Brief Research Communication
No Evidence for Interaction Between MAOA and Childhood Adversity for Antisocial Behavior
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Previous reports have identified an interaction between an MAOA promoter polymorphism and childhood adversity for antisocial behavioral outcomes in males. This study attempted to replicate this finding in an Australian community survey of 1,002 Caucasian men aged 20–24 years. Greater childhood adversity was associated with later antisocial behavior, but no association was observed between MAOA genotype and antisocial behavior, and no interaction was found between childhood adversity and MAOA genotype for antisocial behavior. This study does not support previous reports of an interaction between MAOA genotype and childhood adversity for antisocial behavior in males. © 2007 Wiley-Liss, Inc.

KEY WORDS: antisocial; genetic; interaction


INTRODUCTION

Evidence for gene by environment interactions in the etiology of antisocial behavior comes mainly from adoption and twin studies [MoFitt, 2005; Raine et al., 2005]. Adopted children with a biological vulnerability to both antisocial behavior (i.e., biological parent(s) with a history of antisocial personality disorder or alcoholism) and an unstable adoptive environment (i.e., adoptive parents with mental disorder, marital, legal, and/or substance abuse problems) have been found to be at increased risk for antisocial behavior compared to children having biological vulnerability or environmental risk alone, or neither risk factor [Cloninger et al., 1982; Sigvardsson et al., 1982; Cadoret et al., 1983, 1995].

The specific genes moderating vulnerability to antisocial behavior in the presence of environmental risk factors have yet to be identified. The most promising candidate gene to date is MAOA. Caspi and colleagues [2002] first reported an interaction between a promoter polymorphism within MAOA and the experience of childhood maltreatment for antisocial behavior in young men. In this sample, males with the low activity (short) form of the MAOA polymorphism were more likely than those with the high activity (long) MAOA genotype to exhibit antisocial behavior if exposed to childhood maltreatment.

Several groups have attempted to replicate this finding in different samples but with mixed results [Foley et al., 2004; Haberstick et al., 2005; Huizinga et al., 2006; Kim-Cohen et al., 2006; Nilsson et al., 2006; Widom and Bronstowicz, 2006; Young et al., 2006]. A summary of the methodology and results of each study is given in Table I. All studies reported a significant association between childhood adversity and antisocial behavior. With one exception [Kim-Cohen et al., 2006], none of these studies found a direct association of MAOA genotype with antisocial behavior. Four studies replicated the original study for the interaction between MAOA genotype and childhood adversity for antisocial behavior in Caucasian males. Three studies failed to replicate the interaction.

Kim-Cohen and colleagues also undertook a meta-analysis that included five of the studies mentioned here, four of which reported positive interactions between MAOA and childhood adversity for problem behavior. The authors omitted one study [Young et al., 2006] that failed to replicate the result, citing sample differences as the reason for the omission. The meta-analysis concluded that the interaction was statistically significant ($P < 0.001$). However, the small number of studies included and exclusion of studies reporting negative findings suggests further attempts at replication in larger samples are desirable. For this reason, the current study sought to contribute to the literature about the replicability of the original finding and to do so in a large, representative community sample.

MATERIALS AND METHODS

The research involved participants in the 20+ age cohort of the PATH Through Life Project, a large Australian longitudinal study of three age cohorts that commenced in 1999. The participants were drawn from the Australian Electoral Roll, where enrolment is compulsory for all Australians over 18. For the 20+ age cohort, the response rate was 58.6%. The participants are mostly Caucasian (92%), aged 20–24 years at first contact, and are to be followed up every 4 years over a period of 20 years. Although the sample is derived mainly from the Australian Capital Territory, which is a population of higher mean educational attainment, the pattern and level of psychological distress observed in PATH participants was similar to reports for other populations. Further information about sampling [Parslow et al., 2004] and characterization of the participants in terms of psychological functioning [Jorm et al., 2004, 2005] have been described elsewhere. For this age group, cheek swab DNA samples and two waves of data have been collected. The analyses reported here are based on the first wave of interviews. The Australian National University Human Research Ethics Committee approved this study, and informed consent was obtained from all participants.

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### TABLE I. Comparison of Published Studies Testing for Interaction Between Childhood Adversity and MAOA Genotype

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample characteristics</th>
<th>Measurement of antisocial behavior</th>
<th>Measurement of childhood adversity</th>
<th>Categories of childhood adversity</th>
<th>Analysis methodology</th>
<th>Summary of results*</th>
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</thead>
<tbody>
<tr>
<td>Caspi et al. [2002]</td>
<td><strong>N = 442 males; age = mid twenties; longitudinal study</strong></td>
<td>DSM-IV criteria for conduct disorder; court records of violent convictions; disposition for violence by interview; informant reports of antisocial personality disorder (ASPD) symptoms; composite index of four measures above</td>
<td>Observations of mother-child interactions; parent report of adversity; retrospective self-report</td>
<td>No adversity (68%); probable adversity (28%); definite adversity (8%)</td>
<td>Linear regression for continuous variables; logistic regression for binary variables</td>
<td>Effect of MAOA genotype: NS; effect of childhood maltreatment: (P &lt; 0.001); interaction effect: composite index gave significant interaction (P = 0.01). Those with the short MAOA genotype were more likely to exhibit antisocial behavior when exposed to childhood adversity than those with the long genotype</td>
</tr>
<tr>
<td>Foley et al. [2004]</td>
<td><strong>N = 514 male twins; Caucasians; age = adolescents</strong></td>
<td>Child and parent report of conduct disorder by interview</td>
<td>Parent report (by interview); participant report (by interview)</td>
<td>No adversity (71%); probable adversity (25.5%); definite adversity (3.5%)</td>
<td>Logistic regression</td>
<td>Effect of MAOA genotype: NS; effect of childhood adversity: (P = 0.001); interaction effect: when grouping for childhood adversity levels, interaction was not significant. When childhood adversity raw scores used, interaction significant (P = 0.04)</td>
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<tr>
<td>Nilsson et al. [2006]</td>
<td><strong>N = 81 males; Caucasians; age = adolescents</strong></td>
<td>Self-report of stealing, vandalism, and violence; composite index combining three measures above</td>
<td>Self-report questionnaire; taped interview</td>
<td>Multi-family residence (28%); single-family residence (74%); violent victimization (14%); no violent victimization (6%)</td>
<td>Linear regression; non-parametric test based on aligned ranks</td>
<td>Effect of MAOA genotype: NS; effect of victimization: maltreatment/victimization (P = 0.001); low status residence: (P = 0.013); interaction effect: significant interaction when measuring adversity by type of residence (P = 0.006) and violent victimization (P = 0.03) using linear regression. Non-parametric tests also gave significant interaction</td>
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<tr>
<td>Widom and Brzustowicz [2006]</td>
<td><strong>N = 268, 176 white males, 92 non-white males; age = 49; case-control childhood abuse prospective study</strong></td>
<td>Official arrest information; self-report of violent behavior; clinical assessment of conduct disorder ASPD symptoms by interview; composite measures of “juvenile” (up to age 18) and “lifetime” (up to and beyond age 18) antisocial behavior (ASB)</td>
<td>Court records of maltreatment cases featuring physical abuse, sexual abuse, or neglect</td>
<td>History of abuse (57%); no history of abuse (43%)</td>
<td>Linear regression</td>
<td>Whites: effect of MAOA genotype: NS; effect of abuse: juvenile ASB (P &lt; 0.01), lifetime ASB (P = 0.01); interaction effect: significant interaction for juvenile ASB (P &lt; 0.01), lifetime ASB (P = NS). Non-whites: effects of MAOA genotype: NS; effect of abuse: NS; interaction effect: interaction was not significant; note: no association between abuse/neglect and juvenile or lifetime ASB</td>
</tr>
<tr>
<td>Haberstick et al. [2005]</td>
<td><strong>N = 774 males; Caucasians; age = adolescents; longitudinal study</strong></td>
<td>Assessment of frequency of fighting, violence, delinquency, and conviction for violent offense by interview. Composite index created from measures above</td>
<td>Retrospective self-report of childhood and adolescent adversity assessed separately</td>
<td>No childhood maltreatment (76.1%); one childhood maltreatment (18.6%); &gt; 1 childhood maltreatment (5.3%); no adolescent victimization (60.7%); one to two adolescent victimizations (14.2%); &gt; 2 adolescent victimizations (14.2%)</td>
<td>Linear regression for continuous variables; logistic regression for binary variable</td>
<td>Effect of MAOA genotype: NS; effect of childhood maltreatment: (P = 0.0001); adolescent victimization (P = 0.0001); interaction effect: NS</td>
</tr>
<tr>
<td>Young et al. [2006]</td>
<td><strong>N = 247 males; age = adolescents; clinical sample; parent report of conduct disorder</strong></td>
<td>Conduct disorder severity determined by lifetime count of conduct disorder symptoms assessed by interview and corrected for age</td>
<td>Self-report of neglect, verbal, physical, or sexual abuse by detailed interview. Abuse events summed and weighted to give a score for abuse</td>
<td>Adversity left as continuous variable</td>
<td>Linear regression</td>
<td>Effect of MAOA genotype: NS; effect of adversity: (P &lt; 0.01); interaction effect: NS</td>
</tr>
<tr>
<td>Huizinga et al. [2006]</td>
<td><strong>N = 277 males; Caucasians; age = 11–15 years; prospective study of problem behavior</strong></td>
<td>Self-report of antisocial and violent behavior; official arrest records; composite index of problem behavior</td>
<td>Self-report of victimization by interview</td>
<td>Victimization (9%); no victimization (91%)</td>
<td>Ordinary least squares regression for continuous variables; logistic regression for binary variables</td>
<td>Effect of MAOA genotype: NS; effect of maltreatment: (P &lt; 0.0005); interaction effect: NS</td>
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</table>
Some participants were not Caucasian or refused to give DNA samples, and some DNA samples were not of sufficient quality to allow for genotyping, hence 86% of males in the PATH sample (N = 1,002) were genotyped at the MAOA locus as part of a custom multiplex assay described previously [Prichard and Easteal, 2006]. Alleles were classified as either ‘‘short’’ (38%) or ‘‘long’’ (62%) according to previous classifications [Caspi et al., 2002]. Allele frequencies reported here were consistent with those previously reported in Caucasian male populations [Sabol et al., 1998].

Participants were asked about their childhood up to the age of 16 years. Six items covered lack of affection, nervous or emotional trouble, and drinking or other drug use in father or mother figures. Two items covered conflict in the household and parental divorce or separation. Eight items covered neglect, authoritarian upbringing, parental psychological abuse, the witnessing of physical or sexual abuse, parental physical abuse, physical punishment, and sexual abuse by a parent. One item covered childhood poverty or financial hardship. These items were summed to form a scale (Cronbach α = 0.76), as previously described [Rosenman and Rodgers, 2006]. Participants were grouped for their score on this scale (no adversity = 47.1%, one or two adversity exposures = 34.0%, >2 adversity exposures = 18.9%). In order to attempt replication of previous findings, responses were also categorized to approximately match adversity proportions reported previously [Foley et al., 2004; Haberstick et al., 2005] by grouping as follows; no or one adversity (65.1%), two to five adversities (27.7%), and >5 adversities (6.2%).

As there was no measure in the PATH study designed specifically to measure antisocial behavior, externalizing problems and antisocial behavior were assessed using established indicator variables. This follows from the work of McGue and Iacono [McGue and Iacono, 2005], who demonstrated, using a population-based longitudinal study of 1,252 males and females, that an early age (<15 years) of nicotine dependence, alcohol and substance abuse/dependence, police problems, and sexual intercourse all predicted externalizing psychopathology at age 20. Similar indicators of antisocial behavior were selected in the current study and included pseudo-maturity variables (early age of first sex (<15 years), early age of leaving home (<18 years), early age of living with partner (<18 years), and early age of childbirth (<18 years)), substance use/abuse variables (current smoking status, past hazardous/harmful drinking, early marijuana use (<16 years), frequent marijuana use (weekly or more)), and unstable lifestyle indicators (frequent financial problems, low educational attainment (<5 years of secondary school education), current unemployment, and problems with the police with a court appearance in the last 6 months). Indicators of an unstable lifestyle were selected on the basis of their similarity to items in the DSM-IV criteria for Antisocial Personality Disorder.

Factor analysis of these indicators coded as binary variables (present/absent) was undertaken using Mplus Version 3.12 [Muthén and Muthén, 2004]. This program is suitable for the factor analysis of binary data. All twelve indicators loaded substantially on a single factor (range of factor loadings: 0.30–0.83, median loading: 0.63), which provided a good fit to the data. Therefore, this measure was used to assess antisocial behavior in subsequent analyses. Participants’ score on this antisocial behavior measure were highly correlated with the unweighted sum of the original binary indicators of the trait (r = 0.88). There was no significant difference in mean scores for antisocial behavior between men who were genotyped and those who were not.

Two-way ANOVA models were fitted using the Statistical Package for the Social Sciences (SPSS, Version 12), to test MAOA genotype and childhood adversity exposure, main and interaction effects on antisocial behavior.
RESULTS

Results for tests of MAOA genotype and childhood adversity main and interaction effects are shown in Table II. The report of experiencing more than two childhood adversity exposures was associated with antisocial behavior, consistent with prior reports [Caspi et al., 2002; Haberstick et al., 2005]. There was no association between MAOA genotype and antisocial behavior, and interactions were not significant (Analysis 1).

When the analysis was repeated (Analysis 2) after re-coding childhood adversity exposures to give group proportions similar to those reported in prior literature, the results for the main effects were unchanged, although one interaction was significant. Specifically, individuals with the long MAOA genotype who were exposed to two to five adversities, scored significantly higher for antisocial behavior. While this interaction was statistically significant, the direction of the association was in the opposite direction to that originally reported. In the current study, the long rather than the short genotype conferred vulnerability to antisocial behavior in those exposed to childhood adversity (Fig. 1). In addition, the effect was only observed in the grouping with two to five adversity exposures. There was little evidence of an interaction effect for levels of adversity beyond five exposures.

DISCUSSION

This study fails to confirm previous findings of an interaction between the MAOA polymorphism genotyped here and childhood adversity for antisocial behavior in males [Caspi et al., 2002; Foley et al., 2004]. One significant interaction result was observed after re-grouping adversity categories. However, the risk genotype implicated was different to that originally reported. The current study observed that individuals with the long, rather than short MAOA genotype had significantly higher scores for antisocial behavior when reporting moderate levels of childhood adversity. Curiously, the interaction was not significant where individuals reported exposure to greater than five adversities, which is difficult to explain given that the exposure to greater than five adversities is a stronger predictor of antisocial behavior than exposure to between two and five adversities. It is possible that the interaction was detected at the moderate level of adversity exposure because there were more individuals in this group, and consequently there was a greater power to detect the interaction at this level of exposure.

Table II. ANOVA Models Testing MAOA Genotype and Exposure to Childhood Adversity Main and Interaction Effects on Antisocial Behavior

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOA genotype</td>
<td>–0.018</td>
<td>0.045</td>
<td>–0.391</td>
</tr>
<tr>
<td>Number of adversity exposures (1–2)</td>
<td>0.069</td>
<td>0.055</td>
<td>1.244</td>
</tr>
<tr>
<td>Number of adversity exposures (&gt;2)</td>
<td>0.204</td>
<td>0.067</td>
<td>3.059</td>
</tr>
<tr>
<td>MAOA genotype x adversity exposures (1–2)</td>
<td>0.016</td>
<td>0.070</td>
<td>0.230</td>
</tr>
<tr>
<td>MAOA genotype x adversity exposures (&gt;2)</td>
<td>0.160</td>
<td>0.085</td>
<td>1.894</td>
</tr>
</tbody>
</table>

Another possible reason for our different results may be that we aggregated both exposures to childhood adversity and antisocial behavior when gene action may be associated with only quite specific exposures or behaviors. In defense of this approach, our factor analysis and those of other researchers.

Although the use of different measures for antisocial behavior and childhood adversity may be considered to be a plausible reason for the failure to replicate, it does not explain why some studies that used less direct measures still managed to detect the interaction. For example, Nilsson and colleagues found a stronger interaction when using the distal childhood adversity measure of “type of residence” than the more proximal measure of “violent victimization.”

In addition, the status of some studies as replications of the original study of Caspi et al. is unclear. For example, Kim-Cohen et al. reported a replication of the interaction in a sample of boys. However, of the component scales that comprised the derived composite index for which the interaction was reported, only the interaction for the attention deficit hyperactivity disorder (ADHD) subscale was significant. The interaction for the antisocial behavior subscale was not. It is difficult to see how this can be considered a replication when the outcome phenotype indicated was ADHD, not antisocial behavior. Similarly, Foley et al. also reported a replication when using raw scores of childhood adversity but their results were not significant when using a similar scale of aggregated exposure to childhood adversity as that reported by Caspi et al.

Another possible reason for our different results may be that we used different measures for antisocial behavior and childhood adversity, it would be expected to be reasonably robust to the use of different instruments to measure the underlying socio-biological construct and to monotonic transformations of the variables concerned [Loftus, 1978]. Looking across studies, it is apparent that this is not the case, despite the fact that the current and all other studies have found significant associations between the measures of childhood adversity and antisocial behavior they have used.

MAOA and Childhood Adversity in Antisocial Behavior

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<th>Parameter Estimate</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOA genotype</td>
<td>–0.028</td>
<td>0.037</td>
<td>–0.747</td>
</tr>
<tr>
<td>Number of adversity exposures (2–5)</td>
<td>0.092</td>
<td>0.056</td>
<td>1.645</td>
</tr>
<tr>
<td>Number of adversity exposures (&gt;5)</td>
<td>0.316</td>
<td>0.117</td>
<td>2.713</td>
</tr>
<tr>
<td>MAOA genotype x adversity exposures (2–5)</td>
<td>0.168</td>
<td>0.071</td>
<td>2.367</td>
</tr>
<tr>
<td>MAOA genotype x adversity exposures (&gt;5)</td>
<td>0.123</td>
<td>0.158</td>
<td>0.781</td>
</tr>
</tbody>
</table>

aReference genotype: short (low activity), reference number of adversity exposures (0).

bReference genotype: short (low activity), reference number of adversity exposures (<2).

Kendler et al. 2005. This, however, still does not explain why the interaction direction was reversed.

There are several differences between the current study and those reporting different results. These include different approaches to measuring childhood adversity and antisocial behavior and the use of a different sample. However, it is difficult to see how these factors could be responsible for the failure to replicate, or indeed, reverse the direction of the interaction. If the effect of the short MAOA genotype on antisocial behavior is potentiated by exposure to childhood adversity, it would be expected to be reasonably robust to the use of different instruments to measure the underlying socio-biological construct and to monotonic transformations of the variables concerned [Loftus, 1978]. Looking across studies, it is apparent that this is not the case, despite the fact that the current and all other studies have found significant associations between the measures of childhood adversity and antisocial behavior they have used.
Fig. 1. Graph showing means and standard errors for antisocial behavior after categorizing childhood adversity level experienced to match proportions in each group reported in prior literature. A statistically significant interaction was observed, where individuals with the long MAOA genotype were more likely to exhibit antisocial behavior when exposed to two to five adversities when compared with those with the short MAOA genotype.

[Caspi et al., 2002; McGue and Iacono, 2005] have established the scalability of these indicators.

In conclusion, failure to replicate the interaction in a large, representative sample must raise some doubts about the robustness of this finding, given that it does not appear to generalize across samples. When more is known about the specific influence of the MAOA gene on behavioral traits, perhaps the pattern of results reported in the literature will be more readily interpreted.

ACKNOWLEDGMENTS

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REFERENCES


