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Early-Emerging Cognitive Vulnerability to Depression and the Serotonin Transporter Promoter Region Polymorphism

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Abstract

Background—Serotonin transporter promoter (5-HTTLPR) genotype appears to increase risk for depression in the context of stressful life events. However, the effects of this genotype on measures of stress sensitivity are poorly understood. Therefore, this study examined whether 5-HTTLPR genotype was associated with negative information processing biases in early childhood.

Method—Thirty-nine unselected seven-year-old children completed a negative mood induction procedure and a self-referent encoding task designed to measure positive and negative schematic processing. Children were also genotyped for the 5-HTTLPR gene.

Results—Children who were homozygous for the short allele of the 5-HTTLPR gene showed greater negative schematic processing following a negative mood prime than those with other genotypes. 5-HTTLPR genotype was not significantly associated with positive schematic processing.

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Limitations—The sample size for this study was small. We did not analyze more recently reported variants of the 5-HTTLPR long alleles.

Conclusions—5-HTTLPR genotype is associated with negative information processing styles following a negative mood prime in a nonclinical sample of young children. Such cognitive styles are thought to be activated in response to stressful life events, leading to depressive symptoms; thus, cognitive styles may index the "stress-sensitivity" conferred by this genotype.

Keywords

5-HTTLPR; depressogenic cognitive style; depression

Introduction

Genetic association studies of depression have traditionally examined the extent to which a particular genotype is associated with a diagnosis of major depressive disorder. This approach has yielded largely inconsistent findings. One compelling explanation for the lack of consistent results is the failure of most association studies to include measures of relevant environmental contexts that control the strength of genotype-phenotype associations (Moffitt et al., 2005).

To test this argument, seminal research has been conducted examining gene-environment interactions (GXE) in predicting depression onset, largely focusing on polymorphisms of the serotonin transporter promoter (5-HTTLPR) and stressful life events. The first of such studies provided evidence that individuals with putative genetic vulnerability to depression, as evinced by having short alleles of the 5-HTTLPR gene, developed depression more frequently in the context of stressful life events than those without this genotype (Caspi et al., 2003). Several replications have been published, as have failures to replicate (Zammit and Owen, 2006).

Although the use of GXE designs is still in its infancy, these multivariate approaches are consistent with the larger literature showing that both environmental and biological influences are important in depression (Gotlib and Hammen, 2002). However, to date, few GXE studies have considered the mechanisms by which genetic and environmental factors promote depression onset. More proximal factors under genetic influence may mediate the process by which individuals with genetic vulnerability express an adverse response to stress. This suggests the importance of looking at the genetic bases of factors implicated in vulnerability to depression, especially those thought to operate in conjunction with environmental stress. Such factors may play a mechanistic role in gene-environment interactions.

Of the many factors proposed to increase depression vulnerability, cognitive mechanisms are thought to play a central role. Cognitive theories invoke a diathesis-stress framework, positing that depressogenic cognitive styles are activated in response to negative life events. For example, Beck's cognitive theory (Beck, 1976) posits that biases in information processing (schemas), which are activated in stressful contexts, contribute to depression. Experimental measures of the cognitive constituents of Beck's theory include information processing tasks validated in samples of children with depression (Garber and Kaminski, 2000) and those at high risk for the disorder (Taylor and Ingram, 1999).

Cognitive vulnerability to depression may represent a mechanism under genetic control that accounts for individual responses to adverse life events. Recently, Segal and colleagues (2006) reported that cognitive reactivity to a negative mood prime predicted relapse in patients successfully treated for depression. These authors proposed that cognitive reactivity represents a pathway through which stress eventuates in depression. Relatedly, candidate genes have been successfully linked to aspects of information processing putatively related to psychopathology (Hariri et al., 2002). The present study therefore examined whether 5-HTTLPR genotype was

associated with children's performance on the Self-Referent Encoding Task (SRET), a widely-used information processing task designed to tap memory for affectively-charged word stimuli.

Method

Thirty-nine children (19 males) from the community, part of a larger, longitudinal study of depression vulnerability, participated in this project. Children were an average of 7.0 years old (SD = 0.51, range = 6.1–7.9 years). Thirty-six of the children were Caucasian, two were Hispanic, and one child's ethnic status was unknown. After a complete description of the study to a parent, written informed consent was obtained. Given the young age of the children, child assent was not obtained.

A negative mood induction procedure (MIP) was administered prior to the SRET. These procedures have been described in detail elsewhere (Hayden et al., 2006). Briefly, for the MIP, children were shown a sad video clip from a children's film to prime a negative mood (Brenner, 2000). Children were videotaped during the MIP for facial affect coding by trained raters blind to the purpose of the task. The MIP was effective; children displayed significantly greater negative affect in the second half of the mood induction (M = −1.40, SD = .48) than in the first half (M = −.83, SD = .34), t (60) = 8.83, $p < .001$, $d = 1.34$. Next, children were presented with a series of 18 positive and 18 negative trait adjectives matched for frequency and selected for beginner reading level (Carroll et al., 1971). Adjectives were shown to them on flashcards and spoken aloud by the experimenter, followed by a self-referent question ("is this word like you?"). The experimenter noted the child's response to each query. An incidental recall period immediately followed in which children were asked to recall as many of the adjectives as possible. The first and last three words from the list were not counted to eliminate primacy and recency effects. Two schematic processing scores were calculated: a positive schematic processing score (proportion of positive words rated self-descriptive and recalled, relative to all words rated self-descriptive), and a negative schematic processing score (derived in the same manner). At the end of the task, children were allowed to select several small toys to reverse the effects of the MIP. After the MIP reversal, no child endorsed experiencing a negative mood state, assessed by asking children to select one of four facial icons (depicting happy, sad, angry, and neutral expressions) that was the most like how they currently felt.

Cellular extracts from buccal swabs prepared according to manufacturer instructions (Epicenter Biotechnologies, Madison, WI, USA) were used as the source of DNA template for genotyping. Briefly, swabs were rotated a minimum of 5 times in 0.5ml of QuickExtract DNA extraction solution, in 1.5ml microcentrifuge tubes. Tubes were vortexed 10 seconds, heated at 65°C for 1 min, vortexed 15 sec, heated at 98°C for 2 min, and vortexed 15 sec. Extracts were stored at −20°C.

The 5-HTT gene promoter polymorphism was typed by DNA polymerase chain reaction (PCR) using flanking primers 5′-CTT GTT GGG GAT TCT CCC GCC TGG CGT T-3′ (forward) and 5′-TCG AGG CTG AGC GTC TAG AGG GAC TGA GCT GG-3′ (reverse). PCR was performed in a 30-μl reaction containing 10–20 μl extract, 20 mM Tris-HCl (pH 8.4), 50 mM KCl, 1.5 mM MgCl2, 0.1 μg each primer, 0.083 mM 7-deaza-2-deoxyGTP/dGTP, 0.17 mM dATP, dCTP, dTTP, and 1 U Taq DNA polymerase (Roche, Indianapolis, IN, USA). DNA was denatured at 95°C for 5 min and subjected to 35 cycles of 45-s denaturation at 95°C, 1 min annealing at 66 °C and 1 min extension at 72 °C. Amplification products were resolved by electrophoresis on 4.5% polyacrylamide gels and visualized with ethidium bromide staining. Alleles were designated short (s; 484 bp) or long (l; 528 bp) by individuals blind to child SRET data.

Results

Eight children were homozygous for short alleles (s/s) of the 5-HTTLPR. Twenty were heterozygous (s/l) and ten were homozygous for the long allele (l/l). Assumptions about allele dominance were not made as studies of the 5-HTTLPR in depression have implicated different categorizations of genotype (Eley et al. 2004, Kendler et al. 2005). Figure 1 shows means and standard deviations for SRET scores for each genotype.

Analysis of variance (ANOVA) was used to examine differences across the three genotypes for the SRET positive processing scores. The Kruskal-Wallis H test (a nonparametric analog of ANOVA) was used to analyze SRET negative processing scores due to non-normal distribution (some children did not endorse any negative trait adjectives, and hence scored '0' on this scale). All tests were two-tailed.

Positive SRET scores did not differ significantly by genotype, $F(2, 35) = 2.12$, $p = .133$. Genotype had a significant effect on SRET negative schematic processing scores, $X^2(2) = 8.31$, $p = .012$. Mann-Whitney tests with a Bonferroni adjustment applied indicated that s/s children showed significantly greater negative SRET scores than those with the l/l genotype ($Z = -2.45$, $p = .036$). Children in the s/s group also showed greater SRET negative processing at trend-level than those in the s/l group ($Z = -2.32$, $p = .069$). Children with the s/l genotype were not significantly different from the l/l group on negative SRET scores ($Z = -.96$, $p = .999$).

Discussion

We examined associations between 5-HTTLPR genotype and measures of information processing implicated in vulnerability to depression. Children homozygous for the short allele of this gene showed significantly greater negative information processing on the SRET. The effect appears to be specific to negative information processing, as an association between 5-HTTLPR genotype and positive information processing was not found.

Our findings suggest a pathway through which genetic vulnerability enhances stress sensitivity. Mediating processes in psychiatric genetics have received little research attention; thus, the present study suggests a novel new direction for further research to pursue. However, our study had a number of limitations, including a small sample size. We did not analyze subtypes of the 5-HTTLPR long alleles (Hu et al., 2005) that may have functional significance for psychopathology, nor did we genotype an SNP located upstream of the 5-HTT gene promoter. Experts disagree on the extent to which population stratification, which can produce false positive associations, is a concern in studies such as ours (Hutchison et al., 2004), which used a relatively ethnically homogenous sample. It is also possible that the 5-HTTLPR gene is in linkage disequilibrium with another gene that has functional effects on the SRET.

To our knowledge, this study is the first to examine genetic associations with indices of cognitive vulnerability to depression in young children. One benefit to using a young, non-clinical sample is that one can have greater confidence that the association between 5-HTTLPR genotype and negative information processing is relatively direct, rather than negative cognitive styles being a "by-product" of the experience of depression. However, whether cognitive vulnerability mediates the association between 5-HTTLPR genotype, stressful life events, and the development of depression can only be established by examining larger samples of children over time.

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References

Beck, AT. Cognitive Therapy and the Emotional Disorders. International Universities Press; Oxford, England: 1976.

Brenner E. Mood induction in children: Methodological issues and clinical implications. Review of General Psychology 2000;4:264–283.

Carroll, JB.; Davies, P.; Richman, B. Word Frequency Book. American Heritage Publishing; New York, NY: 1971.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386–389. [PubMed: 12869766]

Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, McGuffin P, Plomin R, Craig IW. Gene-environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 2004;9:908 –915. [PubMed: 15241435]

Garber J, Kaminski KM. Laboratory and performance-based measures of depression in children and adolescents. J Clin Child Psychol 2000;29:509–525. [PubMed: 11126630]

Gotlib, IH.; Hammen, CL. Handbook of Depression. Guilford Press; New York, NY.: 2002.

Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. Science 2002;297:400–403. [PubMed: 12130784]

Hayden EP, Klein DN, Durbin CE, Olino TM. Positive emotionality at age three predicts cognitive styles in seven-year-old children. Development & Psychopathology 2006;18:409–423. [PubMed: 16600061]

Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. Alcohol Clin Exper Res 2005;29:8–16. [PubMed: 15654286]

Hutchison KE, Stallings M, McGeary J, Bryan A. Population stratification in the candidate gene study: Fatal threat or red herring? Psychol Bull 2004;130:66–79. [PubMed: 14717650]

Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. Arch Gen Psychiatry 2005;62:529 –535. [PubMed: 15867106]

Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry 2005;62:473–481. [PubMed: 15867100]

Taylor L, Ingram RE. Cognitive reactivity and depressotypic information processing in children of depressed mothers. J Abnorm Psychol 1999;108:202–210. [PubMed: 10369030]

Segal ZV, Kennedy S, Gemar M, Hood K, Pedersen R, Buis T. Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. Arch Gen Psychiatry 2006;63:749–755. [PubMed: 16818864]

Zammit S, Owen M. Stressful life events, 5-HTT genotype and risk of depression. Br J Psychiatry 2006;188:199–201. [PubMed: 16507957]

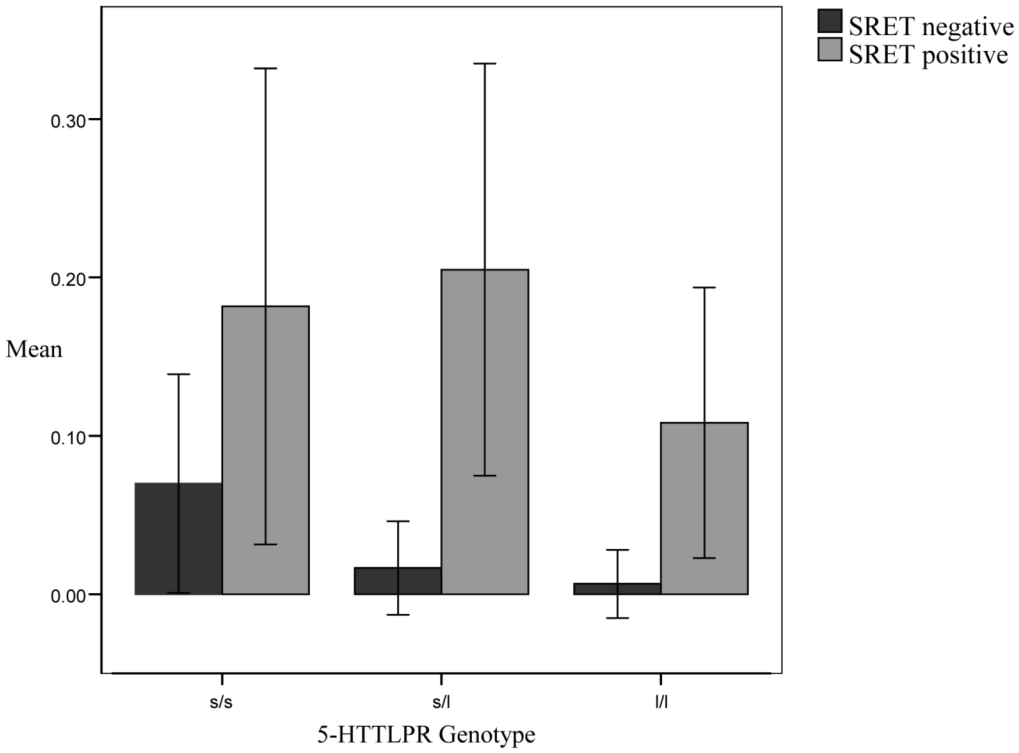

Figure 1.
Means and standard deviations for SRET negative and positive information processing scores for children grouped by 5-HTTLPR genotype
Note: SRET = Self-Referent Encoding Task; 5-HTTLPR = serotonin transporter promoter; s/s = homozygous short allele group; s/l = heterozygous group; l/l = homozygous long allele group.