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MAOA GENOTYPE, CHILDHOOD MALTREATMENT, AND THEIR INTERACTION IN THE ETIOLOGY OF ADULT ANTISOCIAL BEHAVIORS

Brett C. Haberstick[1], **Jeffrey M. Lessem**[1], **John K. Hewitt**[1], **Andrew Smolen**[1], **Christian J. Hopfer**[2], **Carolyn T. Halpern**[4], **Ley A. Killeya-Jones**[4], **Jason D. Boardman**[5], **Joyce Tabor**[4], **Ilene C. Siegler**[6], **Redford B. Williams**[6], and **Kathleen Mullan Harris**[3]

[1]Institute for Behavioral Genetics, University of Colorado, Boulder, Boulder, Colorado, USA

[2]Department of Psychiatry, Health Sciences Center, University of Colorado, Denver, Colorado, USA

[3]Department of Sociology and Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina, USA

[4]Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina, USA

[5]Institute of Behavioral Science, University of Colorado at Boulder, Boulder, Colorado, USA

[6]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA

Abstract

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 males (ages 24 to 34) participating in the National Longitudinal Study of Adolescent Health (Add Health).

Results—Primary analysis indicated that childhood maltreatment was a significant risk factor for later behaviors that violate rules and the rights of others ($p < 0.05$), 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, where, maltreatment was not a significant predictor of antisocial behavior. Post-hoc analyses also revealed a main effect of MAOA genotype on having a disposition towards violence in both samples and for violent convictions among our

Corresponding Author: Brett C. Haberstick, Institute for Behavioral Genetics, University of Colorado, Boulder, Campus Box 447, Boulder, Colorado 80309-0447, Telephone: 303-735-5388, Fax: 303-492-8063, Brett.Haberstick@Colorado.edu.

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Black sample. None of these post-hoc findings, though, survived correction for multiple testing ($p > 0.05$). Power analyses indicated that these results were not due to insufficient statistical power.

Discussion—We could not confirm the hypothesis that MAOA genotype moderates the relationship between childhood maltreatment and adult antisocial behaviors.

Keywords

Maltreatment; Antisocial Behavior; MAOA; Add Health; Gene-Environment Interaction; Depression

Introduction

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 (HPA) axis, as well as elevated neurotransmitter levels [13–16].

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 mRNA 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, though, 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 prior to 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, though with mixed results: some studies have reported a replication [7, 27 – 33] of the Caspi findings [17], while 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, do 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 0.14 and 0.18, but these estimates are considerably lower than the 0.29 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 sub-sample (n = 2612) of 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 = 15701], 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 males with and without a history of childhood maltreatment.

Materials & Methods

Subjects

Add Health is a nationally representative, probability-based survey of adolescents in the United States, who were aged 12–19 years in the 1994–1995 school year, when the study began. A detailed description of the study design and sampling strategy utilized is available elsewhere [41, 42]. Participants for the current study were drawn from the full sample at Wave IV (2008–2009). Among Whites and Blacks 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 (CASI) – Conduction problems, Antisocial behavior, Violent convictions, Disposition towards 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 while 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 a 1 while 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-IPIP [43] were used to assess a disposition towards 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 five-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 towards violence scales. Participants were assigned one 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 towards 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 the Supplement.

Childhood Maltreatment—Maltreatment occurring before entry into sixth grade (prior to 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 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 "B*efore 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 hose examined by Caspi et al [17] are presented in Table S1 in the Supplement.

Genotyping—The 30 base-pair (bp) MAOA VNTR polymorphism was characterized from genomic DNA collected and isolated using the Oragene system (DNAgenotek, Ottawa, Ontario, 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 while 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(MAOAxMaltreatment)*, 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 towards violence) variables were developed independently, and the analyses were planned and reviewed by a panel of six investigators prior to testing in order to minimize 'fishing expeditions' through the data.

Statistical power was calculated using a Monte Carlo approach and implemented in SAS Version 9.3. 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 10000 iterations a significant result was found.

Results

We examined the gene-environment hypothesis in separate samples of White and Black young adult males, 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 (< 0.05) the 3.5R and 5R were more frequent in the White sample while 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 while in Blacks, the pattern is the opposite.

The majority of the White male sample reported experiencing no maltreatment prior to 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 (χ^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 towards violence. Inter-correlations between these four outcome measures were highly significant (p < 0.001) and ranged from 0.12 and 0.24 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 males, 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 = 0.10, F = 39.04, df = 3566, p < 0.0001) and Blacks (b = 0.15, F = 23.38, df = 1034, p < 0.0001). 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 males whether the risk for adult antisocial behavior increased as a function of having experienced maltreatment prior to age 12. As the severity of maltreatment increased, antisocial behavior also increased (Figure 1A; b = 0.24, S.E. = 0.07, t = 3.40, p < 0.001, 95% confidence interval, CI: 0.10 – 0.39). There was no main effect of MAOA genotype (b = −0.06, S.E. = 0.04, t = 1.48, p = 0.14, 95% CI: −0.02 – 0.14). The formal test of whether MAOA genotype moderated the association between maltreatment and antisocial behavior (b = −0.13, S.E. = 0.08, t = −1.67, p = 0.10, 95% CI: −0.29 – 0.02, partial r^2 = 0.000015) 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 0.001138, 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 towards violence ($p = 0.006$, 95% CI: 0.15 to 0.87), 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 non-significant. Interaction terms for both adult violent convictions and disposition towards violence trended towards significance. However, following correction for multiple testing, all p-values were non-significant ($p > 0.05$).

We further tested the gene-environment interaction hypothesis by Caspi and colleagues [17] in a sample of Black males participating in Add Health. In weighted regression analyses (Figure 1C), childhood maltreatment did not significantly predict our CASI outcome measure ($b = 0.15$, S.E. = 0.16, $t = 0.96$, $p = 0.34$, 95% CI: −0.16 – 0.47). Further, there were no main effects of MAOA genotype ($b = -0.03$, S.E. = 0.10, $t = -0.37$, $p = 0.71$, 95% CI: −0.23 – 0.16) or a significant interaction between MAOA genotype and maltreatment ($b = -0.15$, S.E. = 0.20, $t = -0.76$, $p = 0.45$, 95% CI: −0.55 – 0.25; partial r2 = 0.000967). Similarly, maltreatment did not significantly predict any of our four dependent variables that comprised the CASI (Table 3). Except for adult violent convictions ($p = 0.006$, 95% CI: −0.11 to −0.02; 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 0.004, suggesting our results are not 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). Though similar, that index also included visits and/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 non-significant results. Further, we examined the concordance between Waves III and IV of self-reported maltreatment prior to age 12 in our White and Black samples. A total of 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 non-significant.

Discussion

In the current 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 males participating in Add Health. In this sample, maltreatment prior to age 12 was a strong predictor of adolescent conduct disorder, adult antisocial behavior, adult violent convictions, and a disposition towards violence. Further, other than for a disposition towards 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 non-significant.

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, where samples sizes were the smallest, though 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 0.001. 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 as compared to Whites. In comparison 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 sub-sample 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 towards 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 utilized 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 by 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 males. As 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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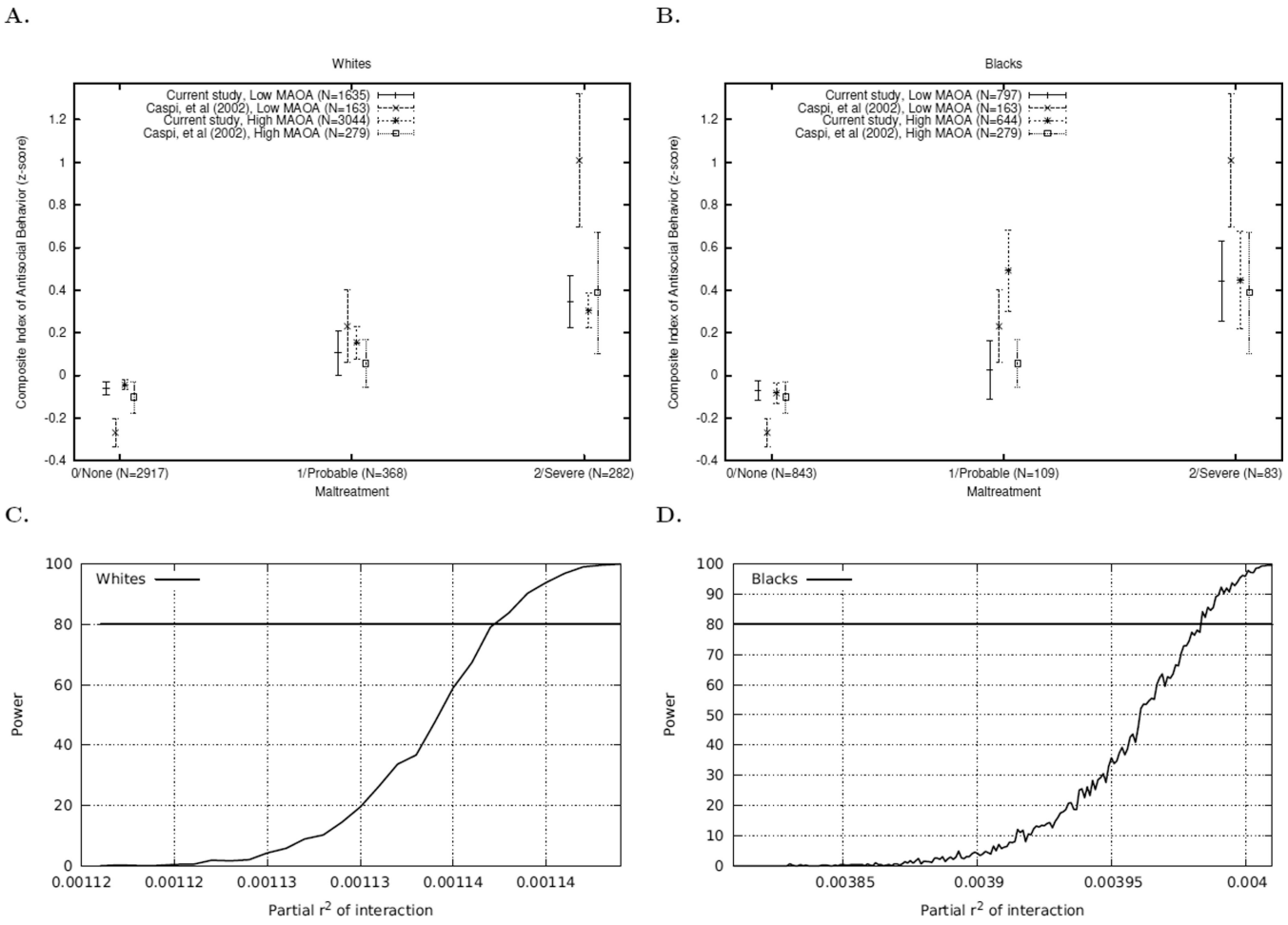

Figure 1.

A & B. Mean levels (z-scored) of antisocial behavior as a function of maltreatment status and MAOA genotype for Whites (**Figure A**) and Blacks (**Figure B**). 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 deviations kindly provided by Caspi et al [17] (personal communication, 2004). **Figures C and D** graphically show increasing statistical power as a function of the gene-environment interaction effect size (partial r2) for White (**Figure C**) and Black (**Figure D**) samples.

Table 1

Monoamine Oxidase A (MAOA-VNTR) Allele and Genotype Frequencies in White (n = 3356) and Black Males (n = 960).

	Allele Frequencies, n (%)		Genotype Frequencies, n (%)	
MAOA Repeat	White Males	Black Males	White Males	Black Males
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)	--	--

Table 2

Standardized Parameter Estimates and Significance Statistics - White Males. ‡

	Childhood Maltreatment				MAOA genotype				Interaction				
	b	**SE**	***t/z*†**	***p***	***b***	**SE**	***t/z***	***p***	***b***	**SE**	***t/z***	***p***	**R^2**
1	0.54	0.21	2.61	.0100	−0.01	0.09	−0.07	0.94	−0.19	0.23	−0.82	0.42	0.02
2	0.60	0.25	2.43	.0165	0.07	0.07	1.03	0.31	−0.32	0.25	−1.26	0.21	0.03
3	0.06	0.03	2.10	.0376	0.00	0.01	0.49	0.62	−0.05	0.03	−1.56	0.12	--
4	0.77	0.23	3.28	0.001	0.51	0.18	2.81	0.01	−0.47	0.28	−1.71	0.09	0.01

Note: Outcome: (1) Adolescent conduct problems; (2) Adult antisocial behavior; (3) Convictions for violent crimes; (4) Disposition towards violence. SE, Standard Error.

‡Values presented are from weighted regression analyses.

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

Table 3

Standardized Parameter Estimates and Significance Statistics – Black Males. ‡

	Childhood Maltreatment				MAOA genotype				Interaction				
	b	**SE**	***t/z*†**	***p***	***b***	**SE**	***t/z***	***p***	***b***	**SE**	***t/z***	***p***	**R^2**
1	0.44	0.31	1.43	0.15	0.02	0.35	0.08	0.94	−0.42	0.45	−0.94	0.35	0.01
2	0.20	0.17	1.19	0.24	0.10	0.21	0.49	0.63	0.02	0.34	0.07	0.94	0.01
3	0.01	0.05	0.23	0.82	−0.06	0.02	−2.82	0.01	−0.01	0.05	−0.25	0.80	--
4	0.12	0.43	0.28	0.78	−0.63	0.36	−1.72	0.09	0.01	0.66	0.02	0.98	0.01

Note: Outcome: (1) Adolescent conduct disorder; (2) Adult antisocial behavior; (3) Convictions for violent crimes; (4) Disposition towards violence.

‡Values presented are from weighted regression analyses.

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