

MAOA, abuse exposure and antisocial behaviour: 30-year longitudinal study

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Background

Recent studies have raised issues concerning the replicability of gene \times environment ($G \times E$) interactions involving the monoamine oxidase A (*MAOA*) gene in moderating the associations between abuse or maltreatment exposure and antisocial behaviour. This study attempted to replicate the findings in this area using a 30-year longitudinal study that has strong resemblance to the original research cohort.

Aims

To test the hypothesis that the presence of the low-activity *MAOA* genotype was associated with an increased response to abuse exposure.

Method

Participants were 398 males from the Christchurch Health and Development Study who had complete data on: *MAOA* promoter region variable number tandem repeat genotype; antisocial behaviour to age 30; and exposure to childhood sexual and physical abuse.

Results

Regression models were fitted to five antisocial behaviour outcomes (self-reported property offending; self-reported violent offending; convictions for property/violent offending; conduct problems; hostility) observed from age 16 to 30, using measures of childhood exposure to sexual and physical abuse. The analyses revealed consistent evidence of $G \times E$ interactions, with those having the low-activity *MAOA* variant and who were exposed to abuse in childhood being significantly more likely to report later offending, conduct problems and hostility. These interactions remained statistically significant after control for a range of potentially confounding factors. Findings for convictions data were somewhat weaker.

Conclusions

The present findings add to the evidence suggesting that there is a stable $G \times E$ interaction involving *MAOA*, abuse exposure and antisocial behaviour across the life course.

Declaration of interest

None.

In 2002, Caspi and colleagues published a paper examining the role of the monoamine oxidase A gene (*MAOA*) in the development of antisocial behaviours.¹ This research was motivated by earlier evidence suggesting that carriers of the low-activity variant of *MAOA* were an at-risk group for criminality and violence.^{2–4} Using data from the Dunedin Multidisciplinary Health and Development Study (DMHDS) Caspi *et al* were able to show consistent gene \times environment ($G \times E$) interactions between exposures to childhood maltreatment and *MAOA* genotype in the development of antisocial behaviours. Their findings showed that associations between childhood maltreatment and antisocial behaviour were modified by *MAOA*, with those having the low-activity variant being more responsive to the effects of maltreatment than the high-activity group.

These results attracted considerable interest and a number of attempts have been made to replicate the findings of this study.^{5–14} As has been the case with other research into $G \times E$ interactions in the area of psychosocial adjustment,^{15,16} findings have been mixed, with a number of studies confirming the original findings,^{10–13,15–22} other studies finding no interaction^{14,23–26} and some studies finding effects in the reverse direction, with some reversals being observed only among females.^{9,17,18,27} However, a meta-analysis of five studies reported by Kim-Cohen *et al*⁸ found evidence for a consistent $G \times E$ effect involving *MAOA* and child maltreatment. These conclusions were supported by a further meta-analysis of eight studies by Taylor and Kim-Cohen.¹⁵ Such findings raise important issues about the stability and replicability of $G \times E$ interactions. Specifically, it may be argued that failures to replicate $G \times E$ interactions across studies reflect between-study variations in research design and measurement methods rather than an absence of $G \times E$ interaction. Alternatively, failure

to replicate findings may reflect an absence of a stable $G \times E$ association.^{16,17}

In a previous paper¹⁸ we attempted to address issues of cross-study replication by using data from a study that has strong similarities to the DMHDS in terms of geographical region, research design and measurement methods to replicate and extend the findings of Caspi *et al*.¹⁹ In that analysis we examined the relationship between the serotonin transporter promoter polymorphism (5-HTTLPR), life stress and mental disorder. Despite extensive attempts to replicate the findings of Caspi *et al*, we were unable to locate a replicable $G \times E$ interaction between 5-HTTLPR and life stress. In this paper we extend the approach used in our earlier paper to examine the $G \times E$ interaction effects between *MAOA*, childhood maltreatment and the development of antisocial behaviour. The specific aims of this analysis were to examine the extent to which there is a stable $G \times E$ interaction between *MAOA*, childhood maltreatment and a series of measures of antisocial behaviour including: adolescent conduct disorder; self-reported crime in adolescence and adulthood; officially recorded convictions for offending; and self-reported hostility.

Method

Sample

The data were gathered during the course of the Christchurch Health and Development Study (CHDS). In this study a birth cohort of 1265 children born in the Christchurch (New Zealand) urban region in mid-1977 has been studied at birth, 4 months, 1 year and annually to age 16 years, and again at 18, 21, 25 and 30 years.^{20,21} Sample retention rates were high throughout the study

and at age 30 the study was still able to assess over 80% of the surviving cohort. All phases of the study were subject to ethical approval from the Canterbury Regional Health and Disability Ethics Committee, and all forms of data collection were subject to the signed consent of study participants. The present analysis is based on a sample of 398 male cohort members who were assessed on antisocial behaviour outcomes in late adolescence and early adulthood (ages 16–30 years) and who were successfully genotyped for *MAOA*. This sample represented 65% of the surviving cohort of males.

DNA preparation

Between the ages of 28 and 30, participants were asked to provide a peripheral blood sample for DNA analysis: 446 male participants agreed, with most (91%) providing a blood sample from which DNA was extracted using a sodium chloride precipitation procedure. For the remaining participants, saliva was collected using Oragene collection kits (DNA Genotek, Ottawa, Canada) and DNA was extracted according to the supplier's instructions.

MAOA genotyping

The polymerase chain reaction (PCR) was performed essentially as described by Sabol *et al.*²⁵ and Caspi *et al.*¹ Reactions were carried out on an Eppendorf MasterCycler-EP using the primers MAO APT1 (5'-ACAGCCTGACCGTGGAGAAG-3') and MAO APB1 (5'-GAACGGACGCTCCATTCGGA-3') (Invitrogen). The MAO APT1 was 5'-labelled with the FAM fluorophore. The PCR conditions were as follows: initial 2 min denaturing step at 95°C, followed by 35 cycles of 94°C for 30 s, 60°C for 30 s and 72°C for 40 s and a final extension phase of 72°C for 5 min. Reactions were performed in 10 µl volume using PCR buffer with 1.5 mM MgCl₂ (Roche), ~50 ng of genomic DNA, 500 nM of each primer, 200 µM of each dNTP (Fisher Biotec) and 0.5 units of Taq-TI (Fisher Biotec). The PCR products were assayed on an Applied Biosystems 3130xl genetic analyser, set to fragment analysis mode, using POP7 polymer (Applied Biosystems) and GeneScan 500 LIZ (Applied Biosystems) size standard. Results were analysed using GeneMapper v4.0 for Windows (Applied Biosystems). On the basis of this genotyping, 150 cohort members were classified as having the low-activity *MAOA* genotype (one individual had 2.5, the rest had 3 repeats) whereas 249 cohort members were classified as having the high-activity *MAOA* genotype (3.5, 4 or 5 repeats). The 'MAOA activity – allele repeat length' grouping was essentially as described and justified by Caspi *et al.*¹ It should be noted that additional analyses in which the nine male cohort members with five repeats were classified as the low-activity genotype¹ revealed the same pattern of results as those presented below.

Abuse exposure

The following measures were used to assess the extent of exposure to sexual/physical abuse during childhood. Preliminary analyses revealed no evidence of statistically significant genotype × abuse exposure interactions.

Childhood sexual abuse

Exposure to childhood sexual abuse was assessed on the basis of retrospective reports obtained at 18 and 21 years. Participants were questioned about their experience of a range of 15 abusive experiences prior to age 16 and, for each incident reported, further detail was gathered on the nature and context of the abuse.^{22,24} On the basis of this questioning participants were classified into four

groups reflecting the most severe form of abuse reported at either age: no childhood sexual abuse; non-contact childhood sexual abuse (for example indecent exposure, lewd or threatening sexual comments); contact childhood sexual abuse involving inappropriate touching of genital areas; attempted/completed sexual penetration.

Childhood physical abuse

Exposure to childhood physical abuse was assessed on the basis of retrospective reports obtained at 18 and 21 years of the extent to which the participant's parent(s) were reported to have used methods of physical punishment during childhood (<16 years).^{22,25} For the purposes of the present analysis participants were classified into three groups reflecting the severity of physical punishment experienced during childhood. These groups were: parents never or rarely used physical punishment; at least one parent regularly used physical punishment; at least one parent used frequent, severe or harsh physical punishment.

Exposure to significant childhood sexual abuse or childhood physical abuse

In order to create a measure of exposure to significant childhood sexual abuse and childhood physical abuse, cohort members who were exposed to either (a) any form of sexual abuse (non-contact or contact abuse) or (b) either regular or harsh/severe levels of physical punishment, were classified as having been exposed to significant childhood sexual abuse or childhood physical abuse. In addition, analyses were conducted using either the measure of 'any sexual abuse' or 'regular or harsh/severe physical punishment' individually (see below).

Interparental violence

In addition to the above, a measure of exposure to interparental violence was also used. This was assessed at age 18 using selected items from the Conflict Tactics Scale²⁷ to assess the extent to which the participant had witnessed incidents of interparental conflict and physical violence during childhood. These items were combined to form a scale measure reflecting the extent of interparental violence.²⁶

Antisocial behaviour outcomes

The following measures were used to assess antisocial behaviour outcomes during the period 16–30 years.

Self-reported property/violent offending, aged 16–30

At 18, 21, 25 and 30 years, respondents were questioned about their criminal behaviour since the previous assessment using an instrument based on the Self-Report Delinquency Inventory (SRDI)²⁸ supplemented by additional custom-written survey items. This information was used to derive count measures of the number of self-reported property and/or violent offences committed in each year from age 16 to 30. Property offences were defined to include theft, burglary, breaking and entering, vandalism, fire-setting and related offences; violent offences included assault, fighting, use of a weapon or threats of violence against a person. For the purposes of the present analyses, the number of offences committed in each year was summed over the period 16–30 years to create two overall scores reflecting the total number of property and violent offences. Total scores were truncated to a maximum of 100 to avoid the influence of outliers on the data.

Officially recorded property/violence convictions, aged 17–21

Data on convictions over the period 17–21 years were obtained from records held by the New Zealand police. These records were obtained following signed and informed consent from the young person. Of the 1011 cohort members asked for permission to search their police records, 97.3% provided permission and 2.7% declined. For each participant, a record of the date of arrest, type of offence, date of court appearance, number of convictions and sentence was gathered. For the purposes of the present analysis, data on convictions were classified to provide a measure of convictions for property or violent offences. Property offences included theft, burglary, breaking and entering, wilful damage, fire-setting and related offences. Violent offences included assault, fighting, robbery, use of a weapon, threats of violence against a person and similar offences. The number of convictions for each type of offence were then summed over the period to create an index of the number of property and violent convictions during the period 17–21 years.

Conduct problems, aged 14–16

At 15 and 16 years sample members were interviewed on a comprehensive mental health interview that examined aspects of mental health and adjustment over the previous 12 months. A parallel interview was also conducted with the child's mother. The two interviews were conducted at different sites (mothers were interviewed at home and children at school) and by different interviewers. As part of the assessments at each age information was obtained on DSM-III-R²⁹ symptom criteria for conduct disorder³⁰ using the Self-Report Early Delinquency (SRED) scale.³¹ For the purpose of the present analyses, these responses were used to create a continuous scale measure reflecting the number of symptom criteria reported for each disorder. This measure was based on a count of the number of symptoms of disorder reported by either the mother or child over the 2-year period.

Hostility, aged 18, 21 and 25

At 18, 21 and 25 years, items from the 90-item Symptom Checklist (SCL-90)³² were used to assess aspects of current psychiatric symptomatology. Part of this assessment included the hostility subscale of the SCL-90. The hostility subscale comprised a series of six items relating to hostile thoughts and behaviours including: feeling easily annoyed or irritated; temper outbursts that could not be controlled; having urges to beat, injure or harm someone; having urges to smash or break things; getting into frequent arguments; and shouting or throwing things. For each item the individual was asked to report the extent to which they had been troubled by the symptom over the past month. Ratings were made on a 3-point scale (not at all, a little, a great deal), and for each participant a total hostility scale score was computed at each age by summing the scores on each of the six items. The resulting scale scores were of moderate reliability ($\alpha = 0.77$ – 0.79). These scores were averaged over the three assessment periods to create a mean hostility score for the period 18–25 years, scaled to a mean of 100 and a standard deviation of 10.

Covariate factors

A range of covariate factors were chosen for the analyses, based on: their correlation with abuse exposure; and previous research on the present cohort suggesting that the factors were related to antisocial behaviour. The following covariate factors were chosen for inclusion in the analyses.

Sociodemographic background

- (a) Maternal age: maternal age was assessed at the time of the survey child's birth.
- (b) Paternal education: paternal education was assessed at the time of the survey child's birth using a 3-point scale that reflected the highest level of educational achievement attained. This scale was: 1, father lacked formal educational qualifications (had not graduated from high school); 2, father had secondary-level educational qualifications (had graduated from high school); 3, father had tertiary-level qualifications (had obtained a university degree or equivalent qualification).
- (c) Family living standards (0–10 years): each year a global assessment of the material living standards of the family was obtained by means of an interviewer rating. Ratings were made on a 5-point scale that ranged from 'very good' to 'very poor'. These ratings were summed over the 10-year period and divided by 10 to give a measure of typical family living standards during this period.
- (d) Family socioeconomic status (at birth and at age 14): this was assessed at the time of the survey child's birth, and again at age 14 using the Elley–Irving³³ scale of socioeconomic status for New Zealand. This scale classifies socioeconomic status into six levels on the basis of paternal occupation ranging from 1, professional occupations to 6, unskilled occupations.

Family functioning

- (a) Family adversity measure: an index of family problems was calculated using a count of 38 different measures of family disadvantage during the period 0–15 years, including measures of disadvantaged parental background, poor prenatal health practices and perinatal outcomes, and disadvantageous child-rearing practices.³⁴
- (b) Parental alcoholism/alcohol problems, criminal offending and illicit drug use: when sample members were aged 11, their parents were questioned about parental use of illicit drugs. At the 15-year assessment parents were further questioned concerning their history of alcoholism or alcohol problems and criminal offending. On the basis of this questioning 11.9% of the sample were classified as having a parental history of alcoholism/alcohol problems, 12.4% of the sample as having a parental history of criminal offending and 24.9% as having a parental history of illicit drug use.
- (c) Changes of parents: as part of the annual assessments from age 1–16 years information was obtained on changes of parents since the previous assessment. An overall measure of family stability during childhood was developed based on a count of the number of changes of parents experienced by the child from birth to age 16 years. This count included all changes as a result of parental separation/divorce, reconciliation, remarriage/cohabitation, parental death, fostering and other changes of custodial parents.

Individual factors

Child cognitive ability was assessed at the ages of 8 and 9 using the Revised Wechsler Intelligence Scale for Children (WISC-R)³⁵ Total scores were computed on the basis of results on four verbal and four performance subscales. The split half reliabilities of these scores were 0.93 at age 8 and 0.95 at age 9. For the purposes of these analyses the observed WISC-R total IQ scores at age 8 and 9 were combined by averaging over the two administrations.

Statistical analysis

The data were analysed using Poisson regression models (with correction for overdispersion) in the case of count measures (property/violent offending; convictions; conduct problems), and multiple regression with maximum likelihood estimation for the hostility score measure, using SAS version 9.01 for Windows. These models were of the form:

$$f(Y) = B_0 + B_1(\text{maoa}) + B_2(\text{abuse}) + B_3(\text{maoa} \times \text{abuse})$$

where $f(Y)$ was either the log rate (for count measures) of the antisocial behaviour outcome, or the score on the hostility measure; maoa was the dichotomous measure of MAOA activity genotype (low activity/high activity); and abuse was the dichotomous measure of exposure to significant sexual or physical abuse in childhood. The interaction term was centred around the mean for the abuse exposure measure. In this model the coefficient B_1 represents the main effect of genotype; B_2 the main effect of abuse exposure; and B_3 the change in the effect of abuse exposure attributable to having the low- or high-activity MAOA genotype, and B_0 was the intercept term. With the model formulated in this way a negative B_3 coefficient would be consistent with the Caspi *et al*¹ hypothesis of greater responsivity to abuse among those with lower MAOA activity levels. The test of significance of the interaction effect was based on the standard Z -test given by the ratio of the regression parameter B_3 to its standard error (or t -test in the case of the analyses of the hostility scores). In order to account for any potential issues arising from the ethnic stratification of the sample, the analyses were then repeated omitting the 47 cohort members of Maori, Pacific Island and Asian ethnicity.

Then, to examine the sensitivity of the analyses to alternative methods of conceptualising abuse exposure, the above analyses were repeated using, in place of the measure of exposure to significant sexual or physical abuse in childhood: a dichotomous measure of sexual abuse (abuse/no abuse); a dichotomous measure of physical abuse (no physical punishment or occasional punishment/regular or severe physical punishment); and a dichotomous measure representing the highest decile on the measure of interparental violence exposure (no/yes).

In the next step of the analyses, the values of the Z -tests of significance of the interaction terms were plotted separately for the models using either sexual or physical abuse, or sexual or physical abuse alone, using Stata 10.0 for Windows.

In addition, to examine the extent to which the interactions between abuse exposure and MAOA in predicting antisocial behaviour could be accounted for by potentially confounding factors, the models described above were extended to include terms representing the effects of the range of confounding factors described above. These models were of the general form:

$$f(Y) = B_0 + B_1(\text{maoa}) + B_2(\text{abuse}) + B_3(\text{maoa} \times \text{abuse}) + \sum B_j X_j$$

where $f(Y)$, maoa , and abuse were as described above, and where $\sum B_j X_j$ represented the pooled effects of the sociodemographic, family functioning and individual factors noted above. All confounding factors were entered into the models simultaneously.

Results

MAOA, childhood maltreatment and subsequent antisocial behaviour

Table 1 shows the cohort of males stratified into two groups: those participants reporting significant childhood physical or sexual

Table 1 Mean antisocial behaviour outcome scores (ages 16–30) by abuse exposure and MAOA activity level, and tests of genotype, abuse exposure and genotype \times abuse exposure interaction effects from Poisson and multiple regression models

	Exposure to significant sexual/physical abuse		Parameter estimates						
	No (n = 309)	Yes (n = 89)	MAOA, B (s.e.)		Abuse, B (s.e.)		MAOA \times Abuse, B (s.e.)		
			Full cohort	Reduced cohort ^a	Full cohort	Reduced cohort ^a	Full cohort	Reduced cohort ^a	
Violent offences (ages 16–30), mean (s.d.)									
Low MAOA activity level	4.29 (14.35)	24.35 (50.18)	-0.62 (0.19)***	-0.53 (0.21)*	0.87 (0.13)***	0.86 (0.15)***	-0.45 (0.19)*	-0.67 (0.21)**	
High MAOA activity level	3.60 (10.95)	8.36 (18.27)							
Property offences (ages 16–30), mean (s.d.)									
Low MAOA activity level	4.92 (14.30)	22.29 (34.92)	-0.53 (0.19)**	-0.53 (.23)*	0.76 (0.13)***	0.75 (0.15)***	-0.67 (0.19)***	-0.87 (0.23)***	
High MAOA activity level	5.65 (16.08)	6.76 (16.26)							
Convictions for property/violent offences (ages 17–21), mean (s.d.)									
Low MAOA activity level	0.36 (1.34)	1.07 (3.36)	-0.40 (0.17)*	-0.68 (0.21)**	1.09 (0.24)***	0.71 (0.31)*	-0.26 (0.33)	-0.12 (0.43)	
High MAOA activity level	0.26 (1.34)	0.59 (2.34)							
Conduct problems (ages 14–16), mean (s.d.)									
Low MAOA activity level	0.99 (1.88)	2.96 (3.49)	-0.30 (0.10)**	-0.10 (0.11)	1.10 (0.15)***	1.09 (0.19)***	-0.41 (0.20)*	-0.69 (0.25)**	
High MAOA activity level	0.81 (1.43)	1.62 (2.12)							
Hostility scores (ages 18–25), mean (s.d.)									
Low MAOA activity level	99.29 (8.24)	106.22 (13.35)	-1.31 (0.89)	-1.39 (0.92)	6.93 (1.72)***	5.35 (1.91)***	-5.01 (2.14)*	-4.50 (2.33)*	
High MAOA activity level	99.23 (8.08)	101.16 (7.60)							

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
a. Obtained from the model omitting cohort members of Maori, Pacific Island and Asian descent (n = 47).

abuse; and other participants. Table 1 is further stratified by MAOA genotype into high- and low-activity groups. For each combination of childhood maltreatment and genotype the table reports measures of five outcomes: rates of self-reported violent and property crimes during the period 16–30 years; rates of officially recorded property or violent convictions during the period 17–21 years; rates of conduct disorder symptoms during the period 14–16 years; and standardised hostility scores derived from the SCL-90 (see Method). For each outcome, tests of the main effects of childhood maltreatment, genotype and a centred test of the genotype \times maltreatment interaction are reported. Also, in order to account for potential issues arising from ethnic stratification, the Table also shows the parameter estimates derived from models omitting those cohort members of Maori, Pacific Island and Asian ethnicity ($n = 47$). The table shows the following results.

- (a) For self-reported violent and property crimes (16–30 years), there was a clear tendency for genotype to modify the relationship between childhood maltreatment and offending, with those having the low-activity genotype being more responsive to maltreatment than the high genotype. In both cases there was a significant ($P < 0.05$) $G \times E$ interaction. In addition, there was evidence of significant main effects for both childhood maltreatment ($P < 0.001$) and genotype ($P < 0.01$).
- (b) For officially recorded convictions (17–21 years) there was no clear tendency for genotype to modify the relationship between childhood maltreatment and offending. This conclusion was confirmed by the absence of a significant ($P > 0.40$) $G \times E$ interaction between maltreatment and MAOA. There was, however, a significant main effect for both genotype ($P < 0.05$) and childhood maltreatment ($P < 0.001$) reflecting the fact that those with the low activity MAOA genotype and those reporting significant maltreatment had higher rates of conviction.
- (c) For symptoms of conduct disorder (14–16 years) there was a clear tendency for genotype to modify the relationship between childhood maltreatment and offending, with those having the low-activity genotype being more responsive to childhood maltreatment. This conclusion was confirmed by the presence of a significant ($P < 0.05$) $G \times E$ interaction between maltreatment and the MAOA genotype. There was also a significant main effect for childhood maltreatment ($P < 0.001$) and for MAOA ($P < 0.01$).

(d) For SCL-90 symptoms of hostility there was a clear tendency for genotype to modify the relationship between childhood maltreatment and offending, with those having the low-activity MAOA genotype being more responsive to childhood maltreatment. This conclusion was confirmed by the presence of a significant ($P < 0.05$) interaction between childhood maltreatment and MAOA activity level. In addition there was a significant main effect for childhood maltreatment ($P < 0.001$) but not for MAOA activity level.

(e) For each outcome measure, the analyses omitting those cohort members of Maori, Pacific and Asian ethnicity ($n = 47$) revealed a similar set of parameter estimates. For the measures of violent crime, property crime and conduct problems, these analyses yielded somewhat stronger parameter estimates for the interaction between MAOA activity level and maltreatment, whereas for convictions and hostility scores, the parameter estimates for the MAOA \times maltreatment interaction terms were somewhat weaker. As with the models using the full sample, however, four out of the five interaction terms were statistically significant ($P < 0.05$).

With the possible exception of findings for officially recorded convictions from age 17 to 21, Table 1 suggests the presence of a consistent $G \times E$ interaction in which those with the low-activity variant of MAOA were more likely to develop antisocial behaviours following responses to maltreatment.

Extensions and further analysis

The analysis in Table 1 was replicated using specific measures of childhood sexual abuse and childhood physical abuse (see Method). The results of these analyses are depicted in Fig. 1, which shows plots of the Z-test of the $G \times E$ interaction for three series of analysis: the results shown in Table 1; the results obtained using a measure of childhood sexual abuse only; and the results obtained using a measure of childhood physical abuse only. The figure shows evidence of consistent $G \times E$ effects for all measures of childhood maltreatment. For three of the five outcome measures there are consistently significant ($P < 0.05$) $G \times E$ interactions, with the sign of the Z-test indicating that in all cases those with the low-activity genotype were more likely to report antisocial behaviour following exposure to maltreatment. The exceptions to this trend were: the measure of conduct problems, which was significant ($P < 0.05$) for both the overall measure of maltreatment exposure and for sexual abuse exposure; and officially recorded convictions, which was significant ($P < 0.05$) only for sexual

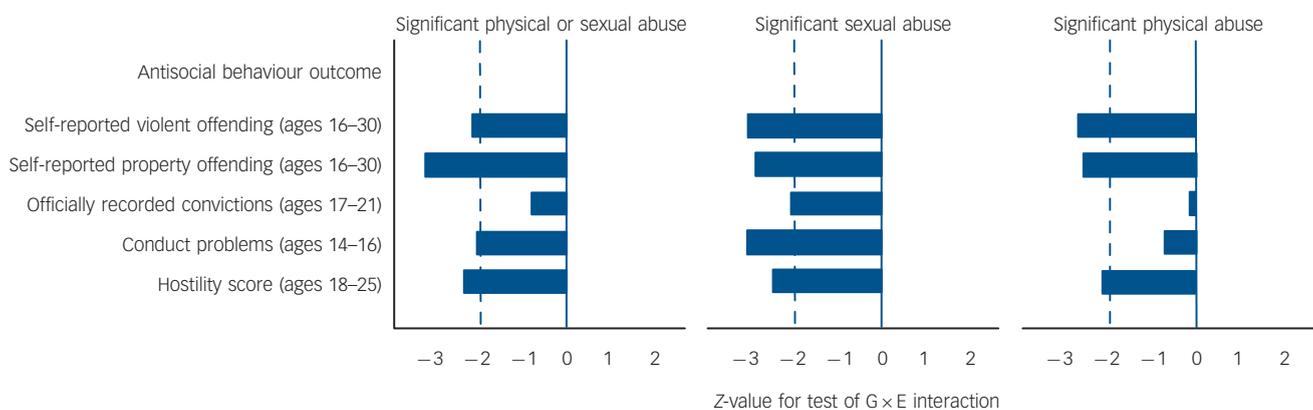


Fig. 1 Z-test values for tests of significance of MAOA activity level \times abuse exposure (Gene (G) \times environment (E) interaction) from fitted models for varying antisocial behaviour outcomes and varying measures of abuse exposure.

abuse exposure. However, it is notable that in all cases the sign of the Z-test was negative, suggesting a general but non-significant trend for those with the low-activity genotype to have higher rates of conviction following exposure to maltreatment.

To examine the robustness of the findings in Table 1 and Fig. 1, these analyses were extended in a number of ways. These included the following measures.

- (a) Using a measure of interparental violence as the measure of exposure to childhood maltreatment (see Method). These analyses failed to show any evidence of a main effect for exposure to interparental violence (all $P > 0.05$), suggesting that exposure to interparental violence was not associated with increased rates of antisocial behaviour outcomes.
- (b) Statistical control for confounding factors including measures of: sociodemographic disadvantage, family dysfunction, and adverse individual factors (see Method). In all cases, extension of the models depicted in Table 1 and Fig. 1 to include terms representing the potentially confounding effects of family sociodemographic background, family functioning and individual factors did not alter the pattern of significant ($P < 0.05$) interactions. The interactions depicted in Fig. 1 remained significant following adjustment for the range of confounding factors.

Discussion

Main findings

In this paper we have attempted to replicate the findings of Caspi *et al*¹ on the $G \times E$ interaction between exposure to childhood maltreatment and *MAOA* activity genotype in the development of antisocial behaviours, using a study that has strong similarities to the DMHDS. The findings of this analysis provided replication and support for the original research. Specifically, we were able to show significant $G \times E$ interactions between *MAOA* and childhood maltreatment for a series of outcomes spanning adolescence to adulthood, and involving both self-reported and officially reported outcomes. Those with the low-activity variant of *MAOA* who were exposed to maltreatment in childhood were significantly more likely to report a range of antisocial behaviours and related outcomes, including property and violent offending, hostility and symptoms of conduct disorder. It should be noted that, for officially recorded convictions, the present study found a significant interaction between *MAOA* and only one of three measures of maltreatment (sexual abuse). The weaker effects for convictions are likely to reflect both the limited time period over which officially recorded convictions were recorded, and the low base rate of convictions in the cohort. Furthermore, officially recorded convictions are not a 'pure' measure of antisocial behaviour since they measure both the individual's offending behaviour and the responses of the criminal justice system to this behaviour.^{36,37} Overall, however, the results of these analyses suggest the presence of a robust and general tendency for respondents with the low-activity variant of *MAOA* to be more responsive to childhood maltreatment in terms of their rates of subsequent antisocial behaviour.

Comparison with findings from other studies

Given the methodological similarities between the CHDS and the DMHDS the present findings provide a replication of Caspi *et al*'s¹ $G \times E$ findings involving *MAOA* and childhood maltreatment. There were, however, some points of difference between our findings and those of Caspi *et al*.¹ First, whereas Caspi *et al* found no evidence for a main effect of *MAOA* on antisocial behaviour,

we found a general tendency for the overall rate of antisocial behaviour to be higher in the low-activity *MAOA* group than in the high-activity group independent of the *MAOA* \times maltreatment interaction, with a statistically significant ($P < 0.05$) main effect for *MAOA* for three outcomes. A limited number of studies have found a main effect for *MAOA* on later antisocial behaviour,^{5,12,14,38,39} but the majority of studies in this area have not observed this main effect. If this main effect is replicated in further studies it may suggest that, independently of environmental effects, those with low-activity *MAOA* are more prone to antisocial behaviours. Second, the present study also found a statistically significant $G \times E$ interaction for conduct problems, whereas Caspi *et al*¹ found only a marginally significant interaction. These differences in findings may largely reflect variations in measurement; whereas Caspi *et al* used diagnoses of conduct disorder, the present study employed a measure of the number of symptoms of conduct disorder.

This is the second study in which we have attempted to replicate the $G \times E$ findings reported by Caspi *et al*, with very different results.¹⁸ In our first study, looking at the relationship between 5-HTTLPR, life stress and mental disorder, we were unable to find any evidence to support the hypothesis that possession of 's' alleles was associated with an increased responsiveness to adverse life events.¹⁸ These findings are consistent with a growing number of studies that have failed to replicate the 5-HTTLPR findings.^{16,17} In complete contrast, the present study has been able to provide a strong replication of the *MAOA* \times childhood maltreatment interaction. The most plausible reason for these differences in findings is that the magnitude of the interactions between *MAOA* and maltreatment are much stronger than the interactions between 5-HTTLPR and negative life events. This is indicated by the fact that *MAOA* interactions have been detected in samples of males ranging in size from 399 to 975.^{1,8} Therefore, problems of replication may be attributable to the magnitude of interactions, and the problems associated with replicating relatively weak interactions. Using the CHDS data, it was not possible to replicate the interactions for 5-HTTLPR, whereas it proved possible to replicate interactions for *MAOA*.

Implications

These results also highlight some of the potential problems of $G \times E$ research into psychopathology based on single genes. Although it does appear to be possible to identify stable $G \times E$ interaction effects involving single genes, because of the small effect sizes involved these interactions prove difficult to replicate, as noted above. Also as the results on 5-HTTLPR illustrate, it may be possible to generate false-positive findings. These considerations suggest that although early research into $G \times E$ interaction involving single genes has been useful in focusing research on the interaction between genes and environment, it is time for the field to move beyond single gene studies and towards a consideration of the ways in which multiple genes combine with multiple environmental factors to influence individual susceptibility to psychopathology.

Limitations

Although the results of this study provide support for the notion of a $G \times E$ interaction between *MAOA* and childhood maltreatment, several limitations need to be considered. First, it is clear that, although the observed interactions were statistically significant, they tended to be limited in magnitude, accounting for only a small portion of the variance in the models. The small magnitude of the interaction effects suggests that the contribution

of these interactions to antisocial behaviour, over and above the main effect of maltreatment exposure, may be somewhat limited in scope. Second, although the MAOA genotype is theoretically related to MAOA expression, at least one study has failed to find links between variations in MAOA genotype and MAOA levels in the brain.⁴⁰ This suggests that further research on the expression of MAOA is needed in order to validate the role of the MAOA genotype in antisocial behaviour.

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