RESEARCH ARTICLE

Genotypes Do Not Confer Risk For Delinquency ut Rather Alter Susceptibility to Positive and Negative Environmental Factors: Gene-Environment Interactions of *BDNF* Val66Met, *5-HTTLPR*, and *MAOA-uVNTR*

Kent W Nilsson, MD; Erika Comasco, MD; Sheilagh Hodgins, MD; Lars Oreland, MD; Cecilia Åslund, MD

Author Affiliations: Centre for Clinical Research, Uppsala University, County Hospital, S-721 89 Västerås, Sweden (Drs Nilsson and Åslund); Department of Neuroscience, Uppsala University, BMC, Box 593 S-751 24 Uppsala, Sweden (Drs Comasco and Oreland); Karolinska Institutet, Stockholm Sweden, and Département de Psychiatrie, Université de Montréal, Montréal, Canada (Dr Hodgins).

Correspondence: Kent W. Nilsson, Centre for Clinical Research, Uppsala University, County Hospital, S-721 89 Västerås, Sweden (kent.nilsson@ltv.se).

Abstract

Background: Previous evidence of gene-by-environment interactions associated with emotional and behavioral disorders is contradictory. Differences in findings may result from variation in valence and dose of the environmental factor, and/ or failure to take account of gene-by-gene interactions. The present study investigated interactions between the brain-derived neurotrophic factor gene (*BDNF* Val66Met), the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*), the monoamine oxidase A *(MAOA-uVNTR)* polymorphisms, family conflict, sexual abuse, the quality of the child-parent relationship, and teenage delinquency.
Methods: In 2006, as part of the Survey of Adolescent Life in Västmanland, Sweden, 1 337 high-school students, aged 17–18 years, anonymously completed questionnaires and provided saliva samples for DNA analyses.
Results: Teenage delinquency was associated with two-, three-, and four-way interactions of each of the genotypes and the three environmental factors. Significant four-way interactions were found for *BDNF* Val66Met × *5-HTTLPR*×*MAOA*-uVNTR × family conflicts and for *BDNF* Val66Met × *5-HTTLPR*×*MAOA*-uVNTR × sexual abuse. Further, the two genotype combinations that differed the most in expression levels (*BDNF* Val66Met Val, *5-HTTLPR* LL, *MAOA*-uVNTR LL [girls] and L [boys] vs *BDNF* Val66Met Val/Met, *5-HTTLPR* S/LS, *MAOA*-uVNTR S/SS/LS) in interaction with family conflict and sexual abuse were associated with the highest delinquency scores. The genetic variants previously shown to confer vulnerability for delinquency (*BDNF* Val66Met Val/Met × *5-HTTLPR* S × *MAOA*-uVNTR S) were associated with the lowest delinquency scores in interaction with a positive child-parent relationship.
Conclusions: Functional variants of the *MAOA*-uVNTR, *5-HTTLPR*, and *BDNF* Val66Met, either alone or in interaction with each other, may be best conceptualized as modifying sensitivity to environmental factors that confer either risk or protection for teenage delinquency.

Keywords: brain-derived neurotrophic factor, gene-environment interaction, juvenile delinquency, monoamine oxidase, serotonin plasma membrane transport proteins

1

Introduction

Teenage delinquency is a ubiquitous problem in industrial countries. Delinquency is positively associated with sexual abuse and family conflict (Widom, 1989), and negatively associated with parental warmth and support (Hoeve et al., 2008). While some evidence shows that specific genotypes, in interaction with childhood adversity, confer vulnerability for delinquency, several studies have failed to replicate these candidate gene-by-environment interactions (cG × E). The failure to replicate cG × E associations with behavioral disorders may be explained by the contribution of many genes with small effects (Duncan, 2013; Rutter et al., 2009), differences in the designs of studies, statistics, outcome variables, the investigated environmental factors and their dose and valence, and gene-by-gene interactions (G × G; Boyce and Ellis, 2005; Belsky and Pluess, 2009; Comasco et al., 2013; Goldman and Rosser, 2014). cG that interact with environmental events may not confer risk for behavioral disorders but rather increase sensitivity to the environment (Belsky and Pluess, 2009; Hankin et al., 2011).Investigations of cG × E have the potential to identify protective factors even among individuals exposed to adverse environments (Keller, 2014). Additionally, investigating interactions of multiple genes and environmental factors may provide further insight into the underlying neurobiological mechanisms. The present study aimed to replicate cG × E associated with delinquency, and investigate the interactions of two and three genotypes with negative and positive environmental factors. A general population sample of 1 337 adolescents was studied, which would detect moderate cG × E with 20% power. Three environmental factors were examined: family conflict, sexual abuse, and child-parent relationship. Each was indexed by a continuous variable to measure dosage.

Childhood maltreatment is a complex phenomenon. A recent review has suggested that the occurrence of abuse may be more important than the form, severity, or duration of the abuse. It is unclear why specific forms of abuse correlate more in some studies than in others (Briere and Jordan, 2009). However, it is clear that many child abuse victims experience more than one occurrence of abuse and different forms of abuse and that they are at greater risk of re-victimization in adolescence and adulthood. As there are cumulative effects of all of the different aspects of childhood trauma, it is difficult to ascertain the specific association between one form of childhood abuse and consequences in adulthood (Briere and Jordan, 2009). Thus, a measure of one form of childhood abuse likely indexes other forms of abuse, and thereby it is taken into account in statistical models.

Monoamine oxidase A (MAOA) is a key enzyme in the catabolism of monoamines, especially serotonin. Meta-analysis (Byrd and Manuck, 2013) indicates a robust association of the short and less-active allele (*MAOA*-uVNTR-S) with antisocial and criminal behavior among males exposed to adversity in childhood, signifying the need for broad-scale cG × E studies (Goldman and Rosser, 2014). Other studies identify associations between an interaction of the long, high-activity allele (*MAOA*-uVNTR-L) and childhood adversity and antisocial behavior among females (Sjoberg et al., 2007; Aslund et al., 2011), and aggressive behavior (Manuck et al., 2000; Beitchman et al., 2004) and violent crime (Tikkanen et al., 2009) among males. We reported that adolescent males carrying *MAOA*-uVNTR-S showed increased levels of delinquency when reared in adverse family environments and decreased levels of delinquency when reared in positive family environments (Nilsson et al., 2006; Oreland et al., 2007).

The brain-derived neurotrophic factor (*BDNF*) gene expresses BDNF in the brain. The *BDNF* Val66Met polymorphism is functional, with lower BDNF expression associated with the Met allele (Hong et al., 2011). BDNF modulates neuronal plasticity (Calabrese et al., 2009) and is implicated in the regulation of hypothalamic -pituitary -adrenal axis (HPA) response to stress (Wichers et al., 2008; Colzato et al., 2011), with carriers of the Met variant showing increased responsiveness. Some (Oades et al., 2008; Wagner et al., 2010), but not all (Tsai et al., 2005), studies report associations of *BDNF* Val66Met with aggression. A study of adolescents showed that carriers of *BDNF* Val66Met Met/Met who affiliated with aggressive peers displayed more aggressive behavior than did carriers of the Val/Val variant (Kretschmer et al., 2013).

Some studies (Retz et al., 2004; Gerra et al., 2005), but not all (Sakai et al., 2007), have reported an association between the short (S) less-active allele of the serotonin transporter, *5-HTTLPR*, and aggression, impulsiveness, and conduct disorder. The interactions of *5-HTTLPR* with delinquent peers (Vaughn et al., 2009) and family socioeconomic status (Aslund et al., 2013) are associated with antisocial phenotypes. In studies of three samples, among individuals homozygous for the S allele, exposure to negative parenting was associated with low positive affect, while exposure to positive parenting was associated with high positive affect (Hankin et al., 2011).

There is contradictory evidence of epistatic mechanisms being modified by environmental factors (Belsky and Pluess, 2009; Stoltenberg et al., 2012). In a study of male offenders, violence was associated with *MAOA*-uVNTR-S, whereas childhood adversity impacted later life violence only if *5-HTTLPR-S* was present (Reif et al., 2007).

The present study examined associations of delinquency with: (1) the high and low activity alleles of *MAOA*-uVNTR, *BDNF* Val66Met, and *5-HTTLPR* genotypes; (2) two-, three-, and four-way interactions of each genotype with family conflict and sexual abuse; and (3) two-, three-, and four-way interactions of each of these genotypes with the child-parent relationship, adjusting for family conflict and sexual abuse.

Method

Additional methodological information is presented in the Supplementary Material (S1).

Participants

The present study was part of the Survey of Adolescent Life in Västmanland, a medium-sized county in Sweden, undertaken in 2006. All students in the second year of high school (age 17–18 years) were asked to complete a questionnaire during class or, if absent, on the subsequent day and to provide a saliva sample for DNA extraction. Participation was anonymous and voluntary. A total of 2 263 students, 77.3% of the target population, completed the questionnaires, and 2 131 provided saliva samples. DNA was successfully extracted from 1 414 participants. The final sample included 661 boys and 676 girls (Aslund et al., 2009).

Genotyping

The *MAOA*-uVNTR polymorphism was analyzed as previously described (Nilsson et al., 2011). The genotypes were defined as

either short (S), with 2 or 3 copies of *MAOA*-uVNTR; S (boys)/ SS (girls), long (L), with 3.5, 4, or 5 (Deckert et al., 1999) copies of *MAOA*-uVNTR L (boys)/LL (girls), or LS for girls if heterozygous for a long and a short allele. In the final analysis, there were no individuals with the rare 2-allele repeats, and only eight girls and five boys with the 5-repeat variant of *MAOA*-uVNTR, due to missing values for other variables (Supplementary Table S1). The *BDNF* Val66Met polymorphism, which consists of a single-nucleotide polymorphism G/A substitution at codon 66 (Val66Met), was analyzed as described previously, Val/Val versus Val/Met or Met/Met (Comasco et al., 2013). The Met allele is less active than the Val allele. The solute carrier family 6 (SLC6A4, neurotransmitter transporter), serotonin transporter-linked promoter region (5-*HTTLPR*) polymorphism, which consists of an insertion/deletion that creates a short 14 repeat (S) or a long 16 repeat (L) allele, was analyzed as described previously (Aslund et al., 2009). Both the *BDNF* Val66Met and 5-*HTTLPR* genes were in Hardy-Weinberg equilibrium ($p = 0.113$ and $p = 0.209$ respectively), as was the *MAOA*-uVNTR gene among girls ($p = 0.866$).

Environmental Factors

Six questions assessed the adolescent's perception of his/her family. Scores for responses were summed to create a family-conflict score that ranged from 0 to 6. Sexual abuse was assessed by three items. Scores were summed to create a sexual-abuse score that ranged from 0 to 9 (Nilsson et al., 2011). The participant's perception of his/her relationship with his/her parents was assessed by four items. Answers were summed to create a child-parent relationship score that ranged from 4 (a poor relationship) to 20 (a good relationship).

Delinquency

Delinquency was measured by 14 questions. Responses were summed to create a total delinquency score that ranged from 0 to 90 (Aslund et al., 2011).

Alcohol Consumption, Symptoms of Depression, and Attention Deficit Hyperactivity Disorder

Swedish adolescent versions of self-report instruments were used to assess alcohol consumption (AUDIT-C; Nilsson et al., 2011); depression (Depression Self-Rating Scale [DSRS]; Aslund et al., 2009); and attention deficit hyperactivity disorder (ADHD; ADHD Self-Report Scale [ASRS]; Kessler et al., 2005; Sonnby et al., 2010).

Ethics

The study was approved by the Regional Ethical Review Board of Uppsala University, Dr.nr 2005:375. Oral informed consent was obtained from the participants.

Statistical Analysis

Univariate comparisons were computed using chi-squared tests, *t*-tests, and analyses of variance. Main and interaction effects of genetic and environmental factors were analyzed by general linear models (GLMs). GLMs were validated using Poisson log-linear models. Only significant main and interaction terms are included and reported for the final models. A *p*-value < 0.05 was considered significant for main effects, and $p < 0.10$ was considered significant for interaction effects (Fleiss, 1986).

A model-dependent realistic analysis (Hawking and Mlodinow, 2010) was performed, taking possible genetic plasticity and susceptibility into account. Analyses were based on the assumption that associations of a genotype with the outcome would change when another related genotype or a positive or negative environmental factor was entered into the statistical model.

Results

Table 1 presents characteristics of the sample. Greater proportions of girls than boys reported a conflicted family environment, having experienced sexual abuse, and a good relationship with their parents. Sex was not associated with genotype, with the exception of *MAOA*-uVNTR. Scores for delinquency were significantly higher among boys than among girls, as was the proportion of individuals reporting any delinquency. There were no differences in scores for family conflict, sexual abuse, and child-parent relationship by genotype, nor any differences in delinquency by genotype. Participants from families with conflict ($t = -8.434$, $p < 0.001$) and those who had experienced sexual abuse ($t = -6.796$, $p < 0.001$) reported higher delinquency scores, whereas participants with a positive child-parent relationship reported lower delinquency scores ($t = 6.668$, $p < 0.001$). There was a strong positive association between family conflict and sexual abuse (boys: $\gamma = 0.426$, $p < 0.001$; girls: $\gamma = 0.440$, $p < 0.001$), a strong negative association between family conflict and child-parent relationship (boys: $\gamma = -0.437$, $p < 0.001$; girls: $\gamma = -0.540$, $p < 0.001$), and a weaker negative association between child-parent relationship and sexual abuse (boys: $\gamma = -0.202$, $p = 0.054$; girls: $\gamma = -0.334$, $p < 0.001$). In univariate analyses, neither the *MAOA*-uVNTR ($p = 0.083$), 5-*HTTLPR* ($p = 0.525$), nor *BDNF* Val66Met ($p = 0.628$) genotype was associated with delinquency (not shown in tables).

The results of the multivariate GLM models are presented in Table 2. The observed power in the final model, after the removal of all nonsignificant interaction effects, was between 0.509 and 1.0 for all interaction effects. Scores for both family conflict and sexual abuse were more strongly associated with delinquency among boys than among girls. The interactions between *BDNF* Val66Met and family conflict and sexual abuse were both significantly associated with delinquency, as were the interactions of 5-*HTTLPR* and *MAOA*-uVNTR with family conflict. Furthermore, delinquency was significantly associated with three-way interactions of *BDNF* Val66Met × 5-*HTTLPR* × family conflict and *BDNF* Val66Met × 5-*HTTLPR* × sexual abuse, as were the interactions of *BDNF* Val66Met × *MAOA*-uVNTR × family conflict and *BDNF* Val66Met × *MAOA*-uVNTR × sexual abuse. The interaction of 5-*HTTLPR* × *MAOA*-uVNTR × family conflict was also significantly associated with delinquency. Finally, four-way interactions (*BDNF* Val66Met × 5-*HTTLPR* × *MAOA*-uVNTR × family conflict and *BDNF* Val66Met × 5-*HTTLPR* × *MAOA*-uVNTR × sexual abuse) were significantly associated with delinquency.

An illustration of the model adjusted for the main and interaction effects is not possible to draw in two dimensions. Instead, Figure 1 shows that in carriers of all combinations of genotypes (range: n = 63–358), delinquency scores varied as a function of family conflict and sexual abuse. Furthermore, the genotype combinations that differed the most in expression levels (*BDNF* Val66Met Val, 5-*HTTLPR* homozygous LL, *MAOA*-uVNTR homozygous LL [girls] and L [boys], vs *BDNF* Val66Met Val/Met, 5-*HTTLPR* S, *MAOA*-uVNTR S/SS/LS) in interaction with family conflict and sexual abuse were associated with the highest delinquency scores.

Because the delinquency score was a positively skewed ordinal scale, the GLM was validated by a Poisson log-linear model.

Table 1. Characteristics of the Participants

	Boys (*n* = 661)	Girls (*n* = 676)	Statistics
Parent or child born outside Scandinavia (%)	106 (16.0)	90 (13.3)	χ^2 = 2.264, *p* = 0.132
Mean (SD) score family conflict	0.407 (.819)	0.646 (1.024)	*t* = –4.713, *p* < 0.001
Individuals with family conflict (%)	177 (26.8)	251 (37.1)	χ^2 = 16.458, *p* < 0.001
Mean (SD) score sexual abuse	3.284 (1.127)	3.729 (1.369)	*t* = –6.478, *p* < 0.001
Individuals who experienced sexual abuse (%)	84 (13.2%)	226 (34.1%)	χ^2 = 78.434, *p* < 0.001
Mean (SD) score child-parent relationship	15.979 (3.132)	16.161 (3.200)	*t* = –1.053, *p* < 0.293
Individuals with strong child-parent relationship (%)	125 (18.8%)	173 (25.6%)	χ^2 = 11.088, *p* = 0.004
BDNF Val66Met[a]			
Val/Val (%)	466 (70.5)	479 (70.9)	
Val/Met (%)	167 (25.3)	181 (26,8)	
Met/Met (%)	28 (4.2)	16 (2.4)	χ^2 = 3.847, *p* = 0.146
5-HTLLPR[b]			
SS (%)	118 (17.9)	144 (21.3)	
SL (%)	329 (49.8)	305 (45.1)	
LL (%)	214 (32.4)	227 (33.6)	χ^2 = 3.704, *p* = 0.157
MAOA-uVNTR[c]			
SS (S Boys; %)	240 (36.3)	89 (13.2)	
LS (%)		301 (44.5)	
LL (L Boys; %)	421 (63.7)	286 (42.3)	
Mean (SD) score delinquency	8.931 (11.954)	3.784 (5.659)	*t* = 10.036, *p* < 0.001
Individuals with at least one delinquent act (%)	510 (77.1)	425 (62.9)	χ^2 = 34.478, *p* < 0.001

[a] Brain-derived neurotrophic factor gene.
[b] Serotonin transporter gene-linked polymorphic region.
[c] Monoamine oxidase A gene.
LL, homozygous for the long alleles; SD, standard deviation; SL, heterozygous; SS homozygous for the short alleles.

The results are presented in Table 2. Generally, the results were similar to those of the GLM, although in the Poisson log-linear model the associations of delinquency with the interaction terms of sex and the two environmental factors were not significant, whereas the sex × genotype interactions were significant for all three genotypes. Notably, according to the χ^2 and *p*-values, there was a strong sex difference in the effect of *MAOA*-uVNTR, and substantially weaker sex differences for *BDNF* Val66Met Val/Met and 5-*HTTLPR*.

Although the analyses presented in Figure 1 suggested that the absence of family conflict and the absence of sexual abuse were associated with low levels of delinquency, regardless of the combinations of genotypes, the quality of the child-parent relationship was entered into the final model to test for susceptibility to environmental influence. The results are presented in Table 3. In the GLM, the child–parent relationship interacted with *BDNF* Val66Met and with *BDNF* Val66Met × 5-*HTTLPR* × *MAOA*-uVNTR after adjusting for family conflict and sexual abuse. The observed power of the interaction was 0.998. Notably, according to the F-values, entering the child-parent relationship into the model strengthened most of the other interaction terms with family conflict and sexual abuse. The results of the Poisson log-linear model indicated that the child-parent relationship interacted with all tested combinations of two genotypes. The results are illustrated in Figure 2. As predicted by the differential susceptibility hypothesis, carriers of the genotype combination that would be expected to have the highest risk for delinquency in an adverse environment according to the sum of the sensitivity alleles (*BDNF* Val66Met Val/Met, 5-*HTTLPR* S, and *MAOA*-uVNTR S) showed the lowest delinquency scores if they reported a positive relationship with their parents.

The GLM and Poisson models were re-run, omitting the eight females and five males with the 5-repeat variant of the *MAOA*-uVNTR, and similar results were obtained. Models were adjusted for self-reported ethnicity, symptoms of ADHD, depression,

co-occurring ADHD and depression, and alcohol use. Ethnicity was unrelated to delinquency. Symptoms of ADHD and depression and alcohol use were each related to delinquency and increased the explained variance from 29.6% to 42.4%. However, these factors did not modify the effect of *BDNF* Val66Met Val/Met, 5-*HTTLPR* S, and *MAOA*-uVNTR S nor the interactions of these genes with the negative and positive environmental factors associated with delinquency (Supplementary Table S2). In an adjustment for multiple comparisons the corrected *p*-value was 0.0015, indicating that 21 of the 25 statistically significant comparisons remained significant in the final Poisson model testing for susceptibility (Table 3).

Analyses were re-run separately among boys and girls and the results are presented in Supplementary Table S3. Among boys, in all cG × E, cG × cG × E, and cG × cG × cG × E models, the interaction terms with family conflict were significantly associated with delinquency. By contrast, among girls family conflict was only associated with delinquency in interaction with 5-*HTTLPR* and in interaction with BDNF Val66Met, 5-*HTTLPR*, and *MAOA*-uVNTR. Unlike boys, among girls, cG × E and cG × cG×E of BDNF Val66Met and *MAOA*-uVNTR with sexual abuse and child-parent relationship were associated with delinquency, and a weak association was detected for the interaction of 5-*HTTLPR*, *MAOA*-uVNTR, and sexual abuse.

Discussion

This is the first study to investigate the interactions of variants of *BDNF* Val66Met × 5-*HTTLPR* × *MAOA*-uVNTR and both environmental risk and protective factors in relation to delinquency. Each of the three genotypes and the three environmental factors were associated with delinquency, as was male sex. Three two-way cG × E were significantly associated with delinquency: *BDNF* Val66Met × family conflict, *5HTLLPR* × family conflict, and *MAOA*-uVNTR × sexual abuse. Five three-way interactions

Table 2. Results of GLM and Poisson Log-linear Models of Genetic Factors and Environmental Risk Factors Associated With Adolescent Delinquency

	GLM				Poisson Log-linear Model	
	df	F	p	Obs. Power	χ^2	p
Sex	1	1.418	0.234	0.221	205.537	< 0.001
1. BDNF Val66Met[a]	1	0.276	0.600	0.082	36.460	< 0.001
2. 5-HTTLPR[b]	1	3.981	0.046	0.514	6.772	0.009
3. MAOA-uVNTR[c]	1	0.063	0.802	0.057	20.054	< 0.001
4. Family conflict	1	39.290	< 0.001	1.000	332.212	< 0.001
5. Sexual abuse	1	3.965	0.047	0.512	481.020	< 0.001
Sex × BDNF Val66Met			n.s.		11.201	0.001
Sex × 5-HTTLPR			n.s.		5.320	0.021
Sex × MAOA-uVNTR			n.s.		32.839	< 0.001
Sex × Family conflict	1	30.245	< 0.001	1.000		n.s.
Sex × Sexual abuse	1	23.549	< 0.001	0.998		n.s.
BDNF Val66Met × Family conflict	1	7.546	0.006	0.784	18.957	< 0.001
BDNF Val66Met × Sexual abuse	1	3.938	0.047	0.509	3.567	0.059
5-HTTLPR × Family conflict	1	11.918	0.001	0.932	17.494	< 0.001
5-HTTLPR × Sexual abuse			n.s.		6.657	0.010
MAOA-uVNTR × Family conflict	1	13.487	< 0.001	0.956	5.105	0.078
MAOA-uVNTR × Sexual abuse			n.s.		34.489	< 0.001
BDNF Val66Met × 5-HTTLPR × Family conflict	1	4.503	0.034	0.564		n.s.
BDNF Val66Met × 5-HTTLPR × Sexual abuse	1	4.040	0.018	0.721	13.273	< 0.001
BDNF Val66Met × MAOA-uVNTR × Family conflict	1	7.212	0.007	0.765	8.393	0.015
BDNF Val66Met × MAOA-uVNTR × Sexual abuse	1	2.934	0.054	0.573	22.559	< 0.001
5-HTTLPR × MAOA-uVNTR × Family conflict	1	12.206	< 0.001	0.937	30.239	< 0.001
5-HTTLPR × MAOA-uVNTR × Sexual abuse			n.s.		14.661	0.001
BDNF Val66Met × 5-HTTLPR × MAOA-uVNTR × Family conflict	1	4.995	0.026	0.608	6.015	0.049
BDNF Val66Met × 5-HTTLPR × MAOA-uVNTR × Sexual abuse	1	3.536	0.029	0.659	37.360	< 0.001

Adjusted R^2 = 0.279

[a] Brain-derived neurotrophic factor gene.
[b] Serotonin transporter gene-linked polymorphic region.
[c] Monoamine oxidase A gene.
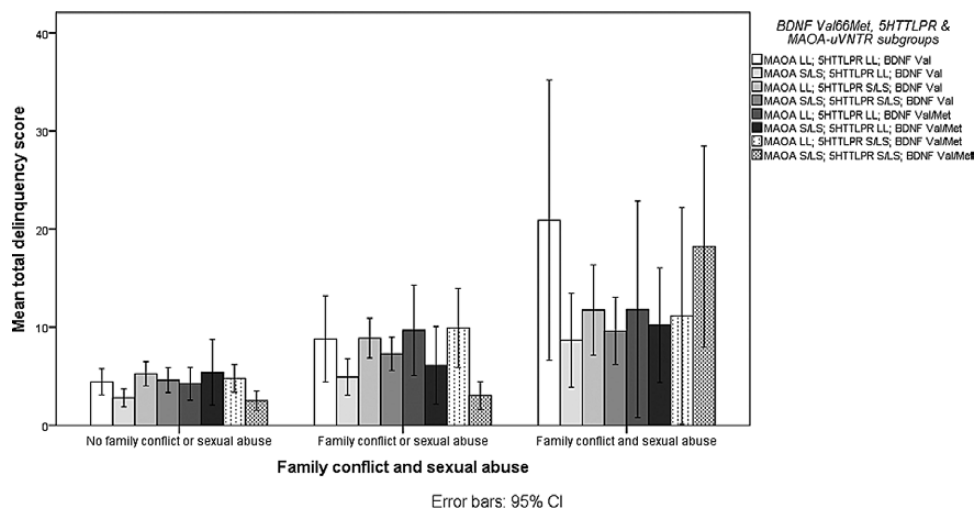GLM, general linear models; n.s., non-significant.

Figure 1. Mean scores for delinquency as a function of combinations of MAOA uVNTR, 5-HTTLPR, and BDNF Val66Met variants and three levels of family conflict and sexual abuse. BDNF, brain-derived neurotrophic factor; LL, girls with long alleles; LS, girls heterozygous for a long and a short allele; S, boys with short allele.

were significantly associated with delinquency: BDNF Val66Met × 5-HTTLPR × sexual abuse, BDNF Val66Met × MAOA-uVNTR × family conflict, BDNF Val66Met × MAOA-uVNTR × sexual abuse, 5-HTTLPR × MAOA-uVNTR × family conflict, and 5-HTTLPR × MAOA-uVNTR × sexual abuse. Two four-way interactions were significantly associated with delinquency: BDNF Val66Met × 5-HTTLPR × MAOA-uVNTR × family conflict and BDNF Val66Met × 5-HTTLPR × MAOA-uVNTR × sexual abuse. The low-activity allele

Table 3. Results of GLM and Poisson Log-linear Models of Genetic Factors, Environmental Risk and Protective Factors Associated With Adolescent Delinquency

	GLM				Poisson Log-linear Model	
	df	F	p	Obs. Power	χ^2	p
Sex	1	2.774	0.096	0.221	205.537	< 0.001
1. *BDNF* Val66Met [a]	1	0.276	0.600	0.384	0.469	0.493
2. *5-HTTLPR* [b]	1	1.292	0.256	0.206	5.065	0.024
3. *MAO-A-uVNTR* [c]	1	0.028	0.866	0.053	25.841	< 0.001
4. Family conflict	1	39.583	< 0.001	1.000	123.413	< 0.001
5. Sexual abuse	1	6.431	0.011	0.717	515.190	< 0.001
6. Child-parent relationship	1	4.947	0.026	0.604	107.829	< 0.001
Sex × *BDNF* Val66Met			n.s.		4.999	0.025
Sex × *5-HTTLPR*			n.s.		3.344	0.067
Sex × *MAOA-uVNTR*			n.s.		22.652	< 0.001
Sex × Family conflict	1	27.119	< 0.001	0.999	12.195	< 0.001
Sex × Sexual abuse	1	28.020	< 0.001	1.000		n.s.
Sex × Child-parent relationship			n.s.		27.520	< 0.001
BDNF Val66Met × Family conflict	1	8.881	0.003	0.846		n.s.
BDNF Val66Met × Sexual abuse			n.s.		54.558	< 0.001
BDNF Val66Met × Child-parent relationship	1	11.960	0.001	0.933		n.s.
5-HTTLPR × Family conflict	1	13.190	< 0.001	0.952	28.377	< 0.001
5-HTTLPR × Sexual abuse	1	3.461	0.063	0.460	11.521	0.001
5-HTTLPR × Child-parent relationship			n.s.			n.s.
MAOA-uVNTR × Family conflict	1	14.346	< 0.001	0.966	9.375	0.009
MAOA-uVNTR × Sexual abuse			n.s.		90.124	< 0.001
MAOA-uVNTR × Child-parent relationship			n.s.			n.s.
BDNF Val66Met × *5-HTTLPR* × Family conflict	1	6.368	0.012	0.713	4.010	0.045
BDNF Val66Met × *5-HTTLPR* × Sexual abuse	1	16.205	< 0.001	0.980		n.s.
BDNF Val66Met × *5-HTTLPR* × Child-parent relationship			n.s.		17.074	< 0.001
BDNF Val66Met × *MAOA-uVNTR* × Family conflict	1	9.190	0.002	0.858	27.091	< 0.001
BDNF Val66Met × *MAOA-uVNTR* × Sexual abuse	1	7.518	0.001	0.944	58.772	< 0.001
BDNF Val66Met × *MAOA-uVNTR* × Child-parent relationship			n.s.		55.089	< 0.001
5-HTTLPR × *MAOA-uVNTR* × Family conflict	1	12.850	< 0.001	0.948	40.284	< 0.001
5-HTTLPR × *MAOA-uVNTR* × Sexual abuse			n.s.		27.205	0.001
5-HTTLPR × *MAOA-uVNTR* × Child-parent relationship			n.s.		14.039	0.001
BDNF Val66Met × *5-HTTLPR* × *MAOA-uVNTR* × Family conflict	1	7.774	0.005	0.796	22.202	< 0.001
BDNF Val66Met × *5-HTTLPR* × *MAOA-uVNTR* × Sexual abuse	1	10.912	< 0.001	0.991	57.768	< 0.001
BDNF Val66Met × *5-HTTLPR* × *MAOA-uVNTR* × Child-parentrelationship	1	10.342	< 0.001	0.988		n.s
Adj R^2 = 0.296						

[a] Brain-derived neurotrophic factor gene.
[b] Serotonin transporter gene linked polymorphic region.
[c] Monoamine oxidase A gene.
GLM, general linear models; n.s., non-significant.

of the *MAOA-*uVNTR gene was associated with delinquency both directly and in interaction with sexual abuse. Furthermore, as predicted by the genetic susceptibility hypothesis (Belsky et al., 2009), the *BDNF* Val66Met Val/met, *5-HTTLPR* S, *MAOA-*uVNTR S/SS/LS × child-parent relationship interaction was protective against teenage delinquency. If these results are replicated, they suggest that promoting positive child-parent relationships, even among children experiencing adversity, would reduce the risk of teenage delinquency.

Poisson models detected gene by sex interactions for *MAOA-*uVNTR, *BDNF* Val66Met Val/Met, and *5-HTTLPR* associated with delinquency, with the strongest gene by sex effect for *MAOA-*uVNTR. We, and others, have previously reported sex differences detected by analyses conducted separately within sex (Sjoberg et al., 2006; Aslund et al., 2009, 2011; Nilsson et al., 2011). However, such analyses only show different directions of the findings in relation to sex, but do not allow for testing

whether those differences in direction are statistically significant. In order to analyze sex differences statistically, both the main and interaction terms of sex and the genes of interest must be included in the same model. However, after finding that the sex interaction term was significant, we re-ran analyses separately by sex. These results showed that the interactions of family conflict and genotypes were significantly associated with delinquency among boys, while among girls interactions of the genotypes with sexual abuse and, to some extent, the child-parent relationship, were associated with delinquency.

None of the genotypes showed significant associations with delinquency in univariate analyses, whereas most interaction terms, as well as several gene main effects, were significant in the multivariate models and validated by complementary statistical analyses. Taken together, these results imply a robust deviation from chance findings. The figures serve as illustrations and should be interpreted with caution, as it is not possible to
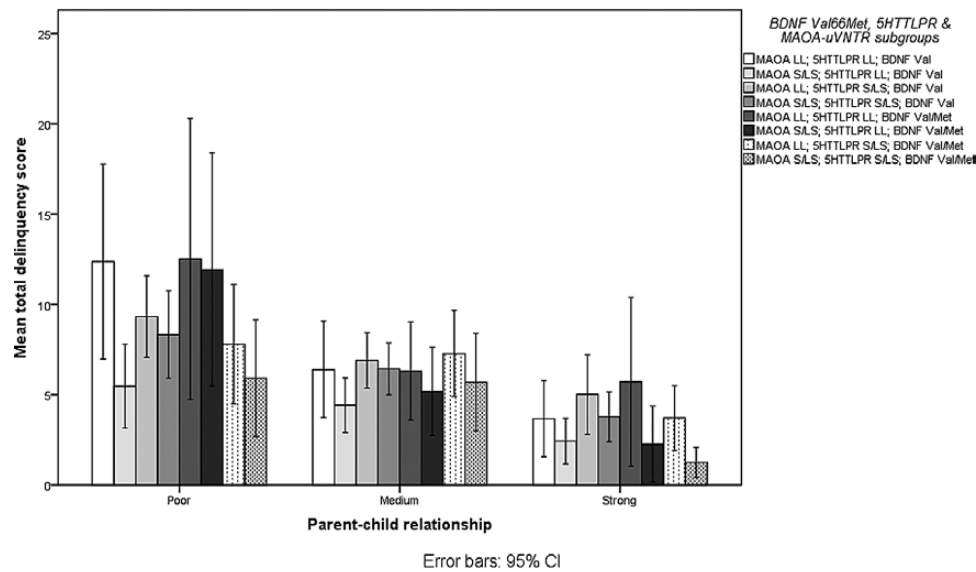
Figure 2. Mean score for delinquency as a function of combinations of *MAOA* uVNTR, *5-HTTLPR*, and *BDNF* Val66Met variants and poor, average, and good child-parent relationships. BDNF, brain-derived neurotrophic factor; LL, girls with long alleles; LS, girls heterozygous for a long and a short allele; S, boys with short allele.

construct a two-dimensional figure that describes the complexity of the interaction effects. Figure 1 illustrates an environmental risk model and Figure 2 illustrates an environmental protective model, not adjusted for each other and not statistically investigated. Moreover, the subgroups presented in the figures are not similar to the analyses in the statistical models since the statistical analyses of the environmental factors are based on scaled variables. However, it is important to note the differences in direction of the effect on delinquency depending on the negative and positive environmental factors. These directional differences indicate susceptibility properties of the investigated genotypes.

We used a model-dependent realistic analysis (Hawking and Mlodinow, 2010) and investigated cG × cG and cG × E in relation to delinquency, and whether the directions of cG × cG varied depending on the different environmental exposures (Comasco et al., 2013; Reiss et al., 2013). Since there is neither any knowledge about the phenotypic effects of various cG interactions, nor with combinations of cG × cG and cG × E, a directional hypothesis-driven method could not be used. This approach differs from belief-dependent realism that relies on reference anchors or small pieces of information, and emphasizes seeking and confirming evidence supporting existing beliefs (Shermer, 2011). When the genetic and environmental factors are truly interacting, a statistical model will constantly change depending on which factors and interaction terms are included in the analysis. Therefore, it is inappropriate to assume an additive genetic risk model of three susceptibility genes by using a genetic risk score if the cG × cG is unknown. For instance, although previous research has shown that an individual carrying a short *5-HTTLPR* genotype is at greater risk for a negative outcome and other research has shown that male carriers of the short *MAOA*-uVNTR variant exposed to a specific negative environmental factor are also at greater risk for the same negative outcome, this does not mean that carriers of both genotypes are at increased risk, as there is no evidence that the combination of genotypes is additive (Goldman and Rosser, 2014). Rather, interactions might be subadditive (i.e. 2 + 2 = 3) or superadditive (i.e. 2 + 2 = 10; Goldman and Rosser, 2014). In the present study, as expected (Briere and Jordan, 2009), there was a medium to strong

association between the environmental factors, which probably affected the cG × E, cG × cG × E, and cG × cG × cG × E. For instance, in the model that included cG × E without adjusting for the cG × cG, none of the cG × E was significant, whereas the models that included adjustment for most of the possible interactions produced significant results. It is important to note that the final interaction term in the model sets the effect of all lower-order interactions. Therefore, some of the two- or three-way interactions will vary depending on the effect of the four-way interaction. Studies of other samples presenting different genetic profiles and different proportions of participants exposed to each environmental factor will detect slightly different associations with the outcome. Therefore, studies of samples with varying genetic profiles and exposures to environmental variables applying multiple models are needed for further understanding of how genes interact with the environment to modify behavior. The present study, in line with previous findings (Stoltenberg et al., 2012), suggests a non-additive model for cG × E associated with teenage delinquency.

Previous studies suggest that the *BDNF* Val66Met Val/Met allele (Kretschmer et al., 2013), the short and less-active (S) allele of *5-HTTLPR* (Retz et al., 2004; Gerra et al., 2005), and the short and less-active *MAOA*-uVNTR (S) allele (Byrd and Manuck, 2013) are related to delinquency, either directly or in interaction with adversity. However, the present study showed that these genotypes confer susceptibility to the environment, thereby providing either vulnerability or protection against delinquency, depending on the negative and positive environmental influences (Hankin et al., 2011). If these results are replicated, future studies will be needed to determine the neurobiological mechanisms underlying these effects. Males carrying *MAOA*-uVNTR-S, relative to those with *MAOA*-uVNTR-L, show reductions in gray matter in the limbic and orbital frontal regions, hyper-responsiveness of the amygdala and hippocampus during aversive recall, and impaired cingulate activation during cognitive inhibition (Meyer-Lindenberg et al., 2006). These neural correlates of the *MAOA*-uVNTR-S genotype in males occur in regions with the highest density of serotonin receptors. *5-HTTLPR* S (Canli et al., 2005; Pezawas et al., 2005) has been associated with limbic structures and functions similar to *MAOA*-uVNTR-S, specifically

increased amygdala activation and relatively decreased responsivity in the cingulate circuitry that regulates the amygdala. Impulsive aggression has been associated with lower serotonergic innervation in the anterior cingulate cortex (Frankle et al., 2005). There are strong functional links between serotonin and BDNF. BDNF moderates HPA activity (Gatt et al., 2009; Shalev et al., 2009), and human (Stoltenberg et al., 2012) and rodent (Ren-Patterson et al., 2005) studies suggest that the low-expressing BDNF Val66Met and 5-HTTLPR genotypes may potentiate each other. Furthering our understanding of the mechanisms by which positive relationships offer protection against teenage delinquency is important and urgent.

The present results have four important implications for the generalizability of most previously-reported cG × E findings. (1) Positive environmental factors are not equal to the absence of adversity. (2) Previous findings may be inconsistent because analyses did not adjust for positive environmental factors. (3) The results of studies of large community samples, which include individuals characterized by multiple risk and protective factors of varying intensity, would be expected to differ from results of studies of high-risk samples exposed to more adverse and fewer protective factors. Consequently, future cG × E studies and meta-analyses of the results of these studies would increase in validity by taking account of both adverse and positive environmental factors. (4) Composite measures of "cumulative genetic plasticity" (a sum of the number of plasticity genotypes; Vaughn et al., 2009) will fail to capture cG × cG and cG × cG × cG × E. The results of the present study suggest that the debate about the validity of cG × E (Duncan and Keller, 2011) and the preferred strategy of genome-wide association studies, rather than studies of candidate genes, merits nuance, as these designs are complementary. Until the mechanisms involved in genetic–phenotypic associations are better understood, studies are needed using various populations with various environmental exposures to provide knowledge about the susceptibility conferred by genes and to prevent the rejection of cG × E interaction models.

Limitations and Strengths

The final sample included only 59% of the target population, mainly due to problems in collecting and extracting DNA. Since participation was anonymous, there was no possibility to obtain more saliva from the individuals with failing DNA analyses. The tri-allelic genotype of 5-HTTLPR and rs2553 was not isolated (Hu et al., 2006). However, the Lg genotype is present among only ~0.9% of the population (Wray et al., 2009), and findings of the effect of the Lg allele on 5-HTT mRNA transcription are contradictory (Philibert et al., 2008). Thus, not measuring this variant probably did not affect the results. In fact, since those individuals would have been re-classified to the susceptibility group, this would have even strengthened the results. Furthermore, models were adjusted for symptoms of ADHD, depression, and alcohol consumption, each of which were related to delinquency and increased the explained variance. However, these variables did not affect the cG × cG × cG × E. We interpret this finding as a further indication of the robustness of the results of the present study. Unfortunately, no data were available on use of medications that could, potentially, affect the results. However, in Sweden at the time the data were collected (2006), very few adolescents age 15–19 years were prescribed medications (i.e. selective serotonin re-uptake inhibitors: boys, 0.15‰, girls, 0.34‰; methylphenidate: boys, 0.13‰, girls, 0.043‰; Socialstyrelsen, 2014) indicating that medication influences in the present sample were negligible. Additional limitations of the present study

include the combination of BDNF Val66Met Val/Met with Met/Met, 5-HTTLPR SS and LS, and MAOA-uVNTR S (boys), SS, and LS. If there is a true difference between the merged genotypes, the results might have been stronger.

The delinquency variable was skewed such that transformations failed to correct the distribution. Consequently, cG × E was interpreted cautiously, calculations of observed power were computed, and data were additionally analyzed using Poisson log-linear regressions, which are suitable for non–normally distributed ordinal variables. The observed power was generally high, and the Poisson log-linear models yielded results that were similar to those of the GLMs. The sample used was relatively large, included as many girls as boys who were likely post-pubertal (Goldman and Rosser, 2014), included a majority of Caucasians, and was recruited in a county with income, education, and employment levels that are similar to those of Sweden as a whole (SCB, 2009). Environmental factors were indexed by self-reports, the prevalence of adversity was low, and continuous variables were used to capture dosage (Österman et al., 1998). Self-reports of delinquency are recommended, as they have been found to be reliable and valid (Smith and Thornberry, 1995; Tikkanen et al., 2009). The current prevalence of delinquency was similar to that of previous reports in Sweden (Svensson and Ring, 2007).

Finally, despite the use of complementary statistical methods and high statistical power, corrections for multiple comparisons indicated that 21 of the 25 statistically significant comparisons remained significant in the final Poisson model testing for susceptibility. However, it is also important to recognize that Type II errors that exclude true differences due to overly strict corrections are as important to avoid as Type I errors (Perneger, 1998).

Conclusions

Teenage delinquency was associated with interactions between MAOA-uVNTR, 5-HTTLPR, and BDNF Val66Met genotypes and family conflict, sexual abuse, and child-parent relationships. Importantly, a positive child-parent relationship conferred protection against delinquency, even after taking family conflict and sexual abuse into account. Future investigations should measure cG × cG × E while considering the range of positive and negative environmental factors to which the participants have been exposed.

Acknowledgements

Statement of Interest

All authors declare no biomedical financial interests or potential conflicts of interest.

References

Aslund C, Leppert J, Comasco E, Nordquist N, Oreland L, Nilsson KW (2009) Impact of the interaction between the 5HTTLPR polymorphism and maltreatment on adolescent depression. A population-based study. Behav Genet 39:524–531.

Aslund C, Nordquist N, Comasco E, Leppert J, Oreland L, Nilsson KW (2011) Maltreatment, MAOA, and delinquency: sex differences in gene-environment interaction in a large population-based cohort of adolescents. Behav Genet 41:262–272.

Aslund C, Comasco E, Nordquist N, Leppert J, Oreland L, Nilsson KW (2013) Self-reported family socioeconomic status, the 5-HTTLPR genotype, and delinquent behavior in a community-based adolescent population. Aggressive Behav 39:52–63.

Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL (2004) MAOA and persistent, pervasive childhood aggression. Mol Psychiatry 9:546–547.

Belsky J, Pluess M (2009) Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull 135:885–908.

Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R (2009) Vulnerability genes or plasticity genes? Mol Psychiatry 14:746–754.

Boyce WT, Ellis BJ (2005) Biological sensitivity to context: I. an evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol 17:271–301.

Briere J, Jordan CE (2009) Childhood maltreatment, intervening variables, and adult psychological difficulties in women: an overview. Trauma Violence Abuse 10:375–388.

Byrd AL, Manuck SB (2013) MAOA, Childhood Maltreatment, and Antisocial Behavior: Meta-analysis of a Gene-Environment Interaction. Biol Psychiatry 75:9–17.

Calabrese F, Molteni R, Racagni G, Riva MA (2009) Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology 34(Suppl 1):S208–216.

Canli T, Omura K, Haas BW, Fallgatter A, Constable RT, Lesch KP (2005) Beyond affect: A role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. Proc Natl Acad Sci USA 102:12224–12229.

Colzato LS, Van der Does AJ, Kouwenhoven C, Elzinga BM, Hommel B (2011) BDNF Val66Met polymorphism is associated with higher anticipatory cortisol stress response, anxiety, and alcohol consumption in healthy adults. Psychoneuroendocrinology 36:1562–1569.

Comasco E, Aslund C, Oreland L, Nilsson KW (2013) Three-way interaction effect of 5-HTTLPR, BDNF Val66Met, and childhood adversity on depression: A replication study. Eur Neuropsychopharmacol 23:1300–1306.

Deckert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D, Nothen MM, Maffei P, Franke P, Fritze J, Maier W, Propping P, Beckmann H, Bellodi L, Lesch KP (1999) Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Gen 8:621–624.

Duncan LE (2013) Paying attention to all results, positive and negative. J Am Acad Child Adolesc Psychiatry 52:462–465.

Duncan LE, Keller MC (2011) A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psych 168:1041–1049.

Fleiss JL (1986) Design and Analysis of Clinical Experiments. New York: John Wiley and Sons.

Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang Y, Hwang D-R, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: A positron emission study with [^{11}C]McN 5652. Am J Psych 162:915–923.

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, Williams LM (2009) Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 14:681–695.

Gerra G, Garofano L, Castaldini L, Rovetto F, Zaimovic A, Moi G, Bussandri M, Branchi B, Brambilla F, Friso G, Donnini C (2005) Serotonin transporter promoter polymorphism genotype is associated with temperament, personality traits and illegal drugs use among adolescents. J Neural Transm 112:1397–1410.

Goldman D, Rosser AA (2014) MAOA-Environment Interactions: results May Vary. Biol Psychiatry 75:2–3.

Hankin BL, Nederhof E, Oppenheimer CW, Jenness J, Young JF, Abela JR, Smolen A, Ormel J, Oldehinkel AJ (2011) Differential susceptibility in youth: evidence that 5-HTTLPR x positive parenting is associated with positive affect 'for better and worse.' Transl Psychiatry 1:e44.

Hawking S, Mlodinow L (2010) The grand design: new answers to the ultimate questions of life, 1 edition. New York: Bantam Books.

Hoeve M, Blokland A, Dubas JS, Loeber R, Gerris JR, van der Laan PH (2008) Trajectories of delinquency and parenting styles. J Abnorm Child Psych 36:223–235.

Hong C-J, Liou Y-J, Tsai S-J (2011) Effects of BDNF polymorphisms on brain function and behavior in health and disease. Brain Res Bull 86:287–297.

Hu X-Z, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet 78:815–826.

Keller MC (2014) Gene x environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. Biol Psychiatry 75:18–24.

Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE (2005) The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med 35:245–256.

Kretschmer T, Vitaro F, Barker ED (2013) The association between peer and own aggression is moderated by the BDNF Val-Met polymorphism. J Res Adolesc 24:177–185.

Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF (2000) A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res 95:9–23.

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, A RH, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci USA 103:6269–6274.

Nilsson KW, Sjoberg RL, Damberg M, Leppert J, Ohrvik J, Alm PO, Lindstrom L, Oreland L (2006) Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biol Psychiatry 59:121–127.

Nilsson KW, Comasco E, Aslund C, Nordquist N, Leppert J, Oreland L (2011) MAOA genotype, family relations and sexual abuse in relation to adolescent alcohol consumption. Addict Biol 16:347–355.

Oades RD, Lasky-Su J, Christiansen H, Faraone SV, Sonuga-Barke EJ, Banaschewski T, Chen W, Anney RJ, Buitelaar JK, Ebstein RP, Franke B, Gill M, Miranda A, Roeyers H, Rothenberger A, Sergeant JA, Steinhausen HC, Taylor EA, Thompson M, Asherson P (2008) The influence of serotonin- and other genes

on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): Findings from a family-based association test (FBAT) analysis. Behav Brain Funct 4:1–14.

Oreland L, Nilsson KW, Hallman J (2007) Monoamine oxidases: activities, genotypes and the shaping of behaviour. J Neural Transm 114:817–822.

Österman K, Björkqvist K, Lagerspetz KMJ, Kaukiainen A, Landau SF, Fraczek A, Caprara GV (1998) Cross-cultural evidence of female indirect aggression. Aggressive Behav 24:1–8.

Perneger TV (1998) What's wrong with Bonferroni adjustments. The BMJ 316:1236–1238.

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8:828–834.

Philibert RA, Sandhu H, Hollenbeck N, Gunter T, Adams W, Madan A (2008) The relationship of 5HTT (SLC6A4) methylation and genotype on mRNA expression and liability to major depression and alcohol dependence in subjects from the Iowa Adoption Studies. Am J Med Genet B Neuropsychiatr Genet 147B:543–549.

Reif A, Rösler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, Lesch K-P, Retz W (2007) Nature and nurture predispose to violent behavior: Serotonergic genes and adverse childhood environment. Neuropsychopharmacology 32:2375–2383.

Reiss D, Leve LD, Neiderhiser JM (2013) How genes and the social environment moderate each other. Am J Public Health 103(Suppl 1):S111–121.

Ren-Patterson RF, Cochran LW, Holmes A, Sherrill S, Huang SJ, Tolliver T, Lesch KP, Lu B, Murphy DL (2005) Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. J Neurosci Res 79:756–771.

Retz W, Retz-Junginger P, Supprian T, Thome J, Rosler M (2004) Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. Behav Sci Law 22:415–425.

Rutter M, Thapar A, Pickles A (2009) Gene-environment interactions: biologically valid pathway or artifact? Arch Gen Psychiatry 66:1287.

Sakai JT, Lessem JM, Haberstick BC, Hopfer CJ, Smolen A, Ehringer MA, Timberlake D, Hewitt JK (2007) Case-control and within-family tests for associations between 5HTTLPR and conduct problems in a longitudinal adolescent sample. Psychiatr Genet 17:207–214.

SCB (2009) Population statistics. Description of the Population in Sweden 2008. In: 1 Edition (Nylin A-K, ed), pp 33-40, 55-60. Örebro: Statistics Sweden, Population Statistics Unit.

Shalev I, Lerer E, Israel S, Uzefovsky F, Gritsenko I, Mankuta D, Ebstein RP, Kaitz M (2009) BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. Psychoneuroendocrinology 34:382–388.

Shermer M (2011) The believing brain: From ghosts and gods to politics and conspiracies---How we construct beliefs and reinforce them as truths. New York: Time Books.

Sjoberg RL, Nilsson KW, Nordquist N, Ohrvik J, Leppert J, Lindstrom L, Oreland L (2006) Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. Int J Neuropsychop 9:443–449.

Sjoberg RL, Nilsson KW, Wargelius HL, Leppert J, Lindstrom L, Oreland L (2007) Adolescent girls and criminal activity: role of MAOA-LPR genotype and psychosocial factors. Am J Med Genet B Neuropsychiatr Genet 144B:159–164.

Smith C, Thornberry TP (1995) The relationship between childhood maltreatment and adolescent involvement in delinquency. Criminology 33:451–481.

Socialstyrelsen (2014) Statistical data base (http://www.social-styrelsen.se/statistik/statistikdatabas/lakemedel). Developement and quality, 1 Jan Edition. Stockholm: The National Board of Health and Welfare.

Sonnby K, Aslund C, Leppert J, Nilsson KW (2010) Symptoms of ADHD and depression in a large adolescent population: Co-occurring symptoms and associations to experiences of sexual abuse. Nord J Psychiatry 65:315–322.

Stoltenberg SF, Christ CC, Highland KB (2012) Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. Prog Neuropsychopharmacol Biol Psychiatry 39:182–191.

Svensson R, Ring J (2007) Trends in Self-Reported Youth Crime and Victimization in Sweden, 1995–2005. J Scand Stud Criminol Crime Prev 8:185–209.

Tikkanen R, Sjoberg RL, Ducci F, Goldman D, Holi M, Tiihonen J, Virkkunen M (2009) Effects of MAOA-genotype, alcohol consumption, and aging on violent behavior. Alcohol Clin Exp Res 33:428–434.

Tsai SJ, Liao DL, Yu YW, Chen TJ, Wu HC, Lin CH, Cheng CY, Hong CJ (2005) A study of the association of (Val66Met) polymorphism in the brain-derived neurotrophic factor gene with alcohol dependence and extreme violence in Chinese males. Neurosci Lett 381:340–343.

Vaughn MG, DeLisi M, Beaver KM, Wright JP (2009) DAT1 and 5HTT are associated with pathological criminal behavior in a nationally representative sample of youth. Crim Justice Behav 36:1113–1124.

Wagner S, Baskaya O, Dahmen N, Lieb K, Tadic A (2010) Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav 9:97–102.

Wichers M, Kenis G, Jacobs N, Mengelers R, Derom C, Vlietinck R, van Os J (2008) The BDNF Val(66)Met x 5-HTTLPR x child adversity interaction and depressive symptoms: An attempt at replication. Am J Med Genet B Neuropsychiatr Genet 147B:120–123.

Widom CS (1989) Child abuse, neglect, and adult behavior: research design and findings on criminality, violence, and child abuse. Am J Orthopsychiatry 59:355–367.

Wray NR, James MR, Gordon SD, Dumenil T, Ryan L, Coventry WL, Statham DJ, Pergadia ML, Madden PA, Heath AC, Montgomery GW, Martin NG (2009) Accurate, Large-Scale Genotyping of 5HTTLPR and Flanking Single Nucleotide Polymorphisms in an Association Study of Depression, Anxiety, and Personality Measures. Biol Psychiatry 66:468–476.