=0.22$), NE ($B=-0.77$, SE=1.16, $p=0.51$) and DA ($B=-0.49$, SE=0.77, $p=0.53$). Furthermore, no ADHD x temperament interactions significantly predicted WD (PRO: $B=0.02$, SE=0.24, $p=0.90$; NE: $B=0.14$, SE=0.28, $p=0.63$; and DA: $B=0.63$, SE=0.41, $p=0.12$).

4. Discussion

Although studies on the etiology of childhood depression have implicated the 5-HTTLPR genotype (Anguelova et al., 2003), this causal association is likely to involve intermediate phenotypes (i.e., endophenotypes) that are more proximal to the functional properties of 5-HTTLPR (Lesch, 2004). Temperament is a plausible endophenotype for depression because it is stable across the lifespan, significantly heritable, and influenced by similar genetic factors to depression (i.e., 5-HTTLPR), and it is a well-established predictor of psychopathology (Whittle et al., 2006). We examined temperament dimensions (i.e., NE, PRO, and DA) as mediators of the association of 5-HTTLPR genotype and multi-informant measures of childhood depression in a well-characterized sample of 6–9 year-old children with and without ADHD. 5-HTTLPR was unrelated to child depression, but the L allele predicted higher NE and lower PRO compared to the S allele (the L allele was unrelated to DA). We also found that the association between 5-HTTLPR with separate measures of parent- and teacher-rated childhood depression was partially mediated by NE. ADHD diagnostic status (i.e., ADHD vs. non-ADHD control) did not moderate any of these mediation effects.

The overall association of 5-HTTLPR and NE and PRO is consistent with existing evidence (Greenberg et al., 2000; Montag et al., 2010), although the current results suggested that greater transcriptional efficiency from the L allele (and subsequently, lower serotonin availability) was associated with higher NE and lower PRO in children. This specific finding diverges from previous studies of 5-HTTLPR and youth depression (see review by Dunn et al., 2011). One possibility for this inconsistency may be developmental timing given that 5-HTTLPR expression differs across age (Greenberg et al., 2000). The 5-HTTLPR S allele, for instance, was associated with greater fearful distress and NE in infants at 2 months of age, but with less distress and NE when the same infants were assessed at 12 months of age (Auerbach et al., 2001). There is also emerging evidence that the effects of the low expressing 5-HTTLPR genotype may not manifest until late adolescence/early adulthood. Children and adolescents with the low expressing genotype (S/S and S/Lg carriers) exhibited the greatest decrease in amygdala activation as a function of age, compared to youth with the higher expressing genotypes (La/La and S/La) (Wiggins et al., in press). Furthermore, youth with the low expressing genotype showed a sharper decline in connectivity between the amygdala and prefrontal cortex. Depression and NE are associated with amygdala overactivation (Monk et al., 2008) and amygdala–prefrontal underconnectivity (Carballedo et al., 2011). Thus, age-related variability between studies (e.g., our sample featured relatively young school-age children) may also contribute to the inconsistent findings for 5-HTTLPR genotype. However, given that few genetic association studies of temperament have explored prospectively across development, this requires further refinement.

These results suggest that NE may serve as an intermediate construct between genetic variation and psychopathology. In other words, dimensions of temperament may be plausible endophenotypes for molecular genetic studies (Gonda et al., 2006), especially given that the role of NE was evident in separate parent and teacher ratings of depression. In fact, the strongest evidence of genetic mediation via NE was indicated by the association between 5-HTTLPR and teacher-rated anxious/depressed scale. This finding is particularly noteworthy given the stringent use of parent-reported NE and teacher reported anxiety/depression, which avoids shared method variance that typically inflates associations. Furthermore, ADHD did not moderate the mediation of NE on 5-HTTLPR and depression (i.e., no evidence of moderated mediation), suggesting that NE may confer a general liability towards developmental psychopathology (Eley et al., 2004; Nobile et al., 2009). For example, NE prospectively predicted internalizing problems (e.g., anxiety, depression), externalizing problems (e.g., aggression, ADHD), *and* co-occurring internalizing/externalizing problems in a longitudinal study of 214 infants and toddlers (Eisenberg et al., 2009). However, some specificity was suggested when NE was separated into anger/irritability vs. sadness/fear components (Rothbart and Bates, 1998), such that children high on anger were more prone to externalizing and co-occurring problems whereas children high on sadness were more likely to have internalizing problems (Eisenberg et al., 2009). These findings have also been replicated in adults where neuroticism accounted for the most variance in internalizing (e.g., major depression) and externalizing disorders (e.g., substance dependence, antisocial personality disorder) (Khan et al., 2005). Thus, elevated NE may contribute to a *general* vulnerability for psychopathology, and genetic factors may confer greater specificity in outcome[2] (Kendler et al., 2003).

[2] Per reviewer recommendation, we tested the same mediational path models on other outcome measures (i.e., ODD symptoms, CBCL anxiety problems) to determine whether our original findings were specific for depression. We found that NE and PRO also partially mediated the association between 5-HTTLPR and ODD, but not for CBCL anxiety. Future studies should continue to examine biological and/or psychological endophenotypic markers, which may disentangle the complex pathways to psychopathology. These data are available upon request.

However, the role of NE as an intervening variable between 5-HTTLPR and child depression may also be explained by potential gene–environment interaction, which was not tested in this study. That is, genetic variations may be associated with child problem behaviors only under specific environmental conditions, such as negative parenting or maltreatment (Moffitt et al., 2006). Children with the met allele of BDNF and two S alleles of the 5-HTTLPR gene had the highest levels of depression, but only when they experienced maltreatment (Kaufman et al., 2006). Kaufman et al. (2004) also found that without social support, maltreated children with the SS genotype exhibited significantly higher depression than non-maltreated comparison children with the same genotype. However, maltreated children with the SS genotype who received social support exhibited only a minimal increase in depression, suggesting that social support moderates the association of 5-HTTLPR and depression in maltreated children. Thus, although these results suggest that NE may constitute a causal mediator between genetic influences and psychopathology, possible effects due to an unmeasured gene–environment interaction and epistasis (i.e., gene–gene interaction) were not accounted for. This hypothesis requires further attention, particularly in the context of a genetic mediation study (i.e., mediated moderation).

Several study limitations bear mentioning. First, mediation models were based on cross-sectional data. Without longitudinal data, temporal ordering is unknown for temperament and depression and we cannot discern how these processes unfold over time. That is, interpreting mediation effects without temporal separation between the putative cause (i.e., temperament) and its effect (i.e., depression) is ambiguous (Collins et al., 1998; Maxwell and Cole, 2007). However, given the near absence of mediation studies in psychiatric genetics, these findings provide evidence of concurrent mediation of childhood depression by a biologically plausible endophenotype. Future genetic studies of mediation must use longitudinal designs (e.g., autoregressive models) to establish temporal separation of each construct (Maxwell and Cole, 2007). In addition, child temperament was assessed exclusively from the parent, which may partially reflect unique biases. However, a recent psychometric analysis of the CADS compared parallel youth self-reports from the CADS with the parent-rated CADS. Congruence coefficients between parent and child-self-reports were 0.96, 0.97, and 0.89 for PRO, NE, and DA dimensions, respectively, suggesting that dimensions were relatively invariant across informants (Lahey et al., 2010). Parent- and self-report CADS ratings also independently predicted the same psychopathology and personality outcomes in children over time (Lahey et al., 2010). Finally, acknowledge that unmeasured single nucleotide polymorphisms (SNPS) may have affect out findings, particularly the rs25531 SNP, which contains two variants within the L allele (La and Lg) in which the Lg functions similarly to the S allele (Hu et al., 2005). The Lg allele was more prevalent among African-Americans relative to Caucasians, although crucially, this was only documented in a single study of depressed adults (Mrazek et al., 2009). Nonetheless, we acknowledge that the absence of these data is a potentially important limitation to these findings.

The present study is an important contribution by virtue of having formally tested mediation using a biologically-plausible and theoretically-derived set of putative endophenotypes for depression. Our approach utilized multiple mediation to account for the simultaneous influence of several temperament dimensions. Findings suggested that temperament dimensions may be an intermediate link between 5-HTTLPR genotype and childhood depression, over and above the effects of ADHD. The function of 5-HTTLPR may be more proximal to the processes and mechanisms underlying depression, suggesting the utility of temperament as an endophenotype in future molecular genetic studies. More importantly, the present findings reaffirm the unique contributions of genetically-sensitive designs that simultaneously incorporate putative endophenotypes and careful measurement of clinically significant phenotypes.

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