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Serotonin Transporter (5-HTTLPR) Genotype, Childhood Abuse, and Suicide Attempts in Adult Psychiatric Inpatients

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There is growing evidence that a functional polymorphism in the serotonin transporter gene (5-HTTLPR) moderates the impact of negative life events (e.g., childhood abuse) on the development of depression. However, it is unclear whether the gene × environment interaction predicts suicide attempts specifically. In addition, previous studies have not examined different forms of childhood abuse separately. In the current study, we found that 5-HTTLPR genotype moderated the link between childhood physical and sexual, but not emotional, abuse and adult psychiatric inpatients' histories of suicide attempts.

To date, the majority of studies examining risk for suicide have focused on environmental and intrapsychic factors (see Gould, Greenberg, Velting, & Shaffer, 2003). For example, studies have supported the hypothesis that a history of childhood abuse increases one's risk for suicide (for reviews, see Mina & Gallop, 1998; Wagner, 1997). The effect sizes observed in these studies, however, are modest and fairly heterogeneous (see Rind, Tromovitch, & Bauserman, 1998). This heterogeneity suggests the need for studies examining factors that may moderate the effects of abuse. That is, studies are needed that will identify which individuals are most likely to suffer the most deleterious effects of childhood abuse.

Given the moderate heritability of suicide, estimated in a recent review (McGuffin, Marusic, & Farmer, 2001) as approximately 43%, recent investigations have examined genetic factors that may confer risk for suicide. The majority of these studies have focused on genes in the serotonergic system, given the strong link between altered serotonergic functioning and suicide, an association that appears to be independent of patients' diagnoses (for reviews, see Gould et al., 2003; Mann, Brent, & Arango, 2001). Although these studies have identified several genetic polymorphisms in the serotonergic system that may confer risk for suicide, including the serotonin transporter gene (5-HTT, 5-HTTLPR allele), their results have been decidedly mixed (Arango, Huang, Underwood, & Mann, 2003).

Recent research suggests that these

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mixed results may have been due, in part, to a failure to account for the role of environmental stress in moderating the effect of genetic vulnerabilities upon attempted and completed suicide. That is, rather than having direct effects on suicidal behavior, these genetic polymorphisms may confer risk for suicide in the presence, but not absence, of environmental stress (e.g., history of childhood abuse). For example, Caspi et al. (2003) found that a polymorphism in 5-HTTLPR (one or two copies of the short allele vs. two copies of the long allele) was related to the presence of suicidal ideation or attempts only among individuals who also experienced high levels of life stress in the previous 5 years. The researchers also found that a history of childhood abuse moderated the effect of the 5-HTTLPR genotype on onsets of major depression (see also Kaufman et al., 2004). The results for childhood abuse suggest that the presence of the short 5-HTTLPR allele combined with early life stress may contribute chronic vulnerability to depression and suicide.

The goal of the current study was to identify individuals at chronic risk for suicide. In so doing, we sought to both replicate and extend the findings of Caspi et al. (2003). Specifically, despite the strengths of Caspi et al.'s study, there were several important limitations. First, the researchers did not actually examine the link between childhood abuse and suicidal ideation/attempts. Second, suicidal ideation and attempts were grouped into a single outcome variable, which is problematic because results for suicidal ideation are less generalizable to completed suicide than are results for nonfatal suicide attempts (see Gould et al., 2003). Third, all forms of childhood abuse were grouped together, not allowing an investigation of which may be the most strongly linked to suicide attempts. To address these limitations, we focused specifically on adult psychiatric inpatients' histories of suicide attempts. In addition, we focused specifically on patients' reports of childhood emotional, physical, and sexual abuse. We hypothesized that reports of each form of childhood abuse would be more strongly related to patients' histories of suicide attempts among those at high genetic risk (1 or 2 short 5-HTTLPR alleles) than among those at low genetic risk (2 copies of the long allele).

METHOD

Participants

Participants were recruited from a general psychiatric inpatient unit at Butler Hospital in Providence, Rhode Island, between May and August 2003. The only exclusion criteria were an inability to understand English or active psychotic symptoms that would preclude participation. Thirty of the 31 (97%) participants who started the study protocol completed all the assessments. These 30 individuals were retained for analyses. Gentoyping indicated that 14 participants had two long alleles and 16 participants had at least 1 short allele of the 5-HTTLPR gene. These frequencies do not differ from Hardy-Weinberg Equilibrium. Participants' demographic characteristics, stratified according to 5-HTTLPR genotype, are presented in Table 1. The two groups did not differ significantly on any of the demographic variables (lowest $p = .10$).[1]

TABLE 1
Demographic Characteristics

	5-HTTLPR ss/sl ($n = 16$)	5-HTTLPR ll ($n = 14$)
Age (years)	37.31 (10.74)	34.93 (12.26)
Sex (% women)	50.0	57.1
Race (% Caucasian)	93.8	71.4

Note. 5-HTTLPR = Promoter region of the serotonin transporter gene. ss/sl = at least one copy of the short allele. ll = homozygous for the long allele.

1. We should note that the results of analyses focusing exclusively on Caucasian patients were virtually identical to those obtained with the full sample. Therefore, only the latter are pre-

All participants were receiving inpatient treatment for a psychiatric condition. Chart diagnoses for participants were as follows: major depression = 12 (40.0%); bipolar disorder = 8 (26.7%); adjustment disorder = 2 (6.7%); schizoaffective disorder = 2 (6.7%); substance induced mood disorder = 2 (6.7%); depressive disorder NOS = 1 (3.3%); mood disorder NOS = 1 (3.3%); opioid dependence = 1 (3.3%); and psychosis NOS = 1 (3.3%).

Assessments

DNA Assessment. Participants provided samples of epithelial cells by rubbing swabs along their cheeks and gums and rinsing out their mouth with 10ml of distilled water. Redundant genomic DNA was collected and isolated from buccal cells using published procedures (Freeman et al., 1997; Lench, Stanier, & Williamson, 1988). The 5-HTTLPR alleles were assayed using previously reported methods (Pooley, Houston, Hawton, & Harrison, 2003). The primer sequences are forward, 5'-GCG TTG CCG CTC TGA ATG C-3' and reverse 5' GGA CTG AGC TGG ACA ACC AC-3'. Consistent with several previous studies (e.g., Caspi et al., 2003), two groups of participants were formed based on their genotyping: individuals homozygous for the long allele (ll) and individuals with either 1 or 2 copies of the short allele (ss/sl).

Childhood Abuse. The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) was used to assess patients' levels of childhood emotional, physical, and sexual abuse. Each item on the CTQ is rated on a 5-point Likert-type scale, with response options ranging from *Never true* to *Very often true*. Subscale scores are calculated by summing responses within each abuse type, with higher scores indicating higher levels of childhood abuse. Although the possibility of reporting bias always exists with self-report measures, the CTQ has demonstrated excellent psychometric properties in both clinical and nonclinical samples, including high levels of concurrent validity with therapists' ratings of abuse (Bernstein & Fink, 1998). Dichotomous classifications were created for each of the three forms of abuse, indicating whether or not the participant scored in the *severe* range for that type of abuse. Following Bernstein and Fink, scores greater than 15 on the emotional abuse scale indicated severe to extreme abuse and, for the physical and sexual abuse subscales, scores greater than 12 indicate severe to extreme abuse. Using these criteria, 22 (73.3%) of the patients were classified as having reported severe emotional abuse (12 in the ss/sl group, 10 in the ll group), 12 (40.0%) reported severe physical abuse (7 in the ss/sl group, 5 in the ll group), and 10 (33.3%) reported severe sexual abuse (3 in the ss/sl group, 3 in the ll group).

History of Suicide Attempts. In this study, suicide attempts were operationalized as intentional self-injury with an intent to die (cf. O'Carroll, Berman, Maris, & Moscicki, 1996). Patients' lifetime histories of nonfatal suicide attempts were assessed as part of the clinical interview administered to all patients prior to admission at the hospital. These data were obtained by reviewing patients' medical charts. The intended lethality of patients' suicide attempts was confirmed by reviewing their responses to the Suicidal Behaviors Questionnaire (Linehan, 1996) administered as part of this study. For all analyses, each patient's history of prior suicide attempts was considered dichotomously, indicating whether or not the patient had ever made a previous suicide attempt. In this study, 15 patients (50.0%) reported a history of at least one suicide atttempt with intent to die (6 in the ss/sl group, 9 in the ll group).

Procedure

Study procedures were approved by the Institutional Review Board at Butler Hospital. Study personnel approached patients about participating in the study. Those

sented. Although concerns regarding population stratification are inherent in case-control association studies, the consistency of our results focused exclusively on Caucasian patients suggests that this was not a significant confound in the current study.

who gave informed consent and met inclusion/exclusion criteria were entered into the study. Subjects then provided basic demographic information, completed questionnaire assessments, and provided cheek swabs to obtain genetic material. All of the assessments took place in private, quiet rooms on the inpatient unit at Butler Hospital.

RESULTS

Given the relatively small sample size, phi coefficients (ϕ) were used to examine relations between dichotomous variables. Preliminary analyses were first conducted to determine whether participants' demographic characteristics (e.g., age, sex, race) were related to the study variables. As noted above, there were no significant demographic differences based on 5-HTTLPR genotype. In terms of the other study variables, the only significant differences to emerge were that women were more likely to report childhood sexual abuse, $\phi = .40$, $p = .03$, and to have attempted suicide, $\phi = .54$, $p = .002$ (all other ps $> .16$).[2] Given this, all analyses were conducted using participants' sex as a covariate.

Next, we examined the relations between reports of childhood abuse and suicide attempts as a function of 5-HTTLPR polymorphism. Because we had specific, directional hypotheses, one-tailed p values were used for all analyses. We adjusted our critical alpha level to reduce the likelihood of Type I errors resulting from the six correlation analyses we conducted. This gave us a critical alpha level of .008 (.05/6). Statistically controlling for patients' sex, reports of childhood emotional abuse were not significantly related to suicide attempts among patients with one or two copies of the s allele, $\phi = .40$, $p = .07$, or among patients homozygous for the long allele, $\phi = .22$, $p = .24$. In addition, the difference in the magnitude of these relations was not significant, $z = 0.49$, $p = .31$, suggesting that 5-HTTLPR did not moderate the relation between childhood emotional abuse and suicide attempts. In contrast, reports of childhood physical abuse were significantly related to patients' histories of suicide attempts among those with one or two copies of the s allele, $\phi = .61$, $p < .008$, but not among those homozygous for the long allele, $\phi = -.20$, $p = .25$. The difference between the magnitude of these two relations was significant, $z = 2.24$, $p = .01$, indicating that 5-HTTLPR polymorphism did moderate the relation between reports of childhood physical abuse and patients' histories of suicide attempts. Finally, we examined childhood sexual abuse. Reports of childhood sexual abuse were significantly related to patients' histories of suicide attempts among those with one or two copies of the s allele, $\phi = .61$, $p = .008$, but not among those homozygous for the long allele, $\phi = -.12$, $p = .35$. The difference in the magnitude of these relations was significant, $z = 2.01$, $p = .02$, suggesting that 5-HTTLPR significantly moderated the relation between childhood sexual abuse and suicide attempts.

Comorbidity among the three forms of abuse in our sample was common. Specifically, six patients (20.0%) reported no abuse, eight (26.7%) reported emotional abuse alone, two (6.7%) reported sexual abuse alone, six (20.0%) reported emotional and physical abuse, two (6.7%) reported physical and sexual abuse, and six (20.0%) reported all three forms of abuse. Given this, it is possible that the moderation results were due simply to the presence of any form of childhood abuse. Therefore, we looked at the patients who reported any type of abuse ($n = 24$) versus those reporting no abuse ($n = 6$). In these analyses, reports of any abuse were not significantly related to suicide attempts among patients with one or two copies of the s allele, $\phi = .40$, $p = .07$, or among patients homozygous for the long allele, $\phi = .14$, $p = .33$.

2. According to Cohen (1988), a ϕ of .10 represents a "small" effect, .30 represents a "medium" effect, and .50 represents a "large" effect.

Therefore, it appears that the moderation results were specific to childhood physical and sexual abuse.

DISCUSSION

The primary goal of this study was to examine whether a functional polymorphism in the serotonin gene (5-HTTLPR) moderated the relations among reports of childhood emotional, physical, and sexual abuse and adult psychiatric inpatients' histories of suicide attempts. The moderation hypothesis was supported for childhood physical and sexual abuse, but not for childhood emotional abuse. Specifically, the relationship between childhood physical and sexual abuse and suicide attempts was significantly stronger among patients with one or two copies of the short allele than among patients homozygous for the long allele. In contrast, reports of childhood emotional abuse were not significantly related to suicide attempts among patients in either genotype group.

The current results both replicate and extend previous findings. Specifically, our results add to a growing body or research demonstrating the moderating role of 5-HTTLPR (e.g., Caspi et al., 2003; Eley et al., 2004; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; but see also Gillespie, Whitfield, Williams, Heath, & Martin, 2005). This said, however, the current results also suggest that 5-HTTLPR may be more likely to moderate the effects of some forms of negative life events than others. Specifically, as noted above, we found that 5-HTTLPR moderated the link between suicide attempts and childhood physical and sexual, but not emotional, abuse. If replicated, this may suggest the potential of different developmental pathways to suicide attempts for individuals experiencing different forms of abuse.

Despite the strengths of this study, its limitations should be noted. First, the assessment of childhood abuse was based on patients' self-reports, which may have been subject to recall biases. This said, the measure chosen for this study has demonstrated excellent psychometric properties, including strong convergent validity with therapists' ratings of abuse. In addition, we chose to focus on self-reports of abuse rather than relying on documented cases because relatively few cases of abuse, particularly emotional abuse, are reported (see Hart, Germain, & Brassard, 1987), which would leave us with an unrepresentative sample of abuse survivors. Despite this, future studies should seek to include multi-method assessments of childhood abuse (e.g., questionnaire and interview-based assessments).

Second, we focused on a relatively small, diagnostically heterogeneous sample of psychiatric inpatients. We chose to recruit a diagnostically heterogeneous group of patients because we were interested in suicide attempts generally, rather than suicide risk tied specifically to any one disorder, and because previous research has suggested that the link between altered serotonergic functioning and suicide appears to be independent of patients' diagnoses (for reviews, see Gould et al., 2003; Mann, Brent, & Arango, 2001). Despite this, future research would benefit from larger samples that would allow further investigation of the potential role of patient diagnosis in the link between the gene × environment interaction and suicide risk. Although our focus on psychiatric inpatients may limit the generalizability of the findings to other samples, we chose to focus on inpatients to maximize the base rate of suicide attempts, thereby increasing our statistical power. A drawback of our relatively small sample size was that it limited the specificity of the analyses we could conduct. For example, although comorbidity of abuse types was common, our sample size was not sufficient to examine each potential combination of overlap. Despite this, our results suggest that it was not the mere presence of any form of abuse that contributed to the moderation effect. Future studies with larger samples should more finely examine the relative contribution of each specific form of abuse.

Another potential limitation of our sample size was that all patients with a history of suicide attempts were grouped together. Recent evidence suggests that patients with a history of multiple suicide attempts may be qualitatively distinct from patients with a history of only one or no prior suicide attempts (Esposito, Spirito, Boergers, & Donaldson, 2003; Forman, Berk, Henriques, Brown, & Beck, 2004; Goldston et al., 1999; Rudd, Joiner, & Rajab, 1996). Therefore, it is not clear whether the 5-HTTLPR × abuse interactions may be more strongly related to multiple versus single suicide attempts. The size of our sample also limited the degree to which we could explore the 5-HTTLPR genotype. Specifically, following Caspi et al. (2003), we focused on patients with one or two copies of the short allele versus those with two copies of the long allele. Recent research suggests that it may be useful to examine the three genotypes (ll, sl, ss) separately and that the strongest effects may be seen for individuals homozygous for the short allele (e.g., Kaufman et al., 2004; Kendler et al., 2005). Also, new research (e.g., Hu et al., 2005) suggests a triallelic variation in 5-HTTLPR, which was not examined in the current study. Thus, although our study was sufficiently powered to detect the effects of greatest interest, future studies should seek to employ larger samples, which will allow an investigation of these more focused questions.

A third limitation was the retrospective design of our study. Thus, we could not determine whether the gene by abuse interaction prospectively predicted suicide attempts. And, because we did not determine the date of each reported suicide attempt, we cannot ensure that the abuse preceded the suicide attempt. Future studies should either assess the actual date of suicide attempt(s) to ensure that they occur following the onset of abuse, or conduct longitudinal studies to determine whether these risk factors prospectively predict which patients will make a suicide attempt.

In summary, the current results add to a growing body of research demonstrating the moderating role of 5-HTTLPR. Although conclusions must remain tentative pending replication, the current results suggest that the moderating effects may be stronger for childhood physical and sexual abuse than for emotional abuse. Future studies with larger samples should seek to not only replicate this result, but also to examine whether there may be different etiologic pathways to adult suicide (e.g., cognitively vs. biologically driven) given different types of childhood abuse.

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