MAOA Genotype, Maltreatment, and Aggressive Behavior: The Changing Impact of Genotype at Varying Levels of Trauma

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Background: Childhood adversity has been shown to interact with monoamine oxidase-A (*MAOA*) genotype to confer risk for antisocial behavior. Studies examining this gene-by-environment (G×E) association, however, have produced mixed results.

Methods: Relevant research is reviewed, and results of a study with 114 children (73 maltreated and 41 control subjects) are presented. The maltreated children represent the extreme on a continuum of adversity and were assessed at a time of extreme stress—shortly after removal from their parents' care due to abuse. Measures of aggressive behavior were obtained using standard research instruments, and monoamine oxidase-A *MAOA* genotypes were obtained from saliva-derived DNA specimens. Population structure was controlled for using ancestral proportion scores computed on the basis of genotypes of ancestry informative markers.

Results: Many prior investigations appear to have had reduced power to detect the predicted G×E interaction because of low base rates of maltreatment and antisocial behavior in their samples and failure to use optimal procedures to control for population structure in ethnically diverse cohorts. In this investigation, a significant interaction was detected between exposure to moderate trauma and the "low-activity" *MAOA* genotype in conferring risk for aggression. Children with exposure to extreme levels of trauma, however, had high aggression scores regardless of genotype.

Conclusions: Our study suggests that problems in aggressive behavior in maltreated children are moderated by *MAOA* genotype, but only up to moderate levels of trauma exposure. Extreme levels of trauma appear to overshadow the effect of *MAOA* genotype, especially in children assessed at time of acute crisis.

Key Words: Aggression, antisocial, child abuse, gene–environment interaction, maltreatment, *MAOA*

Child maltreatment has been consistently associated with antisocial behavior in children who were abused (1–9). However, not all maltreated children develop problems with aggression or rule breaking, core symptoms associated with the diagnoses of conduct disorder and antisocial personality disorder. A groundbreaking study by Caspi *et al.* (1) suggested that resilience shown by some maltreated children relates to a polymorphism in the monoamine oxidase-A (*MAOA*) gene promoter. *MAOA* is an X-linked gene encoding an enzyme responsible for metabolizing neurotransmitters, such as serotonin and norepinephrine. The absence of a functional *MAOA* gene has been associated with aggression in animals (2) and humans (3). The number of copies in this variable number of tandem repeats (VNTR) *MAOA* polymorphism affects gene expression and efficiency of gene transcription (4,5). Caspi *et al.* (1) found that adults who were maltreated as children with "low-activity" *MAOA* alleles *(MAOA- L)* were more likely to develop conduct disorder, antisocial personality symptoms, and violence than adults maltreated as children with "high-activity" *MAOA* alleles (*MAOA-H)*, with this latter group having rates of these problems that were comparable to nonmaltreated control subjects.

Subsequent studies examining this gene-by-environment (G×E) interaction, however, have yielded mixed results. Replications (6–9), partial replications (10–13), negative findings (14–16), and even opposite findings (17) have been reported. Two recent meta-analyses reported small to medium effect sizes for the *MAOA* genotype and maltreatment interaction in conferring risk for antisocial behavior. The first (12) included five studies and reported an effect size of .18. The second, which included a total of eight studies, including the five studies in the original meta-analysis (12), showed an effect size of .17 for the G×E interaction involving the *MAOA* gene (18).

Studies included in these meta-analyses differ in terms of sample characteristics and phenotypes examined. Table 1 summarizes findings and key study characteristics of the 13 relevant published studies. Two of four replications included epidemiologic samples with Caucasian males (6,8), similar to the Caspi study (1), and one of the other replication studies was performed with Caucasian males who were referred to a forensic clinic (9). The fourth replication study included Native American females and reported an interaction between *MAOA* genotype and experiences of child maltreatment in conferring risk for antisocial personality (7). No other published articles that included non-Caucasian subjects replicated this G×E interaction for antisocial personality and aggression (10,14,16).

Among the partial replications, Widom (11) studied an ethnically diverse cohort but only found a significant G×E interaction for aggression among Caucasian subjects. Frazzetto's study (13) was limited to Caucasian male and female psychiatric outpatients and control subjects, but the G×E interaction was only significant for male participants (13). In the last two studies classified as partial replications, neither Huang (10) nor Kim-Cohen (12) detected a G×E interaction in predicting aggression or antisocial

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Table 1. Characteristics and Findings of Published Studies Examining MAOA Genotype and Maltreatment in Conferring Risk for Antisocial Behavior

Reference	Sample (*n*)	Cohort	Ethnicity	Sex	Prevalence Maltreatment (%)	Number High-Risk Subjects[a]	Phenotypes Examined	Prevalence Antisocial Behavior (%)	Findings
					Replications				
Caspi 2002[1]	442 adults	Epidemiological	Caucasian	Males	8	13	Conduct disorder, violent disposition, violent offenses, antisocial symptoms	25	G×E (low-activity allele)
Foley 2004[6]	514 children and adolescents	Epidemiological	Caucasian	Males	3.5	6	Conduct disorder	11.5	G×E (low-activity allele)
Nilsson 2006[8]	81 adolescents	Epidemiological	Caucasian	Males	14	5	Violence, vandalism, stealing, total Criminality Index	37	G xE (low-activity allele)
Reif 2007[9]	184 adults	Forensic evaluation referrals	Caucasian	Males	50	63	Recurrent violent behavior	39	G×E (low-activity allele)
Ducci 2007[7]	291 adults	168 alcoholic and 123 control subjects	Native Americans	Females	51	13	Alcohol use disorders and ASPD, ASPD symptoms	13	G×E (low-activity allele)
					Partial Replications				
Widom 2006[11]	409 adults	Maltreated and control subjects	Mixed	Both	50	NR	Juvenile and adult violence	42	G×E only in Caucasians (low-activity allele)
Frazzetto 2007[13]	235 adults	90 psychiatric outpatients and 145 control controls	Caucasian	Both	34	38	Aggression	NR	G×E only in men (low activity allele)
Huang 2004[10]	766 adults	663 Psychiatric outpatients with a mood disorder and 103 healthy controls	Mixed	Both	21	53	Aggression, hostility impulsivity, suicide attempts	NR	G×E for aggression both sexes (ns), positive for impulsivity in men and for suicide attempts in women (low-activity allele); in men, low-activity allele also associated with history of abuse
Kim-Cohen 2006[12]	975 children	Epidemiological	Caucasian	Males	4.7	16	Mental health composite score with antisocial, inattention, and emotional problem subscales	7	G×E negative for aggression, positive for inattention (low-activity allele)
					Negative or Opposite Reports				
Huizinga 2006[15]	277 adults	Epidemiological	Caucasian	Males	9	9	Violence, antisocial behavior	27	ns
Sjoberg 2007[17]	119 adolescents	Epidemiological	Caucasian	Females	11	1	Criminality risk index	38	G×E (high-activity allele, opposite finding)

Table 1. (continued)

Reference	Sample (*n*)	Cohort	Ethnicity	Sex	Prevalence Maltreatment (%)	Number High-Risk Subjects[a]	Phenotypes Examined	Prevalence Antisocial Behavior (%)	Findings
Haberstick 2005[14]	774 adolescents and young adults	Epidemiological	Caucasian	Males	5.3	15	Conduct disorder	9	ns
Young 2006[16]	247 adolescents	Residential patients	Mixed	Males	28	20	Conduct Disorder	100	ns

ASPD, antisocial personality disorder; G×E, gene-by-environment association; MAOA, monoamine oxidase-A; NR, not reported.
[a]High risk = history of maltreatment or adversity and high-risk genotype (e.g., low-activity allele MAOA gene).

personality. Huang (10) reported an interaction between *MAOA* genotype and adversity in predicting impulsivity in adults, and Kim-Cohen (12) reported an interaction in predicting inattention in children.

Among negative studies, two had low rates of maltreatment within their samples, with few "high-risk" subjects—subjects with both a history of maltreatment and *MAOA-L* genotypes (15,17). Although the other two negative studies had more "high-risk" subjects, in one study the prevalence of conduct disorder was low (14), and the other study exclusively included delinquents without a matched no-problem control group (16). Power to detect G×E effects was reduced by the low number of "high-risk," antisocial, or control subjects in these studies.

Studies with mixed ethnic samples have predominantly been negative. However, prior studies that included subjects from multiple populations—a design that can to lead to population stratification artifact—have not optimally controlled for stratification effects. In our study, ancestry proportion scores were generated and included as a covariate in all analyses to prevent spurious associations that can result from variation in allele frequency by population (19). This method allows systematic testing of ethnicity effects without loss of power, which results when ethnic groups are analyzed separately, and characterizes biracial subjects more correctly in terms of ancestry.

The primary goal of this study was to examine in a sample with significant numbers of both "high-" and "low"-risk subjects the G×E interaction between *MAOA* genotype and maltreatment in the development of antisocial symptomatology, including aggression and rule-breaking behavior. The cohort included boys and girls of diverse ethnic backgrounds, but subpopulation differences in allele frequency were systematically controlled. Consistent with the original report by Caspi (1), it was hypothesized that children exposed to trauma with "low-activity" *MAOA* alleles would exhibit more antisocial behavior than nonmaltreated control subjects and children exposed to trauma with "high-activity" *MAOA* alleles. Given the finding by Kim-Cohen (12) suggesting that problems with inattention may represent a developmentally earlier phenotype that could develop into antisocial personality disorder, we also examined inattention.

Methods and Materials

Sample

Participants included 114 children: 73 children who were removed from their parents' care within the past 6 months because of reports of abuse or neglect (or both), and 41 community control subjects demographically matched for low socioeconomic status, with no history of maltreatment or exposure to intrafamilial violence. This sample represents a subset of children included in our prior study examining genetic and environmental predictors of depression (20), with this subsample restricted to children with teacher ratings of aggression (80% of the sample) and female subjects homozygous for *MAOA* genotype. As is depicted in Table 1, several prior reports included women who are heterozygous for *MAOA*, although it is unclear whether the *MAOA* gene escapes X-inactivation, as has been postulated (21). It is therefore impossible to determine what proportion of each allele is expressed in heterozygous females, which is why they were not included in this report.

Inclusion and exclusion criteria, recruitment, and consent procedures are detailed elsewhere (20). Children ranged in age from 5 to 15 years ($\chi^2 = 9.7$, SD = 2.7), with five being the lower age limit when conduct symptoms are reported to first appear

(22). The sample had more male subjects (66%) because heterozygous females were excluded. Twenty-four percent of subjects were European American (EA), 25% Hispanic, 31% African American (AA), and 19% biracial. Maltreated and control groups did not differ in terms of age ($t = -1.27$, $df = 112$, ns), sex ($\chi^2 = .7$, $df = 1$, ns), or ethnicity ($\chi^2 = 5.2$, $df = 4$, ns). The 114 children were from 85 families with various numbers of siblings and half-siblings (range: 1–4) in each family, with a comparable number of siblings included in the study in both of the groups ($F = 1.6$, ns, Maltreated: 1.6 ± .7; Control: 1.8 ± 1.0).

Procedures

Yale University Human Investigations Committee and DCF Institutional Review Board approved this investigation. Ratings of children's behaviors were obtained from children's school teachers, and DNA specimens were collected at a day camp devised specifically for our research purposes, as described previously (20,23).

Measures

Total Trauma Exposure Score (TTES). Multiple informants and data sources were used to obtain a best estimate of children's trauma history (24). An index of total trauma exposure was created for all subjects. Experiences assessed included the following: physical abuse, sexual abuse, domestic violence exposure, multiple out-of-home placements, and community violence exposure. Each adversity was rated on a 0–2 point scale and summed to create the TTES (see Table 2). In general, scores of 0 indicate the child was not exposed to this experience, scores of 1 indicate mild or subthreshold experiences, and scores of 2 indicate clinically significant experiences—experiences of sufficient severity to warrant state intervention. Measures reviewed to derive the TTES for maltreated and control children included the following: state child protective service records, the Child Trauma Questionnaire (25), the Partner Violence Inventory (26), and the posttraumatic stress disorder (PTSD) trauma screen from the psychiatric interview administered in this study (27). The TTES scales are the same as the 0- to 4-point Child Maltreatment Rating Scales we previously published (24), but given that the control subjects were also being rated with these scales, the scoring criteria were limited to 0–2 points to accommodate the restricted range of scores in the control subjects. These rating scales have good predictive and discriminant validity and interrater reliability (intraclass correlation mean: .91, range: .84–.97).

Aggressive Behaviors. Achenbach Teacher's Report Form (TRF) (28) was used as the primary outcome measure. TRF is widely used in clinical and research settings and has excellent psychometric properties (29). Scores derived from the TRF include the aggression (e.g., "gets in many fights"), rule breaking (e.g., "truancy"; "steals outside the home"), and inattention (e.g., "can't concentrate") subscale scores. TRF raw scores are converted to *t* scores normed by age and sex, and the published norms have been validated for use in children of various ethnicities. Scores on these measures were significantly intercorrelated with correlations ranging from .59 to .67. The proportion of children above the clinical range (a score > 63) on the aggression, rule breaking, and inattention subscales were 36%, 32%, and 30%, respectively.

Psychiatric Diagnoses. As previously described (30), a number of standardized parent- and child-report questionnaires and a semistructured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children (27), were used to generate child psychiatric diagnoses. Maltreated children were significantly more likely than control subjects to meet criteria for any psychiatric diagnosis (64% vs. 32%, $p = .001$), PTSD (47% vs. 0%, Fisher's Exact = 50.4, $p < .001$), major depression (MDD; 10% vs. 0%, Fisher's Exact = 4.2, $p < .05$), and any depressive diagnoses (32% vs.12%, Fisher's Exact 5.3, $p < .02$). Although maltreated children were more likely than control subjects to meet criteria for conduct disorder (7% vs. 0%) and oppositional defiant disorder (8% vs. 5%), these differences were not statistically significant within the sample of subjects included in this report. Eighteen percent of the sample met criteria for attention-deficit/hyperactivity disorder (ADHD), and there were no differences in rates of this diagnosis in the two groups.

DNA Specimens. Saliva was collected for DNA extraction using Puregene (Gentra, Minneapolis, Minnesota) kits as previously described (20).

***MAOA* Promoter Genetic Variation.** The 5′ promoter region of the *MAOA* gene was genotyped by polymerase chain reaction followed by size fractionation, similar to the method described by Sabol (4). Eight percent of subjects were regenotyped for quality control with complete concordance. The *MAOA* polymorphism consists of 30-bp repeated sequence presented in 2, 3, 3.5, 4, or 5 copies (4). Sabol (4) found that alleles with 3.5 and 4 copies of the repeat sequence were transcribed more efficiently than those with 3 or 5 copies of the repeat; Deckert (5) found that all longer alleles (3.5, 4, and 5 repeats) were transcribed more efficiently than the 3-repeat allele. This discrepancy in findings has resulted in variations in the definition of genetic risk among

Table 2. Trauma Exposure in Maltreated Children and Control Subjects

	Maltreated Children		Control Children	
	1	2	1	2
Physical Abuse	16%	6%	27%	—
Sexual Abuse	12%	18%	2.4%	—
Domestic Violence	8%	74%	59%	—
Multiple Out-of-Home Placements	67%	33%	—	—
Exposure to Community Violence	26%	8%	20%	—
Mean of Total Trauma Exposure Score	5.2 ± 1.8 (Range: 2–9)		1.1 ± .8 (Range: 0–3)	

Scoring criteria: physical abuse rating—1 = excessive physical discipline (e.g., hit with object, no bruising); 2 = physical abuse with bruising or more serious injury; sexual abuse—1 = exposure to pornography or peer-related sexual misconduct; 2 = sexual abuse with an adult of sufficient severity to warrant criminal or protective services intervention; domestic violence—1 = frequent intense verbal arguments, throw objects at one another; 2 = more serious domestic disputes (e.g, hit other, use weapons, injury); multiple foster placements—1 = first placement in year prior to study entry; 2 = two or more placements before study entry; community violence—1 = gunshots heard in neighborhood, witness serious physical fight; 2 = witness shooting, death, or serious injury of another.

studies. Only one child in the sample had the 5-repeat allele, and the pattern of findings were comparable whether or not this child was included and whether or not the 5-repeat allele was assigned as "low" or "high" activity. Therefore, in our study, 2, 3, and 5 repeat alleles were classified as "low activity," and 3.5 and 4 repeat alleles as "high activity."

Ancestral Proportion Scores. Subjects' ancestries were estimated using a set of unlinked genetic markers by Bayesian cluster analysis, using procedures and software developed by Pritchard (31,32) (http://pritch.bsd.uchicago.edu/software.html). Procedures for determining ancestral proportion scores have been detailed elsewhere (33,34).

Statistical Analyses

In predicting children's scores, to take into account within-group correlations, generalized estimating equations (GEE) were used to model the effects of risk while handling familial correlations between subjects resulting from the inclusion of siblings in the sample. Ancestral proportion scores were entered as a covariate in all models and retained regardless of significance given its relevance in interpreting study results (34). Effects of age and sex were also examined, but these variables were not significant as expected, because the outcome measures are normed by age and sex. Before conducting GEE, distribution of outcome measures (TRF scores) was examined for normality using the Shapiro-Wilks test. Because the measures were non-normally distributed and standard transformations failed to correct distributions, rank transformed scores were used in subsequent analyses. Main effects of *MAOA* genotype (e.g., "low activity" vs. "high activity") and the continuous trauma exposure measure (TTES), as well as the interaction of these two factors, were explored, and Bonferroni tests were performed to control for multiple comparisons in examining outcomes on the three primary measures. Analyses conducted using the categorical classification of subjects (e.g., maltreated vs. control) produced comparable results, but the G×E interactions were easier to interpret using the continuous trauma measure, so these analyses are presented.

Results

Allele Frequencies

Forty-three percent of the sample had the "low-activity" genotype, and 57% had the "high-activity" genotype. There were no statistically significant differences in terms of genotype (classified by functional expression group) between maltreated children and control subjects (χ^2 = .8, *df* = 1, ns) or between children of different ethnicities (χ^2 = 1.6 *df* = 4; ns).

TTES

Table 2 depicts the prevalence of each of the experiences included in the TTES for maltreated and control children. Many of the low-SES control children experienced mild trauma (e.g., excessive discipline, exposure to mild domestic and community violence) but were markedly less traumatized than the maltreated children. Among control subjects, 30% had no exposure to trauma, 44% met criterion for one mild experience of trauma, 24% met criteria for two mild experiences of trauma, and 2% met criteria for three mild experiences of trauma, as detailed in Table 2. The TTES was significantly correlated with children's aggression (rho = .26, $p < .005$), rule breaking (rho = .40, $p < .001$), and inattention (rho = .21, $p < .03$) problems. Age correlated with TTES scores (F = .2; p = .01); the older children were, the more trauma they had. Trauma scores were comparable for boys and girls (F = .12; ns).

Each experience contributing to the TTES also independently correlated with the outcome measures. Children's aggression scores were significantly correlated with ratings of physical abuse (rho = .24, $p < .05$) and out-of-home placement history (rho = .30, $p < .001$). Children's rule-breaking scores correlated significantly with ratings of physical abuse (rho = .33, $p < .005$), sexual abuse (rho = .27, $p < .005$), domestic violence (rho = .27, $p < .005$), out-of-home placements (rho = .32, $p < .005$), and community violence exposure (rho = .19, $p < .05$); and children's inattention scores correlated significantly with sexual abuse ratings (rho = .21, $p < .03$) and showed trends toward significant correlations with all the other measures except domestic violence.

Predicting Externalizing Behaviors: *MAOA* Genotype × Total Trauma Exposure Score

Results of the GEE analyses are depicted in Figure 1 and Table 3. Ancestry proportion scores significantly predicted children's aggression (χ^2 = 11.5; p = .0007) and rule breaking (χ^2 = 4.6; p = .03) scores, TTES was also a significant predictor of aggression (χ^2 = 4.7; p = .03) and rule breaking (χ2 = 14.3; p = .0002), and *MAOA* genotype (χ2 = 3.8; p = .05) and *MAOA* genotype in interaction with TTES (χ^2 = 6.2; p = .01) predicted

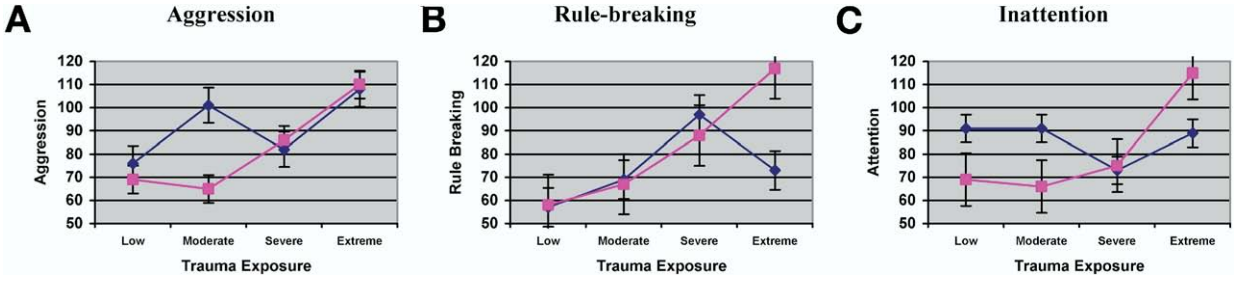

Figure 1. The low-activity *MAOA* gene (blue) was associated with increased aggression in the low to moderate range on the Trauma Exposure index. With Trauma Exposure Scores greater than this, genotype made no difference in children's aggression scores **(A)**. In predicting rule-breaking scores, only the Trauma Exposure Index was a significant predictor of children's scores, with greater adversity associated with more rule-breaking behavior, regardless of genotype **(B)**. There was a main effect for genotype and a *G×E* interaction in predicting children's inattention scores. Overall, higher inattention scores were associated with the low-activity version of the *MAOA* gene. At low to moderate levels of Trauma Exposure, higher inattention scores were associated with the low-activity version of the gene. At the most extreme level of Trauma Exposure, both genotypes were associated with high inattention scores, with the greatest scores observed in children with the high-activity *MAOA* gene **(C)**. Analyses were conducted using the continuous Trauma Exposure scale. For illustrative purposes, children were grouped into low (N=30), moderate (n=14), severe (N=42), and extreme (N=28) categories, but analyses were conducted using the full TTES range of scores (0–9).

Table 3. Results of Generalized Estimating Equation Analysis Examining the Effect of Total Trauma Exposure Score and *MAOA* Genotype on Externalizing Behaviors ($n = 114$) (WALD Type 3 Statistic)

	df	Parameter Estimate	Standard Error	χ^2	*p* Value
Aggression					
Ancestral Proportion Score	1	37.9	11.1	11.5	.007[a]
TTES	1	5.9	2.1	4.7	.03
MAOA	1	13.9	15.0	0.9	ns
MAOA × TTES	1	−4.4	3.2	1.9	ns
Rule-breaking					
Ancestral Proportion Score	1	−22.8	10.6	4.6	.03
TTES	1	9.0	2.0	14.3	.0002[a]
MAOA	1	12.2	14.4	0.7	ns
MAOA × Total Trauma Exposure Score	1	−5.3	3.4	2.4	ns
Inattention					
Ancestral Proportion Score	1	−22.1	11.8	3.5	.06
TTES	1	7.6	2.3	2.3	ns
MAOA	1	31.6	16.1	3.9	.05
MAOA × Total Trauma Exposure Score	1	−9.5	3.8	6.2	.01[a]

MAOA, monoamine oxidase-A; TTES, Total Trauma Exposure Score.
[a]Results significant after controlling for multiple Bonferroni correction.

inattention. After controlling for multiple comparisons using Bonferroni corrections, ancestry proportion scores in predicting aggression, TTES in predicting rule breaking and the G×E interaction of *MAOA* genotype and TTES in predicting inattention remained significant.

As depicted in Figure 1, *MAOA-L* was associated with increased inattention for children with low or moderate trauma exposure, and *MAOA-H* was associated with increased inattention for children with extreme histories of trauma. Approximately 20% of the cohort met diagnostic criteria for ADHD, with comparable rates for children in the low, moderate, severe, and extreme trauma exposure categories (Kendall's tau-b = –.25, ns). In contrast, none of the children in the low to moderate trauma exposure range, 33% in the severe range, and 71% in the extreme trauma exposure range met diagnostic criteria for PTSD (Kendall's tau-b = 11.6, $p < .001$). Children in the severe and extreme trauma exposure range were also more likely to meet criteria for MDD (Kendall's tau-b = 2.6, $p < .01$) or any depressive diagnosis (Kendall's tau-b = 2.4, $p < .02$). Elevated inattention scores were associated with each of these diagnoses: ADHD ($F = 11.8$, $p < .001$), PTSD ($F = 4.4$, $p < .04$), and depression ($F = 3.4$, $p < .05$).

Exploratory Analysis

The graph of the aggression data suggests that *MAOA-L* was associated with increased aggression scores for children with moderate trauma histories, but that *MAOA* genotype had little effect for children with extreme trauma experiences (Figure 1). To test this hypothesis, an exploratory GEE analyses was conducted examining the effect of trauma exposure and genotype for children with low to moderate trauma histories (e.g., scores 0–2) and proposing no effect of genotype for children with more severe trauma exposure (e.g., scores ≥ 3). In the moderate trauma range, 25% of the children had a history of verified maltreatment and removal from home. The analysis used the whole sample to estimate the model. For children with trauma scores below the threshold (TTES < 3), the main effects and interaction term were estimated. When an individual child's trauma score exceeded the threshold, the model converted the effect of *MAOA* genotype and the G×E interaction term to zero.

Results of this exploratory analysis ($n = 114$) were consistent with this hypothesis. Ancestral proportion scores were still significant in the model ($\chi^2 = 12.2$, $p < .001$), as were TTES ($\chi^2 = 5.6$, $p < .02$) and the G×E interaction term when it was only calculated for children with low to moderate trauma exposure ($\chi^2 = 3.8$, $p < .05$).

Minority Analyses

The above exploratory GEE analyses was tested in African American and biracial subjects ($n = 58$). Consistent with the results reported earlier, ancestral proportion scores ($\chi^2 = 19.3$, $p < .001$), TTES ($\chi^2 = 9.3$, $p < .005$), and the G×E interaction term ($\chi^2 = 7.8$, $p < .006$) were significant predictors of aggression.

Discussion

This study examined the G×E interaction of *MAOA* genotype and maltreatment in predicting risk for aggression, rule breaking, and inattention in children of different racial backgrounds. The children in our study represent the extreme on a continuum of adversity and were assessed at a time of extreme stress—shortly after removal from their parents' care due to abuse or neglect. The interaction between *MAOA-L* and adversity held up to moderate levels of trauma exposure, with the maltreated children with moderate level of trauma in our study roughly comparable in terms of maltreatment experiences to the subjects living with birth families with definite maltreatment in the Caspi study. However, *MAOA-L* did not contribute to explaining variability in children's aggression scores at extreme levels of trauma. The children with the most severe traumatic experiences had high aggression scores, regardless of *MAOA* genotype.

These findings held when controlling for ethnic variation within the entire sample and when examining a subset of minority subjects. Failure to use appropriate statistical approaches (e.g., ancestral proportion scores) to control for ethnicity effects in prior investigations, and instead relying on separate analyses with reduced power for each population group, may have accounted for the failure to detect this association in some prior investigations with racially heterogeneous samples.

When examining children's rule-breaking scores, we did not find a significant G×E interaction between *MAOA* genotype and TTES. Most other published studies examining this G×E interac-

tion in children did not examine aggression and rule breaking as separate entities and instead looked at either conduct disorder or delinquency, which include elements of both aggression and rule breaking. To date, there is no consistent pattern of findings in the literature regarding the relationship among adversity, *MAOA* genotype, and rule-breaking behavior in children.

When examining inattention, we found an interaction between *MAOA* genotype and children's trauma experiences, with *MAOA-L* associated with increased inattention at low and moderate levels of trauma exposure, and *MAOA-H* was associated with increased inattention at extreme levels of trauma. Approximately 20% of the cohort met criteria for ADHD, with comparable numbers of children in the low, moderate, severe, and extreme trauma groups meeting criteria for this diagnosis. Studies looking at main effects of *MAOA* genotype in conferring risk for ADHD have been mixed. Some studies found an association between *MAOA-L* and ADHD symptoms (35,36), whereas others found the opposite (37,38); to the best of our knowledge, no study except the investigation by Kim-Cohen (12) reported a G×E effect with *MAOA-L* conferring vulnerability for inattention in maltreated children.

In this study, as noted earlier, for the children with the most extreme trauma exposure, it was *MAOA-H* that was associated with inattention. More than 70% of the children in this group met criteria for PTSD, with diagnoses of depression also overrepresented in children with the most severe trauma histories. *MAOA-H* has been associated with MDD in some (39,40), but not all (41), studies. If the inattention associated with low to moderate histories of trauma exposure is associated with a different diagnostic profile than inattention associated with more extreme histories of trauma exposure, one might not expect the same genes to confer risk for inattention in both groups.

Studies examining G×E interactions in the prediction of depression have been notably more consistent than studies examining G×E interactions in the prediction of aggression and related phenotypes. Although the diagnosis of depression is frequently comorbid with a range of diagnoses, the symptom of depression is not included in the diagnostic criteria for any other psychiatric disorder. This is in sharp contrast to the symptoms of aggression and inattention, which are included in the diagnostic criteria for multiple behavioral, mood, and anxiety disorders. Integrating dimensional and categorical diagnostic approaches may lead to more refined phenotypes for investigation in future studies.

The use of neuroimaging assays is another means to obtain more refined phenotypes or endophenotypes in genetics studies. For example, in three independent investigations, variation in *MAOA* genotype has been found to relate to anterior cingulate cortex (ACC) activation during completion of tasks assessing impulsivity (42–44). Variation in *MAOA* activity has also been found to be associated with activation in more dorsal regions of ACC in functional neuroimaging paradigms that assess sensitivity to social rejection (45). The ACC is a central locus of information processing and regulation in the brain (46), and these preliminary studies suggest two possible mechanisms by which *MAOA-L* may confer risk for aggressive behavior.

Several caveats and limitations of our study warrant mention. First, findings are based on cross-sectional analyses. Second, aggression ratings were based on a one-time assessment by a single informant (e.g., teachers). In addition, results are based on a relatively small number of subjects. Although power to detect associations was enhanced because the sample was enriched for maltreatment and psychopathology, independent replication in a comparably traumatized cohort is warranted.

Conclusions

Variability in prior research findings is best understood by inadequate power to detect G×E associations, due to the low base rates of maltreatment and antisocial symptoms in most of the investigations that failed to replicate this association. Our investigation is consistent with the findings of Caspi *et al.* (1) and suggests that problems in aggression in maltreated children are moderated by *MAOA* genotype—but only up to moderate levels of trauma exposure.

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