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An examination of the association between the 5-HTT promoter region polymorphism and depressogenic attributional styles in childhood

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Abstract

Although a vast literature examining the role of attributional styles in depression has accumulated, the origins of such cognitions remain poorly understood. Investigators are increasingly interested in whether cognitive vulnerability to depression is linked to genetic variation. As a preliminary test of this hypothesis, we examined whether the serotonin transporter promoter polymorphism (5-HTTLPR) was associated with attributional styles in children. Thirty-eight children completed a self-report measure of attributional styles, the Child Attributional Style Questionnaire-Revised (CASQ-R). Children were also genotyped for the 5-HTTLPR polymorphism, including the single nucleotide polymorphism (SNP) rs25531 in the long allele of the 5-HTTLPR. The short alleles of the 5-HTTLPR and their putative functional equivalents were associated with increased levels of depressogenic attributions for negative events, as measured by the CASQ-R, lending support to the role of 5-HTTLPR polymorphisms in cognitive vulnerability to depression.

Keywords

attributional style; depression; 5-HTTLPR; serotonin transporter gene; SNP

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Cognitive models of depression vulnerability have played an influential role in both theory and practice over the past 40 years. Although several such models exist (e.g., Alloy, Lipman, & Abramson, 1992; Beck, 1976; Seligman, 1975), a common theme prevails in each: individuals whose thinking is characterized by self-blame, pessimism, and helplessness are at risk for the development of depression. In particular, attributional styles characterized by internal, stable, and global attributions for negative events have been linked to the development of depression in the presence of negative life events (Abramson, Seligman, & Teasdale, 1978; Alloy et al., 1992; Conley, Haines, Hilt, & Metalsky, 2001), and a growing literature indicates that cognitive vulnerability to depression may emerge early in life (Ingram, 2003; Jaenicke, Hammen, Zupan, Hiroto, Gordon, & Adrian, 1987).

While generally supportive of the role of attributions in depression, most previous studies have not typically been designed to identify factors that underlie the development of attributional styles. Although early theories posited a role of stressful life events in triggering cognitive vulnerability to depression, stressful life events and attributional styles appear to be only modestly linked (Gibb, 2002). Studies of animal models of depression indicate that behaviors reflecting greater helplessness, a construct closely linked to attributional styles (Seligman, 1975), have a strong genetic component (Solberg et al., 2003; El Yacoubi et al., 2003). A handful of investigators have suggested that helplessness and attributional styles may have a genetic basis in humans (Abramson, Metalsky, & Alloy, 1989; Hamburg, 1998) but little research to date speaks directly to this question.

A logical candidate gene for association with attributional styles related to depression is the serotonin transporter promoter region polymorphism (5-HTTLPR). Variants of the 5-HTTLPR consist of a long (L) allele, comprised of 16 copies of an approximately 22 base pair (bp) repeat unit, and a short (S) allele, consisting of 14 copies (for a review, see Hariri & Holmes, 2006). Compared to the L allele, the S allele is associated with decreased transcriptional efficiency of the promoter (Lesch, Bengel, Heils, Sabol, Greenberg, & Petri, 1996). Additionally, 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). Some evidence indicates that, of the L alleles, only the L_A allele is high functioning with regard to promoter activity, whereas the L_G allele may have the same transcriptional activity as the S allele (Hu, Oroszi, Chun, Smith, Goldman, & Schuckit, 2005; Hu, Lipsky, Zhu, Akhtar, Taubman, & Greenberg, 2006). In previous association studies, the short allele has been associated with predispositions to fear-related behaviors and negative emotionality in children and adults (Hayden et al., 2007; Lesch et al., 1996), and some studies suggest that this allele increases risk for depression in individuals who experience stressful life events (Caspi et al., 2003; Zammit & Owen, 2006). One possible mechanism underlying the interaction between 5-HTTLPR genotype and stress is that this gene is associated with negative attributions about life events, which serve as a more proximal cause of depressive episodes when stressful events occur. However, to our knowledge, there is no study examining whether attributional styles in childhood are associated with measured genetic variants. Further, the majority of studies on the role of the 5-HTTLPR in depression have not examined the effects of the A/G SNP in the long allele.

As a preliminary investigation of whether early-emerging cognitive styles are linked to specific measured genes, we examined whether depressogenic attributions for positive and negative life events, indexed by the Child Attributional Style Questionnaire-Revised (CASQ-R), were associated with 5-HTTLPR genotype in a community sample of children. We predicted that the same genetic variant previously associated with depression in the context of stressful life events (e.g., Caspi et al., 2003), namely the short form of the 5-HTTLPR polymorphism, would also be associated with increased depressogenic attributional styles for negative events. Since the literature examining genetic variation at the 5-HTTLPR locus has emphasized the effects

of this gene in the context of negative events, we did not make specific hypotheses regarding the relationship between this gene and attributions for positive events.

Method

Participants

Thirty-eight children (19 males) from the community, part of a longitudinal study of depression vulnerability, participated in this project. Children were recruited via a commercial mailing list, and through advertisements placed in local newspapers and fliers posted in local preschools (further detail on sample characteristics and study design have been published elsewhere; see Durbin, Hayden, Klein, & Olino, 2007; Hayden, Klein, Durbin, & Olino, 2006). Children were an average of 7.0 years old (*SD* = 0.49). The sample was ethnically homogenous: 36 of the children were white and two were of other ethnic backgrounds. After a complete description of the study to a parent, written informed consent was obtained. During a home visit, a research assistant read all self-report items and response choices aloud to each child participant. The research assistant did not have information on children's genotypes.

Assessment of attributional styles

Children completed the Child Attributional Style Questionnaire-Revised (CASQ-R; Thompson, Kaslow, Weiss, & Nolen-Hoeksma, 1998). The CASQ-R yields two scales reflecting the extent to which the respondent tends to make internal, global, and stable attributions for positive and negative events. While higher scores on the negative composite scale reflect a more depressogenic attributional style, higher scores on the positive composite scale represent a less depressogenic attributional style. Internal consistencies for the positive and negative composite scales in our sample, indexed by coefficient alpha, were .50 and .55 respectively. Although these scale reliabilities are lower than desirable, they are consistent with those reported in literature for this measure (Thompson et al., 1998)

Depression Ratings

Children's ratings of depressive symptoms were obtained using the Depression Self-Rating Scale (DSRS; Birleson, 1981). The DSRS is a self-report measure of affective, cognitive, and behavioral symptoms of depression, and has been shown to adequately discriminate between children with and without depression (Asarnow & Carlson, 1985; Kazdin & Petti, 1982). Consistent with our nonclinical sample, the mean DSRS score was low (*M* = 9.95, *SD* = 5.32) and comparable to other studies of nondepressed children (Asarnow & Carlson, 1985). Coefficient alpha for the DSRS was .75 in our study.

Genotyping

Genomic DNA was purified from buccal swab cellular extracts and stored according to manufacturer instructions (Qiagen, Valencia, CA, USA). PCR and a restriction fragment length polymorphism (RFLP) assay were used to determine the insertion/deletion polymorphism, as well as the rs25531 SNP. Following Chorbov, Lobos, Todorov, Heath, Botteron, & Todd (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. The SNP is part of a recognition site for the *MspI* restriction endonuclease (Fermentas), which cuts one base 5' of the SNP when the G nucleotide is present, and does not cut when the A nucleotide is present. The Invitrogen PCRx Enhancer System kit (Invitrogen) was used for PCR amplification, instead of the 7-deazaGTP (otherwise necessary to amplify the GC-rich region), which impairs the ability of

MspI to completely cut the PCR product. PCR was followed by digestion of amplicons at 37° C overnight with 1 unit of *MspI*, yielding a 249 bp fragment (uncut L_A allele), two fragments of 148 bp and 101 bp (cut L_G allele), or a 206 bp fragment (S allele).

Results

Genotype groups for data analysis were formed using two approaches: first, as described by Lesch et al. (1996), the CASQ-R and DSRS scores of children homozygous for the L alleles (N = 11) were compared to those with at least one S allele (N = 27), hereafter designated the "biallelic" approach to forming 5-HTTLPR genotype groups (Zalsman, Huang, Oquendo, & Burke, 2006). In our second analysis, following recent reviews (Hu et al., 2005; 2006), children with the L_A/L_A alleles (N = 7) were contrasted with those children with a variant of the long allele associated with decreased serotonin functionality or an S allele (i.e., the L_A/L_G, L_G/L_G, S/L_A, S/L_G, and S/S groups; N = 31). We refer to genotypes formed according to this approach as "triallelic" (Zalsman et al., 2006). Multivariate analysis of variance (MANOVA) was used to examine mean differences between CASQ-R scores and their relation to child 5-HTTLPR genotype.

Supporting the notion that the CASQ-R scales are meaningfully related to depression vulnerability, DSRS scores were negatively correlated with the CASQ-R composite attributional style for positive events (r = -.45, $p < .01$) and positively correlated with the composite attributional style for negative events, albeit nonsignificantly (r = .23, p = .17). Neither the biallelic or triallelic approach to creating 5-HTTLPR genotype groups resulted in significantly different mean DSRS scores by genotype ($ps > 0.41$; see Table 1). Child age was not significantly correlated with CASQ-R scale scores ($ps > 0.24$), nor did CASQ-R scores differ significantly for positive or negative events ($ps > 0.38$) between sexes.

Using genotype groups based on the biallelic system, a MANOVA of genotype showed a trend-level effect on the CASQ-R scales, F (2, 35) = 2.92, p = .07. Because we had specific *a priori* hypotheses regarding the effect of genotype on the CASQ-R negative composite scale, we examined mean group differences on this scale. Consistent with our hypothesis, genotype group had a significant effect on the CASQ-R negative composite, F (1, 36) = 5.88, p = .02 (see Table 1). Children with a short allele reported significantly more negative attributions than those who were homozygous for the long allele. A MANOVA examining the effect of genotype on the CASQ-R scales using the triallelic classification approach was significant, F (2, 35) = 5.08, p = .01 (see Table 1). Again, a significant relationship was found between CASQ-R negative scores and the 5-HTTLPR genotype, F (1, 36) = 9.59, $p < .01$, but there was no significant effect of genotype on CASQ-R positive composite scores, F (1, 36) = .19, p = .66. Children with an S or L_G allele had significantly more negative attributions than children who were homozygous for the L_A allele.

Discussion

We examined associations between 5-HTTLPR genotypes and attributional styles in a nonclinical sample of children, finding that children with at least one copy of the short allele of this gene (or its putative functional equivalent) reported higher levels of depressogenic attributional styles for negative events than children homozygous for the long alleles. The possibility that cognitive vulnerability to depression may be partially determined by heritable factors has been suggested by several psychopathologists (e.g., Abramson et al., 1989; Hamburg, 1988); our results provide preliminary evidence for a role of a specific functional genetic variant, the 5-HTT promoter polymorphism.

These data are compatible with previous reports from our group and others of an association between depressogenic information processing styles and the 5-HTTLPR polymorphism (Beevers, Scott, McGeary, & McGeary, in press; Hayden et al., 2008). An added strength of the present study is the screening of a polymorphism in the long allele of the 5-HTT promoter (Hu et al., 2005; 2006), although whether this SNP impacts the functionality of the 5-HTTLPR is still under debate (see Uher & McGuffin, 2008, for a discussion of this issue). In our study, incorporating this SNP resulted in four children without putative genetic risk (i.e., those with the L/L genotype) being reclassified as "at-risk" due to having at least one L_G allele. Despite this change in group composition, incorporating this information yielded results consistent with analyses not factoring in the A to G SNP in the long allele.

Our study has a few limitations. Our sample size was small; it is therefore especially important to replicate this finding in a larger sample. Additionally, population stratification is a concern in any association study, but is less likely to cause problems in an ethnically homogenous sample such as ours (Hutchison, Stallings, McGeary, & Bryan, 2004). The internal consistencies of the CASQ-R were lower than desirable, albeit consistent with previous reports using this measure (Thompson et al., 1998). We relied on self-reports of attributional style in the present study. We used a nonclinical sample of children in the present study, which allows greater confidence in our conclusion that this gene is linked to vulnerability, rather than aspects of current depressive disorder. However, longitudinal designs are needed to conclusively establish whether cognitive vulnerability plays an intermediate role in the relationship between the 5-HTTLPR polymorphism, stressful life events, and the onset of depression.

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Table 1

Means and standard deviations of CASQ-R and DSRS scores in children based on 5-HTTLPR genotype.

	5-HTTLPR biallelic genotypes		5-HTTLPR triallelic genotypes	
	S/S + S/L	**L/L**	**S/S + S/L_A + S/L_G + L_G/L_A + L_G/L_G**	**L_A/L_A**
CASQ-R Positive (*SD*)	20.07 (1.96)	20.50 (2.71)	20.26 (2.02)	19.86 (2.85)
CASQ-R Negative (*SD*)	14.75 (1.35)	13.60 (1.07)	14.75 (1.32)	13.14 (0.69)
DSRS (*SD*)	10.71 (5.42)	7.81 (4.59)	10.29 (5.31)	8.42 (5.45)

Note: 5-HTTLPR = Serotonin promoter region polymorphism; S = short variant; L = long variant; L_A = Long variant with adenine at nucleotide six; L_G = Long variant with guanine at nucleotide six; CASQ-R Positive = Child Attributional Style Questionnaire- Revised positive composite scale; Child Attributional Style Questionnaire- Revised negative composite scale; DSRS = Depression Self-Rating Scale.