MAOA Genotype, Childhood Maltreatment, and Their Interaction in the Etiology of Adult Antisocial Behaviors

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Background: Maltreatment by an adult or caregiver during childhood is a prevalent and important predictor of antisocial behaviors in adulthood. A functional promoter polymorphism in the monoamine oxidase A (*MAOA*) gene has been implicated as a moderating factor in the relationship between childhood maltreatment and antisocial behaviors. Although there have been numerous attempts at replicating this observation, results remain inconclusive.

Methods: We examined this gene–environment interaction hypothesis in a sample of 3356 white and 960 black men (aged 24–34) participating in the National Longitudinal Study of Adolescent Health.

Results: Primary analysis indicated that childhood maltreatment was a significant risk factor for later behaviors that violate rules and the rights of others ($p < .05$), there were no main effects of *MAOA* genotype, and *MAOA* genotype was not a significant moderator of the relationship between maltreatment and antisocial behaviors in our white sample. Post hoc analyses identified a similar pattern of results among our black sample in which maltreatment was not a significant predictor of antisocial behavior. Post hoc analyses also revealed a main effect of *MAOA* genotype on having a disposition toward violence in both samples and for violent convictions among our black sample. None of these post hoc findings, however, survived correction for multiple testing ($p > .05$). Power analyses indicated that these results were not due to insufficient statistical power.

Conclusions: We could not confirm the hypothesis that *MAOA* genotype moderates the relationship between childhood maltreatment and adult antisocial behaviors.

Key Words: Add Health, antisocial behavior, depression, gene–environment interaction, maltreatment, *MAOA*

Positive and negative experiences early in life can have a profound and wide-ranging effect on functioning and well-being in adulthood. In particular, those who experience abuse or neglect in childhood are at high risk for psychiatric illnesses, substance use disorders, and violent and criminal behaviors later in adolescence and adulthood (1–8). Despite the consistency of this finding across community and clinical samples, some children with a history of maltreatment show resilience to the development of these problems. Although the number of episodes, duration, and timing of maltreatment has been suggested to play a role in this heterogeneity (9–12), biological factors have also been hypothesized. Biologically, childhood maltreatment has been shown to promote, among other things, changes in brain structure, atypical development of the hypothalamic-pituitary-adrenal axis, as well as elevated neurotransmitter levels (13–16).

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In 2002, Caspi and colleagues (17) proposed that functional differences in the monoamine oxidase A (*MAOA*) gene could moderate the long-term relationship between maltreatment during childhood and adult conduct and antisocial behavioral problems. The *MAOA* messenger RNA is encoded by a single gene consisting of 15 exons that give rise to two splice variants, both of which code for a 527 amino acid protein, and has been mapped to chromosome Xp11.23-Xp11 (18–20). Transcription of *MAOA* is moderated by two regulatory motifs, one of which is a 30-base pair (bp) variable number tandem repeat (VNTR) polymorphism in the promoter region of the gene (21,22). Population rates of the 30-bp VNTR indicate the 3-repeat (3R) and 4-repeat (4R) alleles are the most prevalent, although prevalence varied by race/ethnicity. In gene fusion and transfection assays, basal transcription rates were determined to be 2-10 times more efficient in the presence of the 4R ("high-activity") than the 2R or 3R ("low-activity") alleles (23–26).

In a test of their gene–environment interaction hypothesis, Caspi *et al.* (17) reported that males with a history of maltreatment before age 12 and the low-activity *MAOA* genotype were at a higher risk for adult conduct and antisocial-related behavioral problems than those with the high-activity *MAOA* genotype. Since this report, there have been many attempted replications, with mixed results: some studies have reported a replication (7,27–33) of the Caspi findings (17), but others have either not demonstrated a successful replication or have conversely implicated the high-activity *MAOA* genotype as a risk factor (34–38). Differences in phenotypic definitions, study populations, and the reduced statistical power accompanying small sample sizes are all potential contributors to this pattern of findings. Two meta-analyses (39,40), however, did find support for the gene–environment hypothesis of Caspi *et al.* (17). Effect sizes from existing meta-analyses and other single-sample studies (28,32,39,40) are similar, demonstrating small to moderate effects ranging between .14

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and .18, but these estimates are considerably lower than the .29 reported by Caspi *et al.* (17).

Authors of the current study previously examined the hypothesized gene–environment interaction reported by Caspi *et al.* (17) in the sibling-pairs subsample ($n = 2612$) of National Longitudinal Study of Adolescent Health (Add Health), finding a similar pattern of results to those originally reported, although formal tests of the interaction were not significant (28). Here, we detail findings from a similar study in the full Add Health sample ($n = 15{,}701$), which recently completed DNA collection. We first tested whether the low-activity *MAOA* VNTR genotype is a risk factor for later antisocial behaviors among males with and without a history of childhood maltreatment. All decisions about the operationalization of phenotypes, environmental measures, and methods of analysis were made strictly before conducting this primary replication test. In a post hoc manner we tested the role *MAOA* genotype in moderating the impact of maltreatment on four additional measures similar to the approach taken by Caspi *et al.* (17). Lastly, we conducted additional post hoc analyses in a sample of black men with and without a history of childhood maltreatment.

Methods and Materials

Subjects

Add Health is a nationally representative, probability-based survey of adolescents in the United States, who were aged 12 to 19 years in the 1994–1995 school year when the study began. A detailed description of the study design and sampling strategy used is available elsewhere (41,42). Participants for the current study were drawn from the full sample at Wave IV (2008–2009). Among white and black participants in the full sample, the mean age was 29.15 (± 1.73, range: 24–34) and 29.09 (± 1.81, range: 24–34). To ensure that the current study was a new independent replication study, we did not include members of the previously analyzed (28) sibling-pairs sample.

Assessment

Composite Antisocial Index: Conduction Problems, Antisocial Behavior, Violent Convictions, Disposition Toward Violence. Conduct problems during adolescence and young adulthood were assessed using responses to 11 questions, each asked during interviews at Wave I (1994–1995), Wave II (1996), and Wave III (2001–2002). Questions assessed the frequency of fighting, theft, use of a weapon, delinquency, and violence. Endorsement of an item as "happening one or two times" was given a score of 1, and endorsement of "more than twice" was given a score of 2. A summed conduct measure was created for each wave of data, and then the mean across all three waves was taken.

Adult antisocial behavior was assessed using 11 questions asked at Wave IV (2008). They included whether participants had engaged in fighting, theft and robbery, or property damage or had been involved with a gang. Responses indicating that they had engaged in these behaviors "one or two times" were scored as 1, and responses of "two or more times" were scored as a 2. The scores were then summed across all items.

Convictions for violent offenses after the age of 18 years were assessed using four questions at Wave IV. They included robbery with a weapon, forcible rape, aggravated assault or murder, or simple assault. Participants were classified as having an adult conviction (0/1) for any conviction after age 18.

Four items from the Mini-International Personality Item Pool (43) were used to assess a disposition toward violence. Anger, irritability, and temper were assessed by the questions: "I get angry easily," "I rarely get irritated," "I keep my cool," and "I lose my temper." Responses were scored on a 5-point Likert scale and ranged from "strongly agree" (1) to "strongly disagree" (5). These four items were then summed into an anger hostility scale, with "I get angry easily" and "I lose my temper" reverse coded for consistency.

The composite antisocial index (CASI) was created from the adolescence conduct problems, adult antisocial behavior, adult violent convictions, and disposition toward violence scales. Participants were assigned 1 point for each of the following indicators: an adolescent conduct problem score greater than 3.9, any antisocial behavior reported, any adult violent conviction, and a disposition toward violence score greater than 12. Therefore, the CASI ranged from 0 (no antisocial behavior) to 4. A comparison of the CASI variables and those examined by Caspi *et al.* (17) are presented in Table S1 in Supplement 1.

Childhood Maltreatment. Maltreatment occurring before entry into sixth grade (before age 12) was assessed by retrospective self-reports using a six-item questionnaire administered during Wave IV. Maltreatment questions included sexual, physical, and emotional abuse and the ages at which they occurred. Sexual abuse was assessed with the question "How often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?" Physical abuse was assessed with the question "Before your 18th birthday, how often did a parent or a caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down stairs?" Emotional abuse was assessed with the question "Before your 18th birthday, how often did a parent or other adult caregiver say things to you that really hurt your feelings or made you feel like you were not wanted or loved?" Follow-up questions determined the age abuse first occurred. For the purposes of the current study, any positive response to an item was scored as an item endorsement, such that the extent of maltreatment experienced equaled the total number of endorsed items. Scores on the resulting maltreatment scale could therefore range between 0 and 3. Similar to Caspi *et al.* (17), scores of 2 or more were collapsed together. A comparison of the maltreatment variables and those examined by Caspi *et al.* (17) are presented in Table S1 in Supplement 1.

Genotyping. The 30 bp *MAOA* VNTR polymorphism was characterized from genomic DNA collected and isolated using the Oragene system (DNAgenotek, Ottawa, Canada). Allele or repeat sizes ranged from 2R (291 bp) to 5R (381 bp), with the most common being the 3R (321 bp) and 4R (351 bp) alleles. Similar to Caspi *et al.* (17), the 2R and 3R alleles were combined into a single low-activity *MAOA* genotype, and the 3.5R, 4R, and 5R alleles were combined into a high-activity group. Genotyping method and primer sets used are detailed elsewhere (28).

Statistical Analysis

Regression models predicting adult antisocial behavior were as follows: Antisocial behavior = b0 + b1(*MAOA*) + b2(Childhood Maltreatment) + b3(*MAOA* × Maltreatment), where b0 is the intercept, b1 is the regression coefficient associated with the influence of *MAOA* genotype status (coded as 1 for high-activity *MAOA* functioning and 0 for low-activity *MAOA* functioning), b2 is the regression coefficient associated with the influence of childhood maltreatment (coded as 0 = "no maltreatment," 1 = "probable maltreatment," 2+ = "severe maltreatment"), b3 is

the coefficient associated with the interaction effect that is the product of *MAOA* genotype and maltreatment status. A logistic regression model was used when analyzing the binary dependent variable adult violent convictions. All analyses took into account the sampling design of Add Health. Independent (maltreatment, *MAOA* genotype) and dependent (adolescent and adult antisocial behavior, convictions, and disposition toward violence) variables were developed independently, and the analyses were planned and reviewed by a panel of six investigators before testing to minimize "fishing expeditions" through the data.

Statistical power was calculated using a Monte Carlo approach and implemented in SAS Version 9.2 (SAS, Cary, North Carolina). Simulations were based on the estimated model and actual data that were manipulated so that the main effects of maltreatment were held constant while the variance accounted for by the interaction term in the model was set to a desired level. A random error term was also included so that the simulated results were normally distributed around the expected values. Our statistical power was determined by testing different scenarios in which the effect size of the interaction was set to different levels and then determining how many times out of 10,000 iterations a significant result was found.

Results

We examined the gene–environment hypothesis in separate samples of white and black young adult men, who participated in Wave IV (2008–2009) of Add Health. The mean age was 29.2 (± 1.73, range: 24–34) and 29.1 (± 1.81, range: 24–34) years, respectively. In these samples, allele and genotype frequencies differed by race/ethnicity (Table 1). Among rare alleles (<.05), the 3.5R and 5R were more frequent in the white sample whereas the 2R was more frequent in the black sample. As a consequence, the low-activity *MAOA* genotype was less frequent among whites than the high-activity genotype, whereas in blacks, the pattern is the opposite.

The majority of the white sample reported experiencing no maltreatment before age 12 (81.8%, $n = 2917$); 10.3% ($n = 368$) reported "probable maltreatment"; and 7.9% ($n = 282$) reported "severe maltreatment." Prevalence rates were similar in the black sample, with 81.5% ($n = 843$) reporting no maltreatment, 10.5% ($n = 109$) reporting "probable maltreatment," and 8.0% ($n = 83$) reporting "severe maltreatment." *MAOA* genotypes did not differ between maltreatment groups ($\chi^2_2 = .97$, $p = .61$), indicating that exposure to maltreatment was independent of genotype status.

Our CASI variable was constructed using identical assessments of adolescent conduct problems across three waves of data collection, adult antisocial behavior, convictions for a violent crime, and a disposition toward violence. Intercorrelations between these four outcome measures were highly significant ($p < .001$) and ranged from .12 and .24 in both the white and black samples. In the white sample, 66.0% ($n = 2365$) scored a zero on our composite index, 25.6% ($n = 918$) had a score of 1, 7.01% ($n = 253$) had a score of 2, and 1.3% (n = 46) scored a 3. Among black men, 64.7% ($n = 681$) scored a zero on the CASI, 27.0% ($n = 284$) had a score of 1, 6.8% ($n = 71$) had a score of 2, and 1.5% ($n = 16$) scored a 3. Our CASI variable was significantly predicted by maltreatment status among whites ($b = .10$, $F = 39.04$, $df = 3566$, $p < .0001$) and blacks ($b = .15$, $F = 23.38$, $df = 1034$, $p < .0001$). Mean CASI scores did not differ by *MAOA* genotype (not shown) and indicated that adult antisocial behavior is independent of *MAOA* genotype.

Our regression analyses were designed to replicate the gene–environment interaction hypothesis tested by Caspi *et al.* (17). We began by examining among white men whether the risk for adult antisocial behavior increased as a function of having experienced maltreatment before age 12. As the severity of maltreatment increased, antisocial behavior also increased (Figure 1A; $b = .24$, SE = .07, $t = 3.40$, $p < .001$, 95% confidence interval [CI]: .10–.39). There was no main effect of *MAOA* genotype ($b = -.06$, SE = .04, $t = 1.48$, $p = .14$, 95% CI: −.02 to .14). The formal test of whether *MAOA* genotype moderated the association between maltreatment and antisocial behavior ($b = -.13$, SE = .08, $t = -1.67$, $p = .10$, 95% CI: −.29 to .02, partial $R^2 = .000015$) did not support the original hypothesis offered by Caspi *et al.* (17). Power analyses indicated that our sample size was large enough to have 80% power to detect an effect size (partial R^2) as small as .001138, suggesting our results are not due to insufficient statistical power (Figure 1B), However if the real effect size is as small as we detected, we would not have had the power to establish it as significant.

Post Hoc Analyses

Similar to Caspi *et al.* (17), we conducted analyses that examined whether *MAOA* genotype status moderated the relationship between childhood maltreatment and the four outcome measures included in the CASI. Results from weighted regression analyses indicated that maltreatment was a significant predictor of each outcome measure (Table 2). For all but a disposition toward violence ($p = .006$, 95% CI: .15–.87), there were no main effects of *MAOA* genotype, and tests of the interaction between *MAOA* genotype and maltreatment in each of our four dependent variables were nonsignificant. Interaction terms for both adult violent convictions and disposition toward violence trended towards significance. However, following correction for multiple testing, all p values were nonsignificant ($p > .05$).

We further tested the gene–environment interaction hypothesis by Caspi and colleagues (17) in a sample of black male participants in Add Health. In weighted regression analyses (Figure 1C), childhood maltreatment did not significantly predict our CASI outcome measure ($b = .15$, SE = .16, $t = .96$, $p = .34$, 95% CI: −.16 to .47). Furthermore, there were no main effects of *MAOA* genotype ($b = -.03$, SE = .10, $t = -.37$, $p = .71$, 95% CI: −.23 to .16) or a significant interaction between *MAOA* genotype and maltreatment ($b = -.15$, SE = .20, $t = -.76$, $p = .45$, 95% CI: −.55 to .25; partial $R^2 = .000967$). Similarly, maltreatment did not significantly predict any of our four dependent variables that comprised the CASI (Table 3). Except for adult violent convictions ($p = .006$, 95% CI: −.11 to −.02; Table 3), there were no main effects of *MAOA* genotype and tests of the interaction of *MAOA* genotype and maltreatment were not significant. Power analyses indicated that our sample size ($n = 960$) was large enough to have 80% power to detect an effect size as small as .004, suggesting our results are not

Table 1. *MAOA* Variable Number Tandem Repeat Allele and Genotype Frequencies in White ($n = 3356$) and Black ($n = 960$) Male Subjects

MAOA	Allele Frequencies, *n* (%)		Genotype Frequencies, *n* (%)	
Repeat	White Subjects	Black Subjects	White Subjects	Black Subjects
2	10 (0.03)	46 (4.79)	—	—
3	1151 (34.3)	490 (51.04)	1161 (34.59)	536 (55.83)
3.5	52 (1.55)	1 (0.01)	—	—
4	2100 (62.6)	416 (43.33)	2195 (65.41)	424 (44.17)
5	43 (1.28)	7 (0.73)	—	—

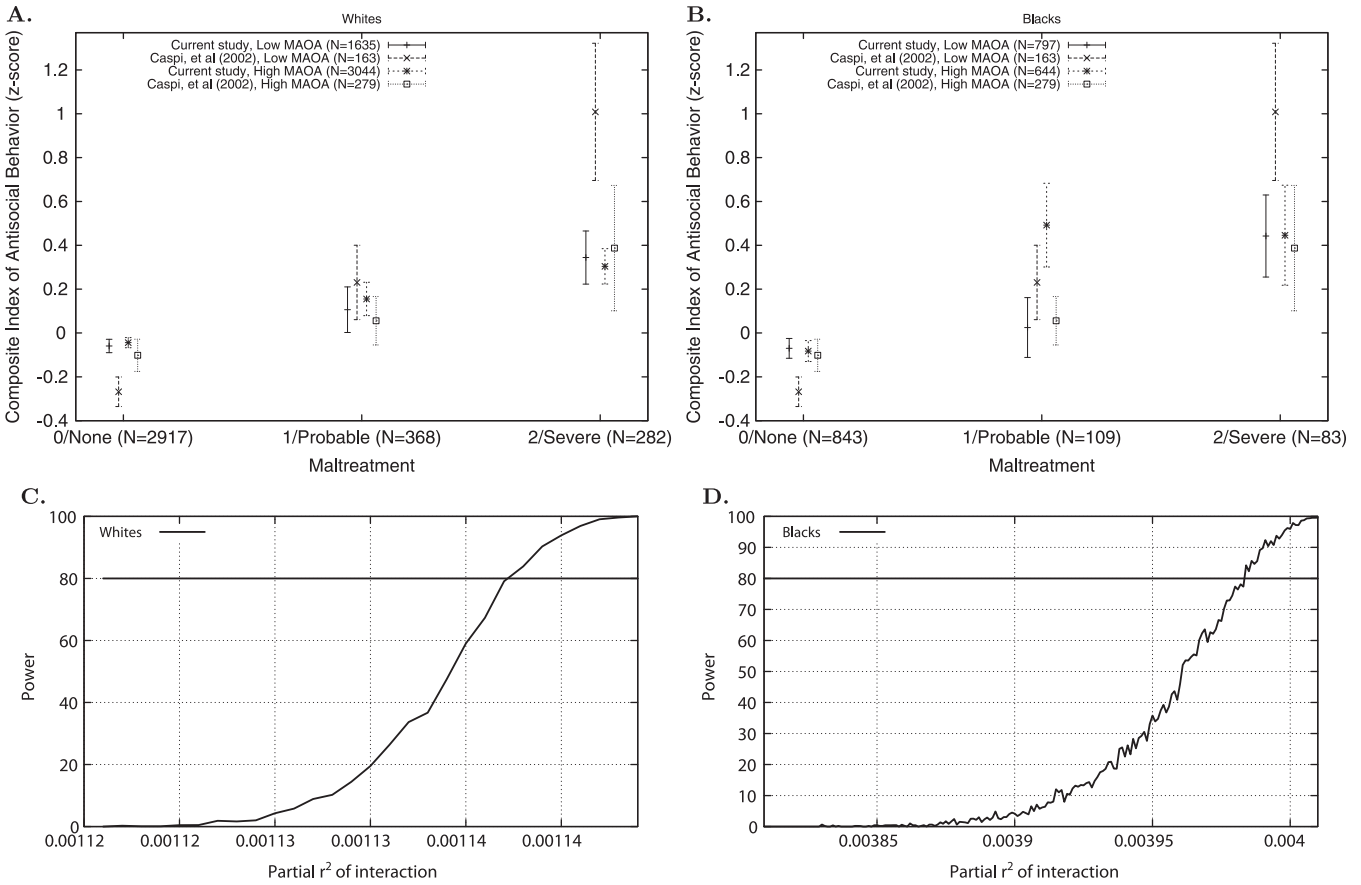

Figure 1. Mean levels (*z* scored) of antisocial behavior as a function of maltreatment status and *MAOA* genotype for **(A)** white and **(B)** black participants. For each of the three maltreatment groups, standard errors around the mean indicate that means did not differ significantly by *MAOA* genotype. Points have been offset slightly from each other for readability purposes but are centered around the appropriate tick marks. Means and standard errors were provided by Caspi *et al.* (17) (personal communication, 2004). Increasing statistical power is shown graphically as a function of the gene–environment interaction effect size (partial R^2) for **(C)** white and **(D)** black samples. From Haberstick BC, Lessem JM, Hopfer CJ, *et al.* "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. Reprinted with permission of Wiley-Blackwell.

due to insufficient statistical power (Figure 1D). However, if the real effect size is as small as we detected, we would not have had the power to establish it as significant.

Lastly, we examined the gene–environment interaction hypothesis offered by Caspi *et al.* (17) using a maltreatment index from self-reports at Wave III (28). Although similar, that index also included visits or removal from the home by social services and thus may have provided a better approximation of "severe maltreatment." Substituting that Wave III maltreatment index for the one examined here did not change the obtained nonsignificant results. Furthermore, we examined the concordance between Waves III and IV of self-reported maltreatment before age 12 in our white and black samples; 453 (9.1%) and 158 (10.2%) were discordant for self-reported maltreatment, respectively. Results from reanalyzing the data following the removal of those with inconsistent reports were also nonsignificant.

Table 2. Standardized Parameter Estimates and Significance Statistics: White Male Subjects[a]

	Childhood Maltreatment				*MAOA* Genotype				Interaction				
	b	SE	*t*/*z*[b]	*p*	*b*	SE	*t*/*z*	*p*	*b*	SE	*t*/*z*	*p*	R^2
1	.54	.21	2.61	.0100	−.01	.09	−.07	.94	−.19	.23	−.82	.42	.02
2	.60	.25	2.43	.0165	.07	.07	1.03	.31	−.32	.25	−1.26	.21	.03
3	.06	.03	2.10	.0376	.00	.01	.49	.62	−.05	.03	−1.56	.12	—
4	.77	.23	3.28	.001	.51	.18	2.81	.01	−.47	.28	−1.71	.09	.01

Outcome: 1, adolescent conduct problems; 2, adult antisocial behavior; 3, convictions for violent crimes; 4, disposition toward violence.

[a]Values presented are from weighted regression analyses.

[b]χ^2 values are reported instead of *t*/*z* values for logistic regression.

Table 3. Standardized Parameter Estimates and Significance Statistics: Male Subjects[a]

	Childhood Maltreatment				*MAOA* Genotype				Interaction				
	b	SE	*t*/*z*[b]	*p*	*b*	SE	*t*/*z*	*p*	*b*	SE	*t*/*z*	*p*	R^2
1	.44	.31	1.43	.15	.02	.35	.08	.94	−.42	.45	−.94	.35	.01
2	.20	.17	1.19	.24	.10	.21	.49	.63	.02	.34	.07	.94	.01
3	.01	.05	.23	.82	−.06	.02	−2.82	.01	−.01	.05	−.25	.80	—
4	.12	.43	.28	.78	−.63	.36	−1.72	.09	.01	.66	.02	.98	.01

Outcome: 1, adolescent conduct problems; 2, adult antisocial behavior; 3, convictions for violent crimes; 4, disposition toward violence.

[a]Values presented are from weighted regression analyses.

[b]χ^2 values are reported instead of *t*/*z* values for logistic regression.

Discussion

In this report, we detail results from an attempted replication of the gene–environment interaction hypothesis that the low-activity *MAOA* genotype moderates the long-term relationship between childhood maltreatment and later antisocial behavior. To this end, we examined responses from white male participants in Add Health. In this sample, maltreatment prior before age 12 was a strong predictor of adolescent conduct disorder, adult antisocial behavior, adult violent convictions, and a disposition toward violence. Furthermore, other than for a disposition toward violence, there were no main effects of *MAOA* genotype on any of these outcomes or the CASI, suggesting that in the absence of childhood maltreatment, *MAOA* genotype was not a risk factor for these behavioral problems. Formal tests of the gene–environment interaction with our composite antisocial index and component behavioral problems were nonsignificant.

Results from our analyses did not support the original gene–environment interaction hypothesis that the *MAOA* VNTR promoter polymorphism moderates the relationship between childhood maltreatment and adult antisocial behaviors. Among whites, results indicated that adult antisocial behaviors, as measured by the CASI, were similar across genotype status in absence of maltreatment and indicated that carriers of the low-activity *MAOA* VNTR genotype were at no higher risk for antisocial behaviors than those with the high-activity genotype. As the occurrence and severity of maltreatment increased, so did behaviors that violated rules and the rights of others. This was most evident among the subset of respondents who experienced severe maltreatment, for which samples sizes were the smallest, although still larger than those examined by Caspi *et al.* (17). The increased sample sizes in our study afforded enough statistical power to detect an effect size, if present, as small as .001. This suggests that previous replications in smaller samples (27,29,30,32,33,37,38) could be false-positives and underscores the potential difficulty of detecting gene–environment interactions involving common genetic variants (44,45).

In the black sample, we also did not replicate the gene–environment interaction hypothesis by Caspi *et al.* (17) despite having sufficient statistical power. Although observed a similar pattern of increasing antisocial behaviors as the severity of maltreatment increased, the results were not significant among blacks. This weakening of the relationship between maltreatment and various problem behaviors among blacks has been observed previously in Add Health (2) and has been attributed to underlying differences in sociodemographic risks and characteristics among blacks compared with whites. Compared with our white sample, we observed a higher frequency of the low-activity *MAOA* genotype that includes the 2R and 3R alleles. Notably, there were substantial frequency differences by race in the 2R *MAOA* VNTR allele, which has been associated with delinquent behavior in an ethnically diverse subsample of Add Health participants (25). Although our results could be interpreted to suggest a main effect of the low-activity *MAOA* genotype on adult violent convictions and a disposition toward violence, they are more probably false-positives given the number of statistical tests conducted and should be interpreted with caution until replicated.

Despite a robust sample size, measures and analysis strategy similar to those used by Caspi *et al.* (17), there are a number of limitations to our study. First, unlike Caspi *et al.* (17), we were not able to include measures of early family functioning or third-party observations in our measures of maltreatment and antisocial behavior, respectively. Second, reports of childhood maltreatment were retrospective. Distorted memories and recall bias are potential problems with retrospective reports (46–49) and may have influenced our data. However, the inclusion of similar questions at an earlier assessment, as done in Wave III, offered a means through which to validate Wave IV retrospective reports and assess the heterogeneity that would reduce our statistical power. Third, our analyses focused only on white and black male subjects. Because differences in antisocial behaviors and the frequency of maltreatment vary by race/ethnicity and socioeconomic factors (50,51), our results may not generalize to other groups. Finally, genetic heterogeneity in the neighborhood of the *MAOA* promoter VNTR (21) as well as across the genomic landscape may influence the levels of *MAOA* functioning used to create the genotype groups examined here.

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