Published in final edited form as:

Psychiatr Genet. 2011 October ; 21(5): 240–248. doi:10.1097/YPG.0b013e3283457c15.

5-HTTLPR as a Potential Moderator of the Effects of Adverse Childhood Experiences on Risk of Antisocial Personality Disorder

Kara Douglas, B.S.^a, Grace Chan, Ph.D.^a, Joel Gelernter, M.D.^{c,d}, Albert J. Arias, M.D.^a, Raymond F. Anton, M.D.^e, James Poling, Ph.D.^c, Lindsay Farrer, Ph.D.^f, and Henry R. Kranzler, M.D.^{a,b}

^aDepartment of Psychiatry, University of Connecticut School of Medicine, Farmington, CT 06030, USA

^bDepartment of Genetics and Developmental Biology, University of Connecticut School of Medicine, Farmington, CT 06030, USA

^cDepartment of Psychiatry, Yale University, New Haven, CT and VA CT Healthcare Center, West Haven, CT 06516, USA

^dDepartments of Genetics and Neurobiology, Yale University, New Haven, CT and VA CT Healthcare Center, West Haven, CT 06516, USA

^eDepartment of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

^fDepartments of Medicine (Genetics Program), Neurology, Genetics & Genomics, Epidemiology, and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, MA 02118, USA

Abstract

INTRODUCTION—Antisocial personality disorder (ASPD) frequently co-occurs with substance dependence (SD). A functional polymorphism (5-HTTLPR) in the serotonin transporter gene has been widely studied as a risk factor for a variety of psychopathologic conditions, including aggressive/violent behavior. Childhood abuse is an important predictor of ASPD. We examined 5-HTTLPR genotype and adverse childhood events (ACEs) as risk factors for ASPD in a SD sample.

METHOD—Study participants [602 European Americans (EAs) and 779 African Americans (AAs)] were interviewed to obtain lifetime diagnoses of ASPD and SD and information on ACEs. Tri-allelic genotypes for 5-HTTLPR were obtained using standard methods. We used logistic generalized estimating equations (GEE) regression to examine ACEs and 5-HTTLPR genotype and their interaction as predictors of ASPD, separately by population group.

RESULTS—There were 203 (14.7%) participants diagnosed with ASPD. The frequency of the low-activity 5-HTTLPR S' allele did not differ by ASPD diagnosis, and there was no overall 5-HTTLPR × ACE interaction. However, among EAs, male sex (OR=3.36; $p<0.001$) and ACE

Correspondence to: Henry R. Kranzler, Department of Psychiatry, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06030-2103, Telephone: 860-679-4151, Fax: 860-679-1316, kranzler@psychiatry.uconn.edu.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

history (OR=1.47; $p=0.002$) were significant predictors of ASPD. Among AAs, there was a significant interaction of sex $\times$ 5-HTTLPR genotype $\times$ ACEs ($\chi^2=13.92$, $p<0.001$). Among AA men, each additional ACE significantly increased the odds of ASPD irrespective of genotype, while among AA women, the effect of ACEs on ASPD was significant only among S' homozygotes. However, these results are limited by the small sample size in each subgroup, (particularly AA women with S'S' genotype; $N=7$) and require replication.

CONCLUSIONS—Childhood maltreatment contributes to the risk of antisocial personality disorder, an effect for which there is preliminary evidence of moderation by 5-HTTLPR genotype in AA women.

Keywords

Serotonin Transporter Gene; *SLC6A4*; Child Abuse; Antisocial Personality Disorder; gene $\times$ environment

INTRODUCTION

Antisocial personality disorder (ASPD) is characterized by a pattern of aggression, deceitfulness, impulsivity, and unlawful behavior (American Psychiatric Association, 2000). In the United States, the lifetime population prevalence of ASPD has been estimated to be 3.6% (Compton et al., 2005), though it is higher among individuals with substance use disorders (SUDs) (Anthony and Helzer, 1991; Goldstein et al., 2007a; Goldstein et al., 2007b). Among individuals with SUDs, the presence of ASPD is associated with an earlier onset of substance-related problems, a more severe clinical course, and poorer treatment outcomes (Bucholz et al., 2000; Cottler et al., 1995; Goldstein et al., 2007a; Goldstein et al., 2007b; Kranzler et al., 1996; Rounsaville et al., 1987).

Childhood abuse is an important environmental risk factor for the development of antisocial behavior (Bierer et al., 2003; Hosser et al., 2007; Luntz and Widom, 1994). In a prospective study of 699 individuals, including 416 subjects abused and/or neglected as children, childhood abuse was a significant predictor of an ASPD diagnosis and of the number of lifetime ASPD symptoms endorsed (Luntz and Widom, 1994). A retrospective history of physical and/or sexual abuse was also associated with an increased likelihood of ASPD in a sample of adults (Bierer et al., 2003). A study of 1,526 incarcerated men showed a correlation between a history of maltreatment in childhood and increased levels of self-reported violence (Hosser et al., 2007).

In addition to the effects observed among the victims of childhood abuse, *witnessing* a traumatic event (e.g., domestic violence, violent crime) in childhood can also contribute to psychopathology, including antisocial behavior (Finkelstein and Yates, 2001; Knapp, 1998). However, studies often fail to differentiate between being a victim of violence and witnessing violence perpetrated against others. Knapp (1998) concluded that children who observe the battering of their mothers are at increased risk of violence later in life. Similarly, Malmquist (1986) found that boys who observe violence against their mothers, committed by their fathers, have a ten-fold risk of committing abuse against their own spouses as adults.

Adoption studies have shown that both environmental and genetic factors and their interaction effects may contribute to risk of antisocial behavior (for reviews see Raine, 2002 and Rhee and Waldman, 2002). The heritability of ASPD has been estimated to be 30-50% (Maes et al., 2007; Slutske, 2001), with gene $\times$ environment effects being important determinants of risk. In a study of 862 male Swedish adoptees, 40% of individuals with both inherited and environmental risk factors for criminality had histories of such behavior,

compared to 12.1% with genetic factors only, 6.7% with environmental risk only, and 2.9% with neither risk factor (Cloninger et al., 1982). A study of female adoptees also showed a similar interactive effect of genetics and environment on the likelihood of antisocial behavior (Cloninger and Gottesman, 1987). Cadoret et al. (1995) found that an antisocial biological parent and an adverse adoptive home environment were independent predictors of antisocial behaviors in adopted-away men and women, and these two factors (genetic and environmental) interacted significantly to predict increased aggression and conduct disorder.

From a neurochemical point of view, serotonergic neurotransmission has been implicated in impulsive and aggressive behavior and may be relevant to the observed effects of childhood adversity on risk of antisocial behavior. Cerebrospinal fluid (CSF) concentrations of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) are inversely related to aggressive and impulsive behavior in non-human primates (Higley et al., 1992; Mehlman et al., 1994) and humans (Brown et al., 1979; Linnoila et al., 1983; Roy and Linnoila, 1988). The serotonin transporter (5-HTT), which is responsible for the reuptake of serotonin, plays an important role in the regulation of serotonergic tone (Ramamoorthy et al., 1993). A functional insertion-deletion polymorphism (5-HTTLPR) in the 5' promoter region of *SLC6A4*, the gene that encodes 5-HTT, has been widely studied for its contribution to the risk for a variety of psychopathologic conditions. The long (L) allele of 5-HTTLPR was associated with greater transcriptional efficiency than the short (S) allele (Heils et al., 1996; Lesch et al., 1996). The presence of a single nucleotide polymorphism (A/G) in the L allele modifies its function, such that the transcriptional rate of the L_G allele is similar to that of the S allele (Hu et al., 2006). This tri-allelic polymorphism thus consists of two low-activity alleles (S and L_G , referred to here as S') and a high-activity allele (L_A , referred to here as L').

Some pre-clinical evidence suggests that early life experience may interact with serotonin transporter genotype to produce lasting effects on serotonin neurotransmission (Bennett et al., 2002; Higley et al., 1991). In rhesus monkeys, the rh-HTTLPR polymorphism (which is orthologous to the human 5-HTTLPR polymorphism) was associated with reduced CSF 5-HIAA concentrations only in animals with adverse early rearing experiences (Higley et al., 1991). A meta-analysis of 5-HTTLPR genotype and 5-HIAA concentrations in humans showed a significant inverse relationship of 5-HIAA concentrations with antisocial behavior (Moore et al., 2002). Williams et al. (2003) also examined the 5-HTTLPR polymorphism in relation to CSF 5-HIAA levels, with stratification by population group and sex. They found that, among Caucasians and men, individuals homozygous for the low-activity allele had lower 5-HIAA levels, while the opposite effect was seen among African Americans (AAs) and women.

Clinical studies have shown an association of the 5-HTTLPR polymorphism with aggressive and violent behaviors. Specifically, low-activity 5-HTTLPR alleles have been associated with conduct disorder (CD) in adolescents (Sakai et al., 2006), antisocial personality disorder in alcoholics (Hallikainen et al., 1999), violence in male criminals (Liao et al., 2004), physical violence in men (Retz et al., 2004), and violence in heroin-dependent men (Gerra et al., 2004). In a study of 96 low-income young adults, including 34 individuals with ASPD or borderline personality disorder, the number of 5-HTTLPR S alleles was significantly associated with ASPD (Lyons-Ruth et al., 2007). However, a significant relationship between the L allele and violent/aggressive traits has also been reported (Twitchell et al., 2001; Zalsman et al., 2001). Two studies of aggressive children found no relationship between 5-HTTLPR genotype and aggression (Beitchman et al., 2003; Davidge et al., 2004) and a longitudinal study in adolescents showed no significant relationship between 5-HTTLPR genotype and conduct problems or delinquency (Sakai et al., 2007). More recently, Sadeh et al. (2010) examined youth from two different studies with respect to

the relations between two dimensions of psychopathy and 5-HTTLPR genotype. They found a significant main effect of genotype, such that individuals homozygous for the S' allele showed higher levels of impulsivity, as well as a significant interaction effect in which decreasing socioeconomic status was associated with greater callous-unemotional and narcissistic traits, but only among individuals homozygous for the L' allele. These findings suggest that although the S'/S' genotype is associated with impulsivity, the L'/L' genotype may increase the risk of emotional deficits among disadvantaged populations. Thus, both genotypes could potentially confer risk for antisocial behavior, but under different circumstances.

Mixed results on the association of antisocial behavior with 5-HTTLPR may have resulted from differences in statistical power or sample characteristics or the failure to consider gene by environment effects. The latter possibility is supported by the findings of Reif et al. (2007), who despite not finding a main effect of 5-HTTLPR, reported that adverse childhood experiences (ACEs) were associated with violent behavior among subjects with one or two copies of the low-activity S allele.

In the present study, we examined the main and interactive effects of 5-HTTLPR and ACEs on risk for ASPD in a sample of individuals with SD. We hypothesized that ACEs would be a risk factor for ASPD and that individuals with one or two low-activity 5-HTTLPR S' alleles and a history of ACEs would show the highest rates of ASPD.

MATERIALS AND METHODS

Recruitment and Assessment Procedures

We recruited 1,381 subjects [602 European Americans (EAs) and 779 AAs] dependent on alcohol, cocaine, or opioids at four sites: 709 from Yale University (New Haven, CT), 518 from the University of Connecticut Health Center (Farmington, CT), 107 from McLean Hospital (Belmont, MA), and 47 from the Medical University of South Carolina (Charleston, SC).

The study was conducted in accordance with the Declaration of Helsinki, with review and approval of the study protocol and informed consent documents by the institutional review board at each of the participating institutions. Subjects provided written informed consent after receiving a complete description of the study and were paid for their participation. The study sample was selected from among subjects recruited to participate in family-based linkage or association studies of the genetics of substance dependence (Gelernter et al., 2007; Gelernter et al., 2005; Gelernter et al., 2006). The family-based sample was ascertained through two or more siblings affected with cocaine and/or opioid dependence. The association sample consisted of unrelated individuals with alcohol, cocaine, or opioid dependence. Once an individual was identified as eligible to participate in either a family-based linkage or an association study, all of his or her first-degree family members were invited to participate irrespective of whether they had a SUD diagnosis.

Subjects included 1,040 individuals (86.7%) with no other family members, 141 (11.8%) with 1 other member, 15 (1.3%) with 2 other members, 1 (0.1%) with 3 other members, and 2 (0.2%) with 4 other members. The study sample overlapped substantially with the sample reported on by us (Xie et al., 2009) in which the 5-HTTLPR polymorphism moderated the effects of adverse childhood events on risk for posttraumatic stress disorder (PTSD).

Genotyping

DNA was extracted from whole blood or immortalized cell lines. Polymerase chain reaction (PCR) amplification was used to differentiate the S allele from the L allele of the insertion-

deletion polymorphism. PCR conditions are described in detail in Gelernter et al., (1997). To genotype the A/G SNP (rs25531) present at the sixth nucleotide of the first of two of the 22-bp repeat elements in the 16-repeat L allele (Hu et al., 2005), the PCR product was digested by *MspI* and size-fractionated on agarose gel (Stein et al., 2006). This differentiates the two subtypes of the 16-repeat variant into L_A or L_G . The S and L_G (i.e., S') alleles have a 2-fold lower level of gene expression than the A-allele variant (L_A or L') (Hu et al., 2006). Eight percent of genotypes for both polymorphisms were selected at random and repeated with no discrepancies.

To detect admixture, we genotyped a set of 38 ancestry-informative markers (AIMs) (Yang et al. 2005) to generate African ancestry proportions using the program STRUCTURE (Pritchard et al. 2000, Falush et al. 2003). We used the ancestry proportion scores to determine concordance (as measured using the κ statistic) of the predominant genetic ancestry (EA or AA) with self-reported population group. We also entered the African ancestry proportion as a covariate in the GEE regression models to exclude admixture effects.

Measures

All participants were evaluated using an electronic version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), which provides information on demographics, diagnostic criteria for substance use and a variety of psychiatric disorders, as well as the childhood home environment. A detailed description of the SSADDA, its administration methods, and its reliability are provided elsewhere (Feinn et al., 2009; Pierucci-Lagha et al., 2005; Pierucci-Lagha et al., 2007). The test-retest and inter-rater reliability of ASPD diagnoses were $\kappa=0.52$ and $\kappa=0.57$, respectively.

Of specific relevance here, the SSADDA includes a 44-item assessment tailored to address the 7 DSM-IV diagnostic criteria for ASPD (aggression, impulsivity, lack of remorse, etc.) and questions about childhood behavior to determine the presence of CD. Subjects meeting three or more of the adult diagnostic criteria and full criteria for a diagnosis of CD were diagnosed with ASPD. Information on the childhood home environment included 3 items on ACEs: 1) violent crime exposure, which was defined by the response to the question: "Did you witness or experience a violent crime, like a shooting or a rape, by age 13?" 2) sexual abuse, which was defined by the response to the question: "By the time you were age 13, were you ever sexually abused?" 3) physical abuse was defined as being beaten by an adult so severely before age 13 that medical care was needed or marks on the body remained for more than 30 days. Based on the number of types of adverse event endorsed by each participant, we created the variable "ACE score," which is a summary that ranges from 0–3. The test-retest and inter-rater reliability of the three items used in defining the ACE score ranged from $\kappa=0.84$ –0.99 and $\kappa=0.69$ –0.82, respectively. Some of the same items were utilized in our earlier report on PTSD (Xie et al., 2009).

Analysis

We used logistic regression models to examine the association of ASPD with 5-HTTLPR genotype, ACE score, and their interaction, after controlling for sex. For each population group, we started with a model that included sex, age, 5-HTTLPR genotype, and ACE score as main effects, the 3 2-way interactions of sex, 5-HTTLPR genotype and ACE score, and their three-way interaction. We used a hierarchical backward elimination procedure (with $\alpha = 0.05$) to determine the most parsimonious model. Because age was not a significant covariate, it was removed from the analyses. Because genotype frequencies differed by population (see below), we examined AAs and EAs in separate models. To account for the dependence among family members, we applied generalized estimating equations (GEE)

with an exchangeable correlation structure to fit the logistic regression models in SAS version 9.2. 5-HTTLPR was analyzed under an additive model, i.e., as a 3-level categorical predictor (0–2) based on the number of low-activity S' alleles.

RESULTS

Sample Characteristics

Among the 1,381 participants, 203 (14.7%) met criteria for ASPD, which did not differ by population group ($\chi^2 = 0.48$, $df = 1$, $p = 0.49$) (Table 1). The frequency of ACEs in the study population is shown in Table 2; Table 3 shows the frequency of ACEs among individuals with ASPD. Although the population groups did not differ significantly on the number of types of ACEs ($\chi^2 = 0.57$, $df = 1$, $p = 0.45$), EAs were significantly less likely to have experienced violent crime, but more likely to have been abused, both sexually and physically. EAs were significantly more likely than AAs to be diagnosed with alcohol and opioid use disorders, but AAs were more likely to have a cocaine use disorder.

Table 4 presents the genotype frequencies by sex and ASPD diagnosis within each population group. Although there was a significant difference in genotype frequency by population group when considering the distribution of the 6 tri-allelic genotypes ($\chi^2 = 29.28$, $df = 5$, $p < 0.001$), the frequencies of S' and L' alleles did not differ significantly ($\chi^2 = 1.71$, $df = 1$, $p = 0.19$). All allele frequencies were consistent with Hardy-Weinberg equilibrium, irrespective of whether the bi-allelic or tri-allelic genotype data were considered (all p 's > 0.05).

There was no association between the number of S' alleles and the frequency of an ASPD diagnosis in either population group overall (EAs: $\chi^2 = 0.99$, $df = 2$, $p = 0.61$; AAs: $\chi^2 = 0.82$, $df = 2$, $p = 0.66$) or when analyzed by sex (EA males: $\chi^2 = 0.93$, $df = 2$, $p = 0.63$; EA females: $\chi^2 = 1.76$, $df = 2$, $p = 0.42$; AA males: $\chi^2 = 0.54$, $df = 2$, $p = 0.76$; AA females: $\chi^2 = 0.18$, $df = 2$, $p = 0.92$).

Adjusted Relationship Between Outcome and Risk Factors by Population Group

In EAs, logistic GEE regression analysis showed that only male sex and the number of types of ACEs were significantly associated with an ASPD diagnosis (Table 5). In AAs, the three-way interaction of sex $\times$ number of S' alleles $\times$ ACE score was significantly associated with an ASPD diagnosis (Table 6). Decomposition of the interaction revealed that among AA men, each additional ACE significantly increased the odds of ASPD irrespective of the number of 5-HTTLPR S' alleles. However, among AA women, the effect of ACE score on ASPD was significant only for those with 2 S' alleles.

Although the frequency of the S' allele did not differ by sex either for EAs (men: 51.0%; women: 53.5%) or AAs (men: 46.8%; women: 46.5%), other features varied as a function either of the main or two-way interaction effects of genotype, sex, and population group. Men had a higher prevalence of ASPD (18.7% vs. 9.0%) and an alcohol use disorder (90.8% vs. 81.1%) than women. Women reported having experienced more ACEs (mean $\pm$ SE = 0.64 ± 0.04 vs. 0.41 ± 0.02), particularly sexual abuse (27.9% vs. 8.9%), than men. EA men were more likely than EA women to have experienced or witnessed a violent crime (11.9% vs. 8.1%), but both were less likely to report such an experience than both AA men (29.2%) and AA women (25.1%). The lifetime prevalence of opioid use disorder was higher among AA men than AA women (28.5% vs. 19.9%), but AAs had lower prevalence rates of this disorder than either EA men (54.6%) or women (59.6%).

Admixture as a Potential Confound

Ancestry proportions calculated for all participants showed a high degree of concordance with self-reported population group. Specifically, 595 (98.8%) of the 602 self-reported EAs had an African ancestry proportion < 0.5 and 775 (99.5%) of the 779 self-reported AAs had an African ancestry proportion > 0.5. The concordance rate (κ) for this cross-tabulation was 0.98 (95% confidence interval = 0.97-0.99). Further, the addition of African ancestry proportion as a covariate in the GEE logistic regression model was not significant, so it was removed from the equations.

DISCUSSION

This study examined genetic and environmental risk factors for the development of ASPD in a sample of substance-dependent individuals, among whom the prevalence of ASPD far exceeded that in the general population (Compton et al. 2005; Kessler et al., 1994; Robins et al., 1984). Consistent with epidemiological studies, ASPD was much more prevalent among men than women (Compton et al. 2005; Kessler et al., 1994; Robins et al., 1984). As hypothesized, we found a significant main effect of ACEs on risk of ASPD, consistent with a substantial literature showing that adverse experiences in childhood are predictive of subsequent antisocial behavior. We also found that AA women homozygous for the low-activity S' 5-HTTLPR allele were significantly more likely than any of the other subgroups to manifest ASPD in the context of having experienced ACEs. This finding partially supports the hypothesis that the 5-HTTLPR polymorphism contributes to risk for the development of ASPD, but only among a small number of AA women with the S'S' genotype ($n = 73$), including only 7 AA women diagnosed with ASPD. Although analysis of other potential predictors provided no evidence that they confounded the moderating effect of genotype, this finding requires replication in a larger sample.

Among AA individuals, recent research examining 5-HTTLPR genotype and antisocial behavior has produced mixed results. A recent study (Beaver et al. 2010) evaluated approximately 150 AA males for several "high-risk" polymorphisms (including 5-HTTLPR) and also assessed parental involvement and attachment in childhood. Although there were no main effects of genetic and environmental variables, the interaction of genotype with early rearing experiences significantly predicted some of the variation in the risk of antisocial behavior. A family study of 641 AA adolescents followed for 29 months showed that one or two copies of the low-activity 5-HTTLPR allele significantly predicted risk behavior (i.e., the ingestion of alcoholic beverages and marijuana and participation in sexual intercourse) (Brody et al., 2009). Interestingly, this study also showed that participation in a family intervention program attenuated the genetic risk.

In contrast, a regression analysis of data from 1,736 Caucasian adolescents showed no significant relationship between the low-activity 5-HTTLPR genotype and categorical or continuous measures of conduct problems, controlling for sex, age, and family effects (Sakai et al., 2007). Further, in this study, there was no interaction effect of genotype and self-reported childhood maltreatment on the risk of conduct problems.

Mixed results have also been reported for 5-HTTLPR genotype and early childhood experiences with regard to other negative health outcomes, including substance use (Laucht et al., 2009; Gerra et al., 2007). For example, Laucht et al. (2009) found that an interaction of the high-activity, LL genotype with early psychosocial adversity predicted more hazardous drinking in adulthood, an effect that was limited to males. A study of cocaine users (Gerra et al., 2007) showed that the frequency of the SS genotype was significantly higher among drug users than controls and the risk that an SS individual would become a cocaine user was nearly three times that of individuals with the LL genotype. Greater scores

on the parental care measure rendered the relationship between genotype and cocaine use non-significant, consistent with a mediating effect of parenting on this relationship (Gerra et al., 2007).

We focused our analysis on DSM-IV ASPD rather than the association of 5-HTTLPR with adult antisocial behavioral syndrome (AABS; (Goldstein et al., 1998)). AABS has been proposed as a diagnosis for individuals who meet full adult criteria for antisocial behavior without a history of CD. Its estimated lifetime prevalence in the United States is 12.3% (Compton et al., 2005). Although several studies suggest that AABS and ASPD are essentially the same disorder (Black and Braun, 1998; Goldstein et al., 2007a; Goldstein et al., 2007b; Goldstein et al., 1998; Langbehn and Cadoret, 2001), initial analyses (data not shown) showed that AABS subjects in our sample more closely resembled subjects without ASPD, differing significantly from the ASPD group on many relevant variables. Consequently, we chose to group the AABS subjects with the non-ASPD subjects.

The present study was limited by several factors. First, because of the small number of AA women who were S' homozygotes, the observed association has to be viewed as tentative. Similarly, the failure to observe some other effects may have resulted from inadequate statistical power, particularly among women. Second, because the sample was comprised of drug-dependent individuals, it is not representative of the general population. Third, we collected ACE data using the SSADDA, rather than a more widely used assessment in childhood abuse research, such as the Childhood Trauma Questionnaire (Bernstein et al., 1994) or the Early Trauma Inventory (Bremner et al., 2000). Lastly, we obtained diagnostic and ACE data via retrospective recall by subjects, potentially introducing errors and biases in reporting. A study of the validity of retrospective reporting for childhood sexual abuse, which used medical records as a criterion measure, showed a response bias toward underreporting (Edwards et al., 2001). Therefore, although it is likely that we underestimated the incidence of ACEs in our sample, there is no reason to suspect that this bias would differ by genotype and skew our results. It could, however, have reduced statistical power and obscured effects that might exist in the data.

Other serotonin-related genes have been studied in relation to risk of ASPD. Variation in MAOA, the gene encoding the enzyme monoamine oxidase A (which, among other activities, metabolizes serotonin to 5-HIAA), and its interaction with childhood abuse, has been the focus of a number of studies of antisocial behavior (Caspi et al., 2002; Ducci et al., 2008; Foley et al., 2004; Haberstick et al., 2005; Huizinga et al., 2006; Kim-Cohen et al., 2006; Widom and Brzustowicz, 2006). A meta-analysis of this research supports a modest interaction effect, with individuals possessing the high-risk MAOA genotype and having experienced childhood maltreatment showing a greater risk for ASPD than those with either condition alone (Taylor and Kim-Cohen, 2007).

Other biological risk factors (e.g., cortical underarousal, neuropsychological deficits) have also been implicated in the development of ASPD (Brennan and Raine, 1997; Moffitt, 1990; Raine and Venables, 1981). It is possible that such measures mediate the effects of genetic variation in ASPD risk and the use of mediational models that include genetic information could contribute to a fuller understanding of the etiology and development of the disorder. For example, a recent study of 69 newborn-caregiver pairs showed that infants homozygous for the S' allele expressed greater emotionality and fear in response to the "strange situation" test of attachment. Because the effect was seen as early as 12 months of age, there appears to be an early effect of genotype on complex emotional behaviors (Pauli-Potts et al., 2009). Other genetic and environmental factors that could differ by sex and population group to influence the expression of ASPD in the context of ACEs are important topics for subsequent study.

Acknowledgments

Supported by NIH grants DA12690, DA12849, DA18432, AA03510, AA11330, AA13736, and AA017435. The authors thank the interviewers and laboratory personnel who conducted the study, and the study participants at all of the participating sites. Kathleen Brady, M.D., Ph.D. of the Medical University of South Carolina and Roger Weiss, M.D. of McLean Hospital and Harvard Medical School oversaw study recruitment at their respective sites.

REFERENCES

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-Version IV. American Psychiatric Association; Washington, D.C.: 2000. Text Revision (DSM-IV-TR)
- Anthony, JC.; Helzer, JE. Syndromes of drug abuse and dependence. In: Robins, LN.; Reiger, DA., editors. *Psychiatric Disorders in America: The Epidemiologic catchment Area study*. The Free Press; New York: 1991.
- Beaver KM, Sak A, Vaske J, Nilsson J. Genetic risk, parent-child relations, and antisocial phenotypes in a sample of African-American males. *Psychiatry Res.* 2010; 175(1-2):160–4. [PubMed: 20004478]
- Beitchman JH, Davidge KM, Kennedy JL, Atkinson L, Lee V, Shapiro S, Douglas L. The serotonin transporter gene in aggressive children with and without ADHD and nonaggressive matched controls. *Ann N Y Acad Sci.* 2003; 1008:248–51. [PubMed: 14998889]
- Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD. Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry.* 2002; 7(1):118–22. [PubMed: 11803458]
- Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Sapareto E, Ruggiero J. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry.* 1994; 151(8):1132–6. [PubMed: 8037246]
- Bierer LM, Yehuda R, Schmeidler J, Mitropoulou V, New AS, Silverman JM, Siever LJ. Abuse and neglect in childhood: relationship to personality disorder diagnoses. *CNS Spectr.* 2003; 8(10):737–54. [PubMed: 14712172]
- Black DW, Braun D. Antisocial patients: a comparison of those with and those without childhood conduct disorder. *Ann Clin Psychiatry.* 1998; 10(2):53–7. [PubMed: 9669536]
- Bremner JD, Vermetten E, Mazure CM. Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. *Depress Anxiety.* 2000; 12(1):1–12. [PubMed: 10999240]
- Brennan PA, Raine A. Biosocial bases of antisocial behavior: psychophysiological, neurological, and cognitive factors. *Clin Psychol Rev.* 1997; 17(6):589–604. [PubMed: 9336686]
- Brody GH, Beach SR, Philibert RA, Chen YF, Murry VM. Prevention effects moderate the association of 5-HTTLPR and youth risk behavior initiation: gene x environment hypotheses tested via a randomized prevention design. *Child Dev.* 2009; 80(3):645–61. [PubMed: 19489894]
- Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res.* 1979; 1(2):131–9. [PubMed: 95232]
- Bucholz KK, Hesselbrock VM, Heath AC, Kramer JR, Schuckit MA. A latent class analysis of antisocial personality disorder symptom data from a multi-centre family study of alcoholism. *Addiction.* 2000; 95(4):553–67. [PubMed: 10829331]
- Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Genetic-environmental interaction in the genesis of aggressivity and conduct disorders. *Arch Gen Psychiatry.* 1995; 52(11):916–24. [PubMed: 7487340]
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science.* 2002; 297(5582):851–4. [PubMed: 12161658]
- Cloninger, CR.; Gottesman. Genetic and environmental factors in antisocial behavior disorders. In: Mednick, SA.; Moffitt, TE., editors. *The Causes of Crime: New Biological Approaches*. Cambridge University Press; Cambridge: 1987.

- Cloninger CR, Sigvardsson S, Bohman M, von Knorring AL. Predisposition to petty criminality in Swedish adoptees. II. Cross-fostering analysis of gene-environment interaction. *Arch Gen Psychiatry*. 1982; 39(11):1242–7. [PubMed: 7138224]
- Compton WM, Conway KP, Stinson FS, Colliver JD, Grant BF. Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2005; 66(6):677–85. [PubMed: 15960559]
- Cottler LB, Price RK, Compton WM, Mager DE. Subtypes of adult antisocial behavior among drug abusers. *J Nerv Ment Dis*. 1995; 183(3):154–61. [PubMed: 7891061]
- Davidge KM, Atkinson L, Douglas L, Lee V, Shapiro S, Kennedy JL, Beitchman JH. Association of the serotonin transporter and 5HT1Dbeta receptor genes with extreme, persistent and pervasive aggressive behaviour in children. *Psychiatr Genet*. 2004; 14(3):143–6. [PubMed: 15318027]
- Ducci F, Enoch MA, Hodgkinson C, Xu K, Catena M, Robin RW, Goldman D. Interaction between a functional MAOA locus and childhood sexual abuse predicts alcoholism and antisocial personality disorder in adult women. *Mol Psychiatry*. 2008; 13(3):334–47. [PubMed: 17592478]
- Edwards VJ, Anda RF, Nordenberg DF, Felitti VJ, Williamson DF, Wright JA. Bias assessment for child abuse survey: factors affecting probability of response to a survey about childhood abuse. *Child Abuse Negl*. 2001; 25(2):307–12. [PubMed: 11330927]
- Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: Linked loci and correlated allele frequencies. *Genetics*. 2003; 164(4):1567–1587. [PubMed: 12930761]
- Feinn R, Gelernter J, Cubells JF, Farrer L, Kranzler HR. Sources of unreliability in the diagnosis of substance dependence. *J Stud Alcohol Drugs*. 2009; 70(3):475–81. [PubMed: 19371499]
- Finkelstein J, Yates JK. Traumatic symptomatology in children who witness marital violence. *Int J Emerg Ment Health*. 2001; 3(2):107–14. [PubMed: 11508563]
- Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, Riley B. Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Arch Gen Psychiatry*. 2004; 61(7):738–44. [PubMed: 15237086]
- Gelernter J, Gueorguieva R, Kranzler HR, Zhang H, Cramer J, Rosenheck R, Krystal JH. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. *Alcohol Clin Exp Res*. 2007; 31(4):555–63. [PubMed: 17374034]
- Gelernter J, Kranzler H, Cubells JF. Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Hum Genet*. 1997; 101(2):243–6. [PubMed: 9402979]
- Gelernter J, Panhuysen C, Weiss R, Brady K, Hesselbrock V, Rounsaville B, Poling J, Wilcox M, Farrer L, Kranzler HR. Genomewide linkage scan for cocaine dependence and related traits: significant linkages for a cocaine-related trait and cocaine-induced paranoia. *Am J Med Genet B Neuropsychiatr Genet*. 2005; 136(1):45–52. [PubMed: 15909294]
- Gelernter J, Panhuysen C, Wilcox M, Hesselbrock V, Rounsaville B, Poling J, Weiss R, Sonne S, Zhao H, Farrer L, Kranzler HR. Genomewide linkage scan for opioid dependence and related traits. *Am J Hum Genet*. 2006; 78(5):759–69. [PubMed: 16642432]
- Gerra G, Garofano L, Santoro G, Bosari S, Pellegrini C, Zaimovic A, Moi G, Bussandri M, Moi A, Brambilla F, Donnini C. Association between low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates. *Am J Med Genet B Neuropsychiatr Genet*. 2004; 126B(1):37–42. [PubMed: 15048645]
- Gerra G, Zaimovic A, Garofano L, Ciusa F, Moi G, Avanzini P, Talarico E, Gardini F, Brambilla F, Manfredini M, Donnini C. Perceived parenting behavior in the childhood of cocaine users: relationship with genotype and personality traits. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B(1):52–7. [PubMed: 16972224]
- Goldstein RB, Compton WM, Pulay AJ, Ruan WJ, Pickering RP, Stinson FS, Grant BF. Antisocial behavioral syndromes and DSM-IV drug use disorders in the United States: Results from the

- National Epidemiologic Survey on Alcohol and Related Conditions. Drug and Alcohol Dependence. 2007a; 90(2-3):145–158. [PubMed: 17433571]
- Goldstein RB, Dawson DA, Saha TD, Ruan WJ, Compton WM, Grant BF. Antisocial behavioral syndromes and DSM-IV alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcohol Clin Exp Res. 2007b; 31(5):814–28. [PubMed: 17391341]
- Goldstein RB, Powers SI, McCusker J, Lewis BF, Bigelow C, Mundt KA. Antisocial behavioral syndromes among residential drug abuse treatment clients. Drug Alcohol Depend. 1998; 49(3): 201–16. [PubMed: 9571385]
- Haberstick BC, Lessem JM, Hopfer CJ, Smolen A, Ehringer MA, Timberlake D, Hewitt JK. Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. Am J Med Genet B Neuropsychiatr Genet. 2005; 135B(1):59–64. [PubMed: 15806601]
- Hallikainen T, Saito T, Lachman HM, Volavka J, Pohjalainen T, Ryyanen OP, Kauhanen J, Syvalahti E, Hietala J, Tiihonen J. Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry. 1999; 4(4): 385–8. [PubMed: 10483057]
- Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP. Allelic variation of human serotonin transporter gene expression. J Neurochem. 1996; 66(6):2621–4. [PubMed: 8632190]
- Higley JD, Suomi SJ, Linnoila M. CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. Psychopharmacology (Berl). 1991; 103(4):551–6. [PubMed: 1712115]
- Higley JD, Suomi SJ, Linnoila M. A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. Biol Psychiatry. 1992; 32(2):127–45. [PubMed: 1384725]
- Hosser D, Raddatz S, Windzio M. Child maltreatment, revictimization, and violent behavior. Violence Vict. 2007; 22(3):318–33. [PubMed: 17619637]
- 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 Exp Res. 2005; 29(1):8–16. [PubMed: 15654286]
- Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet. 2006; 78(5):815–26. [PubMed: 16642437]
- Huizinga D, Haberstick BC, Smolen A, Menard S, Young SE, Corley RP, Stallings MC, Grotspeter J, Hewitt JK. Childhood maltreatment, subsequent antisocial behavior, and the role of monoamine oxidase A genotype. Biol Psychiatry. 2006; 60(7):677–83. [PubMed: 17008143]
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994; 51(1):8–19. [PubMed: 8279933]
- Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, Moffitt TE. MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. Mol Psychiatry. 2006; 11(10):903–13. [PubMed: 16801953]
- Knapp JF. The impact of children witnessing violence. Pediatr Clin North Am. 1998; 45(2):355–64. [PubMed: 9568015]
- Kranzler HR, Del Boca FK, Rounsaville BJ. Comorbid psychiatric diagnosis predicts three-year outcomes in alcoholics: a posttreatment natural history study. J Stud Alcohol. 1996; 57(6):619–26. [PubMed: 8913993]
- Langbehn DR, Cadoret RJ. The adult antisocial syndrome with and without antecedent conduct disorder: comparisons from an adoption study. Compr Psychiatry. 2001; 42(4):272–82. [PubMed: 11458301]
- Laucht M, Treutlein J, Schmid B, Blomeyer D, Becker K, Buchmann AF, Schmidt MH, Esser G, Jennen-Steinmetz C, Rietschel M, Zimmermann US, Banaschewski T. Impact of psychosocial

- adversity on alcohol intake in young adults: moderation by the LL genotype of the serotonin transporter polymorphism. *Biol Psychiatry*. 2009; 66(2):102–9. [PubMed: 19358979]
- Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996; 274(5292):1527–31. [PubMed: 8929413]
- Liao DL, Hong CJ, Shih HL, Tsai SJ. Possible association between serotonin transporter promoter region polymorphism and extremely violent crime in Chinese males. *Neuropsychobiology*. 2004; 50(4):284–7. [PubMed: 15539857]
- Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sci*. 1983; 33(26):2609–14. [PubMed: 6198573]
- Luntz BK, Widom CS. Antisocial personality disorder in abused and neglected children grown up. *Am J Psychiatry*. 1994; 151(5):670–4. [PubMed: 8166307]
- Lyons-Ruth K, Holmes BM, Sasvari-Szekely M, Ronai Z, Nemoda Z, Pauls D. Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults. *Psychiatr Genet*. 2007; 17(6):339–43. [PubMed: 18075474]
- Maes HH, Silberg JL, Neale MC, Eaves LJ. Genetic and cultural transmission of antisocial behavior: an extended twin parent model. *Twin Res Hum Genet*. 2007; 10(1):136–50. [PubMed: 17539373]
- Malmquist C. Children who witness parental murder: posttraumatic aspects. *J Am Acad Child Psychiatry*. 1986; 25(3):320–5.
- Mehlman PT, Higley JD, Faucher I, Lilly AA, Taub DM, Vickers J, Suomi SJ, Linnoila M. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. *Am J Psychiatry*. 1994; 151(10):1485–91. [PubMed: 7522411]
- Moffitt, TE. The Neuropsychology of Juvenile delinquency. In: Tonry, M.; Morris, N., editors. *Crime and Justice: a review of research*. Vol. 12. University of Chicago Press; Chicago: 1990.
- Moore T, Scarpa A, Raine A. A meta-analysis of serotonin metabolite 5-HIAA and antisocial behavior. *Aggressive Behavior*. 2002; 28:299–316.
- Pauli-Pott U, Friedel S, Hinney A, Hebebrand J. Serotonin transporter gene polymorphism (5-HTTLPR), environmental conditions, and developing negative emotionality and fear in early childhood. *J Neural Transm*. 2009; 116(4):503–12. [PubMed: 19137235]
- Pierucci-Lagha A, Covault J, Feinn R, Nellisery M, Hernandez-Avila C, Oncken C, Morrow AL, Kranzler HR. *GABRA2* alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. *Neuropsychopharmacology*. 2005; 30(6):1193–203. [PubMed: 15702134]
- Pierucci-Lagha A, Gelernter J, Chan G, Arias A, Cubells JF, Farrer L, Kranzler HR. Reliability of DSM-IV diagnostic criteria using the semi-structured assessment for drug dependence and alcoholism (SSADDA). *Drug Alcohol Depend*. 2007; 91(1):85–90. [PubMed: 17590536]
- Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics*. 2000; 155(2):945–59. [PubMed: 10835412]
- Raine A. Biosocial studies of antisocial and violent behavior in children and adults: a review. *J Abnorm Child Psychol*. 2002; 30(4):311–26. [PubMed: 12108763]
- Raine A, Venables PH. Classical conditioning and socialization - a biosocial interaction? *Personality Indiv Diff*. 1981; 2(4):273–83.
- Ramamoorthy S, Bauman AL, Moore KR, Han H, Yang-Feng T, Chang AS, Ganapathy V, Blakely RD. Antidepressant- and cocaine-sensitive human serotonin transporter: molecular cloning, expression, and chromosomal localization. *Proc Natl Acad Sci U S A*. 1993; 90(6):2542–6. [PubMed: 7681602]
- Reif A, Rosler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, Lesch KP, Retz W. Nature and nurture predispose to violent behavior: serotonergic genes and adverse childhood environment. *Neuropsychopharmacology*. 2007; 32(11):2375–83. [PubMed: 17342170]
- Retz W, Retz-Junginger P, Supprian T, Thome J, Rosler M. Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. *Behav Sci Law*. 2004; 22(3):415–25. [PubMed: 15211560]

- Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull.* 2002; 128(3):490–529. [PubMed: 12002699]
- Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD Jr, Regier DA. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry.* 1984; 41(10):949–58. [PubMed: 6332590]
- Rounsaville BJ, Dolinsky ZS, Babor TF, Meyer RE. Psychopathology as a predictor of treatment outcome in alcoholics. *Arch Gen Psychiatry.* 1987; 44(6):505–13. [PubMed: 3579499]
- Roy A, Linnoila M. Suicidal behavior, impulsiveness and serotonin. *Acta Psychiatr Scand.* 1988; 78(5):529–35. [PubMed: 3068956]
- Sadeh N, Javdani S, Jackson JJ, Reynolds EK, Potenza MN, Gelernter J, Lejuez CW, Verona E. Serotonin transporter gene associations with psychopathic traits in youth vary as a function of socioeconomic resources. *J Abnorm Psychol.* 2010; 119(3):604–9. [PubMed: 20677849]
- Sakai JT, Lessem JM, Haberstick BC, Hopfer CJ, Smolen A, Ehringer MA, Timberlake D, Hewitt JK. Case-control and within-family tests for association between 5HTTLPR and conduct problems in a longitudinal adolescent sample. *Psychiatr Genet.* 2007; 17(4):207–14. [PubMed: 17621163]
- Sakai JT, Young SE, Stallings MC, Timberlake D, Smolen A. Case-control and within-family tests for an association between conduct disorder and 5HTTLPR. *Am J Med Genet.* 2006; 141B(8):825–832. [PubMed: 16972235]
- Slutske WS. The genetics of antisocial behavior. *Curr Psychiatry Rep.* 2001; 3(2):158–62. [PubMed: 11276412]
- Stein MB, Seedat S, Gelernter J. Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. *Psychopharmacology (Berl).* 2006; 187(1):68–72. [PubMed: 16525856]
- Taylor A, Kim-Cohen J. Meta-analysis of gene-environment interactions in developmental psychopathology. *Dev Psychopathol.* 2007; 19(4):1029–37. [PubMed: 17931432]
- Twitchell GR, Hanna GL, Cook EH, Stoltenberg SF, Fitzgerald, Zucker RA. Serotonin transporter promoter polymorphism genotype is associated with behavioral disinhibition and negative affect in children of alcoholics. *Alcohol Clin Exp Res.* 2001; 25(7):953–9. HE. [PubMed: 11505018]
- Widom CS, Brzustowicz LM. MAOA and the “cycle of violence:” childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. *Biol Psychiatry.* 2006; 60(7):684–9. [PubMed: 16814261]
- Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith, Suarez EC, Clary GL, Svenson IK, Siegler IC. Serotonin-related gene polymorphisms and central nervous system serotonin function. *Neuropsychopharmacology.* 2003; 28(3):533–41. [PubMed: 12629534]
- Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, Weiss RD, Farrer L, Gelernter J. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. *Arch Gen Psychiatry.* 2009; 66(11):1201–9. [PubMed: 19884608]
- Yang BZ, Zhao H, Kranzler HR, Gelernter J. Practical population group assignment with selected informative markers: characteristics and properties of Bayesian clustering via STRUCTURE. *Genet Epidemiol.* 2005; 28(4):302–312. [PubMed: 15782414]
- Zalsman G, Frisch A, Bromberg M, Gelernter J, Michaelovsky E, Campino A, Erlich Z, Tyano S, Apter A, Weizman A. Family-based association study of serotonin transporter promoter in suicidal adolescents: no association with suicidality but possible role in violence traits. *Am J Med Genet.* 2001; 105(3):239–45. [PubMed: 11353442]

Table 1

Descriptive Statistics by Population

Variable	European-American N = 602 (43.6%)	African-American N = 779 (56.4%)	Test Statistic ²	P-value
<i>Sex</i>			0.83 (df=1)	0.36
Male	362 (60.1%)	452 (58.0%)		
<i>Age</i>			19.58 (df=1)	< 0.001
Mean $\pm$ S.E. ¹	38.23 $\pm$ 0.45	40.96 $\pm$ 0.30		
<i>5-HTTLPR genotype</i>			29.28 (df=5)	< 0.001
L _A -L _A (0 S' allele)	157 (26.1%)	219 (28.1%)		
L _A -L _G (1 S' allele)	42 (7.0%)	180 (23.1%)		
L _A -S (1 S' allele)	256 (42.5%)	213 (27.3%)		
L _G -L _G (2 S' allele)	5 (0.8%)	43 (5.5%)		
L _G -S (2 S' allele)	31 (5.2%)	77 (9.9%)		
S-S (2 S' allele)	111 (18.4%)	47 (6.0%)		
<i>5-HTTLPR allele frequency</i>			1.71 (df=1)	0.19
f(L')	50.8%	53.3%		
f(S')	49.2%	46.7%		
<i>ASPD</i>			0.48 (df=1)	0.49
Positive	93 (15.5%)	110 (14.1%)		
<i>ACEs</i>				
Violent Crime	92 (15.3%)	214 (27.5%)	28.66 (df=1)	< 0.001
Sexual Abuse	117 (19.4%)	113 (14.5%)	5.82 (df=1)	0.016
Physical Abuse	82 (13.6%)	73 (9.4%)	5.55 (df=1)	0.018
<i>ACE score</i>			0.57 (df=1)	0.45
Mean $\pm$ S.E. ¹	0.48 $\pm$ 0.03	0.51 $\pm$ 0.03		
<i>Alcohol use disorder</i>			8.86 (df=2)	0.012
Dependence	431 (71.6%)	588 (75.6%)		
Abuse	100 (16.6%)	79 (10.2%)		
<i>Cocaine use disorder</i>			15.31 (df=2)	< 0.001
Dependence	409 (67.9%)	620 (79.6%)		
Abuse	29 (4.8%)	11 (1.4%)		
<i>Opioid use disorder</i>			85.30 (df=2)	< 0.001
Dependence	332 (55.2%)	183 (23.5%)		

Variable	European-American N = 602 (43.6%)	African-American N = 779 (56.4%)	Test Statistic ²	P-value
Abuse	8 (1.3%)	11 (1.4%)		

¹ S.E.: standard error

² Type III GEE Wald χ^2 test statistic

Table 2

Number of Adverse Childhood Experiences Among All Participants

N (column %)	European-American (N=602)		African-American (N=779)	
Number of ACEs	Male (N=362)	Female (N=240)	Male (N=452)	Female (N=327)
0	275 (76.0)	143 (59.6)	290 (64.2)	206 (63.0)
1	60 (15.6)	47 (19.6)	127 (28.1)	62 (19.0)
2	15 (4.1)	32 (13.3)	28 (6.2)	43 (13.2)
3	12 (3.3)	18 (7.5)	7 (1.6)	16 (4.9)
≥1	87 (24.0)	97 (40.4)	162 (35.8)	121 (37.0)

Table 3

Number of Adverse Childhood Experiences Among Participants with ASPD

N (column %)	European-American (N=93)		African-American (N=110)	
Number of ACEs	Male (N=73)	Female (N=20)	Male (N=79)	Female (N=31)
0	49 (67.1)	8 (40.0)	31 (39.2)	13 (41.9)
1	13 (17.8)	4 (20.0)	37 (46.8)	10 (32.3)
2	7 (9.6)	7 (35.0)	9 (11.4)	4 (12.9)
3	4 (5.5)	1 (5.0)	2 (2.5)	4 (12.9)
≥1	24 (32.9)	12 (60.0)	48 (60.8)	18 (58.1)

Table 4

5-HTTLPR Genotype and Allele Frequencies by Population, ASPD Diagnosis and Sex

	European-American (N = 602)				African-American (N = 779)			
	ASPD N = 93 (15.5%)		Non-ASPD N = 509 (84.5%)		ASPD N = 110 (14.1%)		Non-ASPD N = 669 (85.9%)	
	Male N = 73 (78.5%)	Female N = 20 (21.5%)	Male N = 289 (56.8%)	Female N = 220 (43.2%)	Male N = 79 (71.8%)	Female N = 31 (28.2%)	Male N = 373 (55.8%)	Female N = 296 (44.3%)
L_A-L_A	20 (27.4%)	5 (25.0%)	67 (23.2%)	65 (29.5%)	19 (24.1%)	8 (25.8%)	104 (27.9%)	88 (29.7%)
L_A-L_G	7 (9.6%)	2 (10.0%)	18 (6.2%)	15 (6.8%)	19 (24.1%)	6 (19.3%)	93 (24.9%)	62 (21.0%)
L_A-S	26 (35.6%)	7 (35.0%)	130 (45.0%)	93 (42.3%)	23 (29.1%)	10 (32.3%)	100 (26.8%)	80 (27.0%)
L_G-L_G	1 (1.4%)	0 (0.0%)	2 (0.7%)	2 (0.9%)	5 (6.3%)	2 (6.5%)	17 (4.6%)	19 (6.4%)
L_G-S	5 (6.8%)	1 (5.0%)	13 (4.5%)	12 (5.5%)	8 (10.1%)	4 (12.9%)	38 (10.2%)	27 (9.1%)
S-S	14 (19.2%)	5 (25.0%)	59 (20.4%)	33 (15.0%)	5 (6.3%)	1 (3.2%)	21 (5.6%)	20 (6.8%)
Allele								
f(L')	50.0%	47.5%	48.8%	54.1%	50.6%	51.6%	53.7%	53.7%
f(S')	50.0%	52.5%	51.2%	45.9%	49.4%	48.4%	46.3%	46.3%

Table 5

Logistic GEE Regression Analysis: European Americans

	Initial Model			Final Model
	χ^2	df	p-value	p-value or order of elimination
Sex	12.89	1	< 0.001	< 0.001
5-HTTLPR	1.12	2	0.57	– 5
ACE score	9.60	1	0.002	0.002
Sex $\times$ 5-HTTLPR	1.62	2	0.45	– 3
ACE score $\times$ 5-HTTLPR	2.23	2	0.33	– 4
ACE score $\times$ Sex	0.05	1	0.82	– 2
Sex $\times$ 5-HTTLPR $\times$ ACE score	1.40	2	0.50	– 1

Final Model ORs

	OR	95% CI	p-value
Sex (Male)	3.34	1.91 – 5.84	< 0.001
ACE score (+1)	1.47	1.15 – 1.87	0.002

Table 6

Logistic GEE Regression Analysis: African Americans

Initial (and Final) Model				
		χ^2	df	p-value
Sex		7.60	1	0.006
5-HTTLPR		7.01	2	0.03
ACE score		33.97	1	< 0.001
Sex $\times$ 5-HTTLPR		5.58	2	0.06
ACE score $\times$ 5-HTTLPR		9.17	2	0.01
ACE score $\times$ Sex		0.04	1	0.85
Sex $\times$ 5-HTTLPR $\times$ ACE score		13.82	2	< 0.001

Final Model ORs				
		OR	95% CI	p-value
ACE score (+1)				
Male	0 S' allele	2.80	1.53 – 5.15	< 0.001
	1 S' allele	1.94	1.20 – 3.14	0.007
	2 S' alleles	1.75	1.03 – 2.98	0.04
Female	0 S' allele	1.36	0.67 – 2.76	0.39
	1 S' allele	0.98	0.57 – 1.70	0.95
	2 S' alleles	6.16	3.15 – 12.03	< 0.001