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MAOA, childhood maltreatment and antisocial behavior: Meta-analysis of a gene-environment interaction

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Abstract

Background—In a seminal study of gene-environment interaction, childhood maltreatment predicted antisocial behavior more strongly in males carrying an *MAOA* promoter variant of lesser, compared to higher, transcriptional efficiency. Many further investigations have been reported, including studies of other early environmental exposures and females. Here we report a meta-analysis of studies testing the interaction of *MAOA* genotype and childhood adversities on antisocial outcomes in predominantly non-clinical samples.

Method—Included were 27 peer-reviewed, English-language studies published through August, 2012, that contained indicators of maltreatment or "other" family (e.g., parenting, sociodemographic) hardships; *MAOA* genotype; indices of aggressive and antisocial behavior; and statistical test of genotype-environment interaction. Studies of forensic and exclusively clinical samples, clinical cohorts lacking proportionally matched controls, or outcomes non-specific for antisocial behavior were excluded. The Liptak-Stouffer weighted Z-test for meta-analysis was implemented to maximize study inclusion and calculated separately for male and female cohorts.

Results—Across 20 male cohorts, early adversity presaged antisocial outcomes more strongly for low, relative to high, activity *MAOA* genotype (P=.0044). Stratified analyses showed the interaction specific to maltreatment (P=.0000008) and robust to several sensitivity analyses. Across 11 female cohorts, *MAOA* did not interact with combined early life adversities, whereas maltreatment alone predicted antisocial behaviors preferentially, but weakly, in females of high activity *MAOA* genotype (P=.02).

Conclusions—We found common regulatory variation in *MAOA* to moderate effects of childhood maltreatment on male antisocial behaviors, confirming a sentinel finding in research on gene-environment interaction. An analogous, but less consistent, finding in females warrants further investigation.

Keywords

MAOA; antisocial behavior; childhood maltreatment; genetics; gene-environment interaction; meta-analysis

Two widely cited reports of putative gene-environment (GxE) interaction, published in 2002 and 2003, described genotype-dependent environmental influences on risk for antisocial behavior and depression, respectively, in a well-characterized, longitudinally studied birth cohort(1-2). In the second of these studies, recent stressful life events and childhood maltreatment predicted depression in young adults in proportion to the number of "short"

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(deletion) alleles carried of a 44-basepair (bp) insertion/deletion (long/short) polymorphism in the regulatory region of the serotonin transporter gene (5-HTTLPR)(2). Two prominent meta-analyses published in 2009 failed to confirm replication of this most frequently cited instance of gene-stress interaction(3-4). Some authors cautioned that these analyses incorporated only a fraction of relevant investigations and relied disproportionately on studies of self-reported life events, rather than contextually sensitive interviews or objective indicators of stress(5-6). In a more comprehensive meta-analysis published subsequently, Karg et al(7) found the 5-HTTLPR to moderate effects of adversity on clinical depression and depressive symptomatology across all published studies (P = .00002), but with some variation among studies of differing methodology. In stratified analyses, 5-HTTLPR genotype interacted with self-reported life events only marginally in predicting depression, whereas the interaction proved robust for studies of childhood maltreatment and of cohorts uniformly exposed to the same stressor or where life events were assessed by structured interview.

The purpose of this paper is to extend meta-analytic review to the first of the two GxE interactions described by Caspi and colleagues(1). There, exposure to maltreatment in childhood predicted later aggressive and antisocial behaviors among males as a function of regulatory variation in the gene encoding monoamine oxidase-A (*MAOA*). A degradative enzyme, MAOA preferentially deaminates the neurotransmitters, serotonin and norepinephrine, and the *MAOA* gene contains a 30-bp repeating sequence (Variable Number of Tandem Repeats) in the 5′-flanking region conferring allele-specific variation in *MAOA* promoter activity(8-10). In this study, early indicators of maltreatment, such as boys' physical or sexual abuse, maternal rejection, or harsh physical punishment, more strongly predicted later conduct problems, antisocial disposition, and violent offending among persons carrying the *MAOA* repeat variant (allele) of lesser transcriptional efficiency ("low activity" *MAOA* genotype) than in those of an alternate ("high activity") genotype. This finding has since been cited over 2800 times and prompted similar studies by other investigators. In 2007, Taylor and Kim-Cohen(11) confirmed the interaction of early maltreatment and *MAOA* genotype on antisocial outcomes by meta-analysis of the original study and seven attempted replications(12-18). These studies all included male participants recruited from largely normal populations (viz., excluding forensic or predominantly clinical samples) and contained either a single or composite index of antisocial behavior. Studies also included a measure of participants' childhood exposure to abuse, neglect, or other harm within the family environment, and all reported such exposure positively associated with study outcomes. Consistent with the initial report of Caspi et al(1), the pooled estimate of correlation between family adversity and indices of later antisocial behavior was greater in individuals of low, compared to high, activity *MAOA* genotype (P < .0001)(11).

Many additional investigations have been reported since publication of Taylor and Kim-Cohen(11). These include further GxE studies of early maltreatment(19-25), studies of other environmental moderators (e.g., neighborhood and family socioeconomic disadvantage, peer deviance, parenting styles, commonly experienced life events, maternal prenatal smoking(25-32)); and studies including females(20-21, 23, 29-31, 33-38) or primarily non-White samples(24, 33-34). Here, we report a further meta-analysis of the accumulated literature addressing interactions of *MAOA* variation and environmental risk factors in the prediction of aggressive and antisocial outcomes. To allow comparison with the parallel literature on 5-HTTLPR variation, life stress and depression (i.e., the second GxE literature emerging from the two seminal studies of Caspi and colleagues(1-2)), we have followed the same analytic procedures employed by Karg et al(7). This approach maximizes inclusion of studies of differing design and analytic strategy or of limited statistical reporting or data availability through application of the common Liptak-Stouffer weighted Z-test for meta-analysis, which combines published reports by tests of statistical significance(7, 39-42).

METHODS

Studies

We sought all peer-reviewed, English-language studies published through August 2012 from: a) reference lists of prior meta-analysis, narrative reviews and individual studies; and b) major publication databases (e.g., PubMed), using as keywords: monoamine oxidase-A or *MAOA and* childhood maltreatment, abuse, adversity or family/family environment *and* antisocial behavior, conduct disorder/problems, delinquency, externalizing behavior, aggression or violence. We only included studies that had genotyped the same *MAOA* VNTR reported by Caspi et al(1), those in which the interaction of *MAOA* genotype and early adversity was tested explicitly; and studies for which outcomes included behaviors or disorders on an externalizing or antisocial spectrum (but not solely alcohol or substance abuse). Following Taylor and Kim-Cohen(11), studies of forensic populations(43-45), exclusively clinical samples or clinical samples lacking proportionally matched controls were excluded(46-47). Also excluded were two studies in which indicators of antisocial behavior could not be distinguished from other life outcomes or events (e.g., financial losses, accidents, unspecified relationship problems, or socioeconomic attainments)(48-49).

We identified 27 independent investigations meeting the foregoing criteria and totaling >18,400 study participants. Of these, 12 studies included only male participants(12-16, 19, 22, 24-25, 27-28, 32), 11 included participants of both sexes(1, 17-18, 20-21, 23, 29-31, 33-34), and 4 included only females(26, 36-38). Study samples were mainly all white (23), with 4 studies of mixed ethnicity or primarily non-white samples(17, 19, 24, 33). To determine if outcomes might vary by similarity to the first reported GxE interaction for *MAOA*, we stratified investigations into 2 groups: studies focusing specifically on early maltreatment and studies of other childhood adversities. Assignment to the “maltreatment” group was made when factors such as physical or sexual abuse, assault or other victimization, severe physical punishment, other exposures to violence, neglect or court-mediated family interventions predominated in indices of early childhood environment. Studies of sociodemographic variables, peer affiliations, maternal prenatal smoking, general life events, or parenting styles, and those with only minor or oblique representation of maltreatment indicators were assigned to the category of “other childhood adversities”. When studies reported on measurements from both categories, these were treated as independent tests in stratified analyses.

Extraction of P-values

The authors independently extracted P-values from each study, without discrepancy. When non-significant findings were reported without exact P-values, we requested more precise values from study authors. If these data were not available or authors declined, we assigned a P-value of 1 (indicating absence of an interaction implicating either low or high activity *MAOA* genotype). Because interaction terms were occasionally collapsed over sex or ethnicity, we also requested P-values from study authors for males and females analyzed separately, and similarly for white and nonwhite segments of multi-ethnic samples. With respect to outcome measures, for primary analyses we used the P-value associated with the most general (e.g., composite) measure of antisocial behavior or computed a weighted mean P-value when multiple dependent variables and/or multiple environmental moderators were analyzed separately in the published report.

Genotypes of MAOA

Because *MAOA* is located on the X chromosome (Xp11.4-Xp11.3), all males are hemizygous for a single allele of the upstream VNTR, for which variants of 2, 3, 3.5, 4 and 5 repeats have been described. In samples of European ancestry, the 3- and 4-repeat alleles

account for >95% of variation. The 2, 3 and 5 repeat variants are commonly grouped as "low activity" alleles and contrasted with "high activity" alleles of 3.5 or 4 repeats, based on in vitro studies of *MAOA* promoter activity(8, 10). Functional characterization of the 5-repeat is somewhat controversial(10, 20), however, though its rarity suggests a negligible effect on study outcomes resulting from differences in allele grouping. Also, some studies disregarded the rare variants altogether, analyzing only the 3- and 4-repeat alleles.

In females, uncertainty regarding extent of X-inactivation at the *MAOA* locus(50-51) has occasioned differing analytic strategies for comparing *MAOA* genotypes, and in some instances, served as rationale for excluding females from study analyses(15). When tested in females, some investigators compared only individuals homozygous for low or high activity variants(17, 21, 33-34, 37), whereas others included a heterozygous grouping defined by presence of both a low and high activity allele(18, 20, 23, 26, 29-31, 36, 38). Here, we treat *MAOA* genotypes in females as they were operationalized in each study, although when a *P*-value for the contrast of homozygous low and high activity participants was available in studies including heterozygotes, we used this value in the meta-analysis to enhance comparability among studies. Finally, because the sentinel report by Caspi et al(1) addressed risk for antisocial behavior specifically in males, and owing to the more variable classification of *MAOA* genotypes in studies of females, analyses were conducted separately for each sex.

Statistical analysis

Like the Karg et al(7) meta-analysis of 5-HTTLPR variation, stress and depression, we combined investigations by the Liptak-Stouffer z score procedure to yield an aggregate outcome based on significance tests from each study, adjusted for sample size. Extracted *P*-values were first expressed as 1-tailed metrics, where *P*-values less than .50 corresponded to liability for antisocial behavior associated with low activity *MAOA* genotype and a *P*-value greater than .50 with high activity *MAOA* genotype. More precisely, a study outcome was considered consistent with Caspi et al(1) when the dependent variable associated more strongly with an environmental risk factor among participants of low, relative to high, activity *MAOA* genotype. As in Karg et al(7), *P*-values were next converted to z-scores, to which positive and negative signs were attached, respectively, for *P*-values less than and greater than .50. Finally, a composite *z* score was calculated by the formula:

$$z_w = \frac{\sum_{i=1}^{k} w_i z_i}{\sqrt{\sum_{i=1}^{k} w_i^2}}$$

where z_i denotes *z* scores of the individual studies, w_i refers to the study sample size, and *k* is the number of studies included in the analysis. The outcome, z_w, is then tested for two-tailed significance by reference to the standard normal distribution.

This statistic was first calculated for all studies together and then, in stratified analyses, for studies partitioned by category of environmental moderator (i.e., "maltreatment"; "other adversities"). As noted, these analyses were run separately by sex. In 4 samples that included both males and females, sex-specific *P*-values were unavailable(17, 33-34). We excluded these investigations in primary analyses, but because males comprised a majority of participants in each, we included these with all other male studies in a secondary analysis.

Any initially significant finding was probed for disproportionate influence of single investigations by re-computing z_w after removing each study individually, and if found unaltered by deletion of individual studies, the following additional sensitivity analyses were conducted. As noted previously, the *P*-value entered into analysis was occasionally averaged over tests involving more than one environmental moderator or, more commonly, over multiple outcomes, such as clinical diagnoses, forensic status (e.g., criminal convictions), and dimensional measures of informant and self-reported aggressive, antisocial, or other externalizing behavior. To determine if results were robust to this variation, we repeated the analysis by: a) iteratively substituting individual outcome variables for composite measures or averaged *P*-values; and b) running 1000 additional iterations of the meta-analysis, in each of which a single dependent measure was selected randomly from all studies with multiple outcomes. We then also ran analyses separately for: a) continuous and dichotomous measures of antisocial behavior; b) outcomes occurring in childhood/adolescence (≤18) and those of adulthood; c) outcomes of overt aggression or violence, non-violent antisocial behaviors (e.g., vandalism, theft), and measures combining violent and non-violent indicators (e.g., Conduct and Antisocial Personality Disorder diagnoses or symptom counts); and d) investigations based on cross-sectional and longitudinally studied cohorts. Regarding maltreatment studies, we also conducted analyses separately for those in which environmental exposures were assessed by family (self or parent) report only and studies including non-familial informant sources (e.g., official record, observation). Finally, to gauge potential publication bias, we: a) computed a fail-safe N by direct computation and calculated the ratio of failsafe N to the number of published studies; and b) followed up with re-analyses stratified by sample size and date of publication.

RESULTS

Male Studies

Our search identified 20 studies of exclusively male samples or mixed sex samples for which results were available in males separately (Table 1). These studies included 11,064 subjects (Table 2). The meta-analysis showed *MAOA* genotype to moderate an association of early life adversities (maltreatment plus “other adversities”) with later aggressive and antisocial outcomes across all male cohorts ($P = .0044$) (Figure 1). This effect persisted: a) on removal of each study individually ($2.5 \times 10^{-6} < P < .018$) (Table 2); and b) with iterative substitution of individual outcome variables for composite measures or averaged *P*-values ($6.6 \times 10^{-5} < P < .014$). Additional analyses showed the interaction significant in all but one of 1000 random combinations of study-specific dependent variables and environmental moderators ($7.1 \times 10^{-6} < P < .06$). Results were significant for outcomes indexed to either childhood/adolescence ($P = .032$) or adulthood ($P = .008$); outcomes of aggression/violence ($P = 3.9 \times 10^{-5}$), non-violent antisocial behaviors ($P = 7.2 \times 10^{-4}$), or combined indices ($P = .022$); for dependent measures of continuous ($P = .008$), but not dichotomous distribution ($P = .36$); and for studies of both cross-sectional samples ($P < .0045$) and longitudinally studied cohorts ($P = .019$). Findings were unaffected by deletion of 2 non-white samples(19, 24) ($P = .0044$) or inclusion of 4 additional cohorts (N=806) of majority-male, mixed sex samples(17, 33-34) ($P = .0034$).

Stratified Analyses

Low activity *MAOA* genotype heightened risk for antisocial behavior among individuals exposed to maltreatment specifically ($P = .0000008$), but not in tests of other childhood adversities ($P = .40$). The interaction with maltreatment remained highly significant: a) when deleting each study individually ($P=2.2 \times 10^{-5} < P < 2.7 \times 10^{-7}$) (Table 3); b) with iterative substitution of individual outcome measures for composite indices or mean *P*-values ($P=3.5 \times 10^{-5} < P < 1.4 \times 10^{-7}$); and c) across all of 1000 random combinations of

individual outcome measures ($1.8 \times 10^{-9} < P < .005$). Among maltreatment studies, findings were again significant when analyzed separately for child/adolescent ($P = 3.6 \times 10^{-5}$) and adult outcomes ($P = .05$); for outcomes of aggression/violence ($P = .01$), non-violent antisocial behaviors ($P = 4.0 \times 10^{-4}$), and combined indices ($P = 3.6 \times 10^{-6}$). They were significant also for dependent variables of both continuous ($P = 1.4 \times 10^{-6}$) and dichotomous distribution ($P = .02$); in cross-sectional studies ($P = .01$) and studies of longitudinal cohorts ($P = 3.5 \times 10^{-5}$); and where assessment of maltreatment exposure rested on family-based report only ($P = 7.8 \times 10^{-7}$) or included nonfamilial informant sources (P = .022). Here, too, results were unaltered by removal of 2 non-white cohorts(19, 24) ($P = 5.4 \times 10^{-7}$) or addition of the 4 majority-male mixed sex samples(17, 33-34) ($P = 5.7 \times 10^{-7}$).

Female Studies

We identified 12 studies involving females only or separately analyzed female cohorts, with a total of 7,588 subjects (Table 1). The meta-analysis showed no significant interaction of *MAOA* genotype with early life adversities (maltreatment and "other adversities") across all studies ($P = .77$).

Stratified Analyses

When analyzed separately, *MAOA* genotype predicted antisocial outcomes in interaction with childhood maltreatment ($P = .020$), but not on exposure to other early adversities ($P = .32$). Unlike males, the interaction with maltreatment reflected an increased risk linked to *high* activity *MAOA* genotype. On deletion of each study individually, however, this finding lost significance with removal of either of 2 study cohorts (.004 < P < .97) (Table 4).

Publication Bias

Our results corroborate the sentinel observation of Caspi et al(1) that childhood maltreatment predicts antisocial outcomes more strongly in males of low, compared to high, activity *MAOA* genotype, and do not show this interaction extended to other categories of early life adversity or to females. To render the *MAOA* x maltreatment interaction in males non-significant ($P > .05$) would require >93 unpublished analyses or undiscovered studies of null effect ($P = .50$) and equal average sample size (N = 447). This yields a failsafe ratio of 7 studies not included for each maltreatment study of males included in the meta-analysis. The *MAOA* x Maltreatment interaction also proved significant in analyses restricted to: a) studies with samples either larger ($P = 1.7 \times 10^{-4}$) or smaller ($P = .01$) than Caspi et al (2002); and b) either recent (dated 2010-2012; $P < 3.0 \times 10^{-4}$) or early replication attempts (2004-2009; $P = .005$).

DISCUSSION

In their provocative first study of GxE interaction, Caspi et al(1) reported that common polymorphic variation in *MAOA* moderated the influence of childhood maltreatment on boys' later aggressive and antisocial behaviors, as seen in a longitudinally studied, normal population. Our purpose was to determine whether this finding replicated in subsequent research addressed to the same hypothesis, when again examined in primarily nonclinical samples and extended to studies of other early life adversities or to females. Across male cohorts, the meta-analysis showed a moderately reliable interaction of *MAOA* variation and environmental risk factors, with childhood adversities presaging antisocial outcomes more strongly in persons of low, compared to high, activity *MAOA* genotype (as in Caspi et al(1)). Moreover, analyses stratified by category of early life adversity showed this finding accounted for principally by the interaction of *MAOA* and childhood maltreatment ($P = 8.2 \times 10^{-7}$), and therefore, where environmental risk most closely matched the sentinel study(1).

The interaction with childhood maltreatment also proved robust to sensitivity analyses and generalized across studies of either cross-sectional or longitudinal design and studies in which maltreatment exposure was assessed by family (self, parent) report only or included independent informant sources. It is noteworthy, too, that *MAOA* variation interacted with childhood maltreatment to predict outcomes referenced to both childhood/adolescence and adulthood; dependent measures of both continuous and categorical distribution; and both violent and non-violent antisocial behaviors. The latter finding suggests that the low activity *MAOA* genotype heightens maltreatment-dependent risk for a range of conduct problems, and not aggression or criminal violence specifically.

These findings are consistent with a broader literature on early risk factors for antisocial behavior, in which maltreatment indicators like domestic violence, physical abuse, neglect and parental rejection figure prominently(52-60). They also accord with findings of a recent twin study, in which maltreatment increased children's risk for conduct problems as a function of "latent" genetic risk, defined by twin-pair zygosity and co-twin diagnostic status for conduct disorder(61). Although biological mechanisms underlying these associations remain unknown, environmental insults like maltreatment presumably compound or otherwise interact with neurobehavioral correlates of *MAOA* to augment aggressive or antisocial potential. Relatedly, individuals of low, compared to high, activity *MAOA* genotype have performed more poorly on some executive processing tasks, such as tests of working memory and attentional control, and exhibited reduced task-dependent activations of frontal brain regions supporting these processes(62-66). The low activity *MAOA* genotype has been linked as well to altered neural responses to affective stimuli, including enhanced amygdala reactions to facial expressions of emotion or emotion recall; lesser engagement of prefrontal regulatory regions; and disrupted functional and effective (top-down) connectivity within corticolimbic circuitry of emotion processing(63, 67-69). It is possible that early maltreatment either exacerbates these neural deficits or engenders antagonistic and antisocial motivations that are abetted by *MAOA*-modulated impairments in inhibitory control.

In contrast to studies of childhood maltreatment, *MAOA* genotype did not moderate the aggregate effects of other early life adversities in males. The collection of environmental risks sampled in these investigations was quite variable, however, and it may be premature to conclude that *MAOA* interacts only with maltreatment to affect antisocial outcomes. For instance, risk associated with maternal prenatal smoking varied by *MAOA* genotype in each of the two studies that examined this variable (weighted $P = .024$)(25, 31). We should note that all but one attempted replication included in the prior meta-analysis by Taylor and Kim-Cohen(11) were categorized here as studies of maltreatment. The one such investigation that we placed instead in the category of other adversities used a measure of family relationships that, although encompassing abuse, emphasized a broader range of difficulties (e.g., separations, disability of self or sibling, marital problems and parental psychopathology) (18). Nonetheless, this study found the interaction of *MAOA* genotype and family difficulties to also predict male aggression, so that if included in meta-analysis with studies focusing more explicitly on maltreatment, the outcome does not differ ($P = 4.3 \times 10^{-7}$).

Unlike males, *MAOA* variation did not interact with early life adversities across 12 female cohorts, but like males, the interaction was significant in studies of childhood maltreatment alone. Yet among girls who were maltreated, the *high*, not low, activity *MAOA* genotype was more strongly associated with antisocial outcomes, although the interaction was weak and lost significance with deletion of some individual studies. Still, it is interesting that a combination of high activity *MAOA* genotype and environmental risk predicted delinquent behavior in several studies of adolescent girls and across different groups of investigators[23,31,36,38]. Elsewhere, symptoms of dysthymia have been found greater in

women who were maltreated in childhood and carry the *MAOA* high activity (4-repeat) variant than among women of homozygous, low activity genotype(70). At present, it is unclear how a reversal of allelic association between males and females might be explained, and existing literature provides few clues. Incomplete X-inactivation at the *MAOA* locus could conceivably produce a different expression profile in women, possibly yielding a sex difference in MAOA product.[50,51] Also potentially relevant to *MAOA* expression is some evidence that CpG residues in the *MAOA* promoter are hypermethylated in women, compared to men, and that differential methylation may be greatest among women of low activity *MAOA* genotype(71). A third possibility is that MAOA interacts with sex differences in perinatal androgen exposure to affect brain development or that gonadal hormones modulate genotype-dependent variation in *MAOA* expression in adolescence(26, 70). These suggestions are highly speculative, however, and do not yet provide a clear mechanism for a bidirectional association of *MAOA* genotype with antisocial behavior among maltreated cohorts of different sexes. Nonetheless, additional research may be warranted to determine if the findings suggesting heightened susceptibility for the high activity genotype in females emerge more prominently in a larger literature.

To recapitulate, our meta-analysis confirms the first seminal study of GxE interaction reported by Caspi et al(1). We find that *MAOA* variation moderates effects of early life adversity on males' aggressive and antisocial behaviors, and this interaction is attributable to studies that, like the initial report, delimit adversity to experiences of maltreatment, such as physical and sexual abuse, harsh discipline, neglect, assault or other ill-treatment. Significance of the weighted z-score for direct replications (i.e., maltreatment studies) is substantial ($P = 8.2 \times 10^{-7}$) and supported by a sizable failsafe ratio. Of course, even a positive meta-analysis does not exhaust validity challenges or vouchsafe a true association. For instance, publication bias may be indicated if reported replications aggregate among smaller rather than larger, better powered studies or in early, but not later, studies. Here however, we found the interaction of *MAOA* genotype and childhood maltreatment no less likely to replicate in studies with sample sizes larger (or smaller) than Caspi et al(1) or in studies published later (in the last three years) or prior to 2010. Indeed, the interaction also proves significant ($P = 5.1 \times 10^{-4}$) if restricted only to maltreatment studies *not* included in the preceding (positive) meta-analysis of Taylor and Kim-Cohen(11). Finally, considering the recent, parallel meta-analysis of 5-HTTLPR variation, life stress and depression(7) alongside our study suggests that the two novel investigations spawning these literatures(1-2) reflect not only prominent, but also durable, examples of GxE interaction. Both analyses also highlight points of methodology affecting study outcomes, such as type of early adversity (here) or, in studies of 5-HTTLPR and depression, stressor type and quality of measurement, which may usefully guide future research aimed at elucidation of etiologic mechanisms. Whether these two instances reflect a more general role of GxE interactions in the genesis of major psychopathologies is unknown, however, and awaits the emergence of comparable literatures addressed to other disorders, genes, and environmental risk factors.

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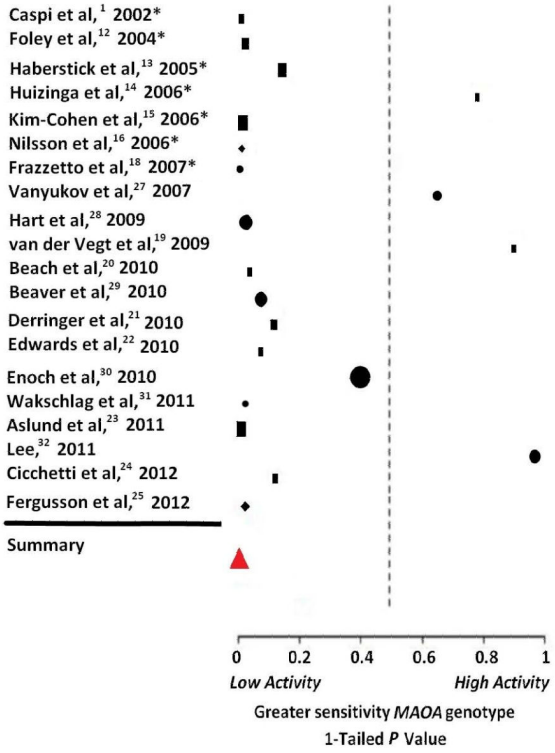

Figure 1.

Forest plot of 20 male samples for the interaction of *MAOA* genotype and early life adversities on aggressive and antisocial behavior. Icons indicate the 1-tailed *P* value for each sample, where lower values denote a greater sensitivity to adversity with *low-activity MAOA* genotype and high values denote a greater sensitivity with *high-activity MAOA* genotype. The size of the icon reflects relative sample size. Squares mark studies that indexed adversity specifically to childhood maltreatment; circles indicate studies of other childhood adversities; and diamonds indicate studies that included both maltreatment and other childhood adversities. The red triangle depicts the overall result of the meta-analysis for all-male samples (2-tailed). Studies marked with an asterisk were included in the prior meta-analysis by Taylor and Kim-Cohen[11].

Table 1

Description of *MAOA*, Early Life Adversity and Antisocial Behavior Studies Included in the Meta-Analysis

					Moderator			Outcome				
Source, Year	**n**	**Male %**	**Race**	**Study Design**	**Adversity Measure**	**Informant**	**Age**	**Antisocial Behavior**	**Informant**	**Age**	**Finding[a]**	**1 Tailed P Value[b]**
Caspi et a,l(1) 2002	442	100%	White	Longitudinal	Maltreatment	INT(C), OBS, PR	3 to 11	CD, Violent Conviction, APD sx, Violent Disposition	INF, INT(C), OR, SR	11 to 18	Positive	0.0050
	229	0%						CD	INT(C)		Negative	0.1285**
Foley et al,(12) 2004	514	100%	White	Longitudinal	Maltreatment	INT(C, P)	<18	CD	INT(C, P)	<18	Positive	0.0200
Haberstick et al,(13) 2005	772	100%	White	Longitudinal	Maltreatment	INT(C), SR	<18	Conduct Problems, Violent Convictions	INT, OR	16, 17 & 22	Negative	0.1423*
Huizinga et al,(14) 2006	277	100%	White	Longitudinal	Maltreatment	SR	<17	CD, Violent Conviction, APD sx, Violent Disposition	INF, INT(C), OR, SR	14 to 28	Negative (Opposite)	0.7794*
Kim-Cohen et al,(15) 2006	975	100%	White	Longitudinal	Maltreatment	INT (P)	≤ 7	ASB; Attention/ Hyperactivity; Emotional Problems	PR, TR	7	Positive	0.0145
Nilsson et al,(16) 2006	79	100%	White	Cross-sectional	Maltreatment; Type of Residence	INT(C), OR	≤ 16 or 19	Stealing, Vandalism, Violence	INT(C)	16 & 19	Positive	0.0078
Widom & Brzustowicz,(17) 2006	261	67%	White	Longitudinal (Case vs. Control)	Maltreatment	OR	<12	CD sx, APD sx, Violent Behaviors	INT(C), OR, SR	<18 to 18+	Positive	0.0143*
	148	62%	NW								Negative	0.5000*
Frazzetto et al,(18) 2007	82	100%	White	Cross-Sectional (Case vs. Control)	Early Adverse Experiences	SR	<16	Physical Aggression	SR	m=30.88	Positive	0.0020
	153	0%									Negative	0.4230
Sjoberg et al,(26) 2007	117	0%	White	Cross-Sectional	Maltreatment; Type of Residence	SR	≤ 16 or 19	Stealing, Vandalism, Violence	INT(C)	16 or 19	Negative (Opposite)	0.9082
Vanyukov et al,(27) 2007	144	100%	White	Longitudinal (High Risk)	Parental Involvement	SR	12 to 18	CD, ADHD	INT (C, P)	12 to 18	Partial Opposite	0.6517*
Ducci et al,(37) 2008	187	0%	White	Cross-Sectional (Case vs. Control)	Maltreatment	INT(C), OR	<16	APSD sx	INT(C)	m=37.80	Positive	0.0002
Hart et al,(28) 2009	672	100%	NW UNS	Longitudinal	Neighborhood Characteristics	OR	r=11-21	Aggression	SR	r=11-23	Positive	0.0250

					Moderator			Outcome				
Source, Year	**n**	**Male %**	**Race**	**Study Design**	**Adversity Measure**	**Informant**	**Age**	**Antisocial Behavior**	**Informant**	**Age**	**Finding[a]**	**1 Tailed P Value[b]**
Prom-Wormley et al,(36) 2009	721	0%	White	Longitudinal	Maltreatment	PR, SR	<18	CD	PR, SR	<18	Opposite	0.9750
van der Vegt et al,(19) 2009	239	100%	NW	Cross-Sectional	Maltreatment	INF	≤15	Externalizing Behaviors (aggression, delinquency)	PR	≤15	Negative (Opposite)	0.9000
Weder et al,(33) 2009	114	66%	NW	Cross-Sectional (Case vs. Control)	Maltreatment	INT(P, C), SR, OR	≤15	Aggression, Rule Breaking, Inattention	TR	≤15	Partial Positive	0.0359*
Beach et al,(20) 2010	244	100%	White	Longitudinal	Maltreatment	INT (C)	<18	APD sx	INT(C)	m=46.48	Negative	0.0300
	294	0%								m=44.95	Positive	0.0240
Beaver et al,(29) 2010	420	100%	White	Longitudinal	Protective-Risk Index	SR	<18	Incarceration, Anger/ Hostility	OR, SR	r=24-32	Partial Positive	0.0694*
	493	0%									Negative	0.1539*
Derringer et al.,(21) 2010	595	100%	White	Longitudinal	Maltreatment	INT (C), SR	<18	CD sx, APD sx	INT(C)	17, 21 & 25	Negative	0.3520*
	246	0%									Partial Positive	0.1057*
Edwards et al,(22) 2010	186	100%	White	Longitudinal (High Risk)	Maltreatment	SR	<6	Externalizing Behaviors (aggression, delinquency)	PR, SR, TR	6 to 22	Negative	0.0675
Enoch et al,(30) 2010	3182	100%	White	Longitudinal	Family Adversity, Stressful Life Events	PR	PN to 7	Conduct Problems, ADHD	PR	4 & 7	Negative	0.3936*
	3976	0%									Partial Positive	0.1635*
Wakschlag et al,(31) 2010	78	100%	White	Longitudinal (High Risk)	Prenatal Smoking	DT, PR	PN	CD sx	PR	m=15	Positive	0.0160*
	99	0%									Opposite	0.9990*
Aslund et al,(23) 2011	780	100%	White	Cross-Sectional	Maltreatment	INT (C)	<18	Stealing, Vandalism, Violence	SR	r=17-18	Positive	0.0048*
	882	0%									Opposite	0.9995*
Lee,(32) 2011	672	100%	White	Longitudinal	Deviant Peer Behavior	SR	m=15.65	Overt/Covert ASB	SR	mr=15-22	Partial Opposite	0.9641*

					Moderator			Outcome				
Source, Year	**n**	**Male %**	**Race**	**Study Design**	**Adversity Measure**	**Informant**	**Age**	**Antisocial Behavior**	**Informant**	**Age**	**Finding[a]**	**1 Tailed P Value[b]**
Reti et al,(34) 2011	283	52%	White	Cross-Sectional	Maltreatment	INT (C)	<18	APD sx	INT(C)	18+	Opposite	0.9236
Cicchetti et al,(24) 2012	312	100%	NW	Cross-Sectional (High Risk)	Maltreatment	OR	≤ 12	CD sx, ASB, Externalizing Behaviors (aggression, delinquency)	INF, INT(C), TR	≤ 12	Partial Positive	0.1190*
Fergusson et al,(25) 2012	351	100%	White	Longitudinal	Maltreatment; PN Smoking; Material Deprivation	INT(C), SR	PN to 15	Violent/Property Offenses, Conduct Problems, Hostility	INT(C), SR, OR	15 to 21; 25 & 30	Positive	0.0192*
McGrath et al,(38) 2012	192	0%	White	Cross-Sectional (High Risk)	Maltreatment	SR	<18	Conduct Problems, Impulsive-Sensation Seeking, Interpersonal Aggression, PN Smoking	SR	m=42.9	Negative (Opposite)	0.9066

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; APD, Antisocial Personality Disorder; ASB, Antisocial Behaviors; C, Child; CD, Conduct Disorder; DT, Drug Test; INF, Other Informant; INT, Interview; m, mean age; mr, mean age range; n, number of participants; NW, Non-white; OBS, Observation; OR, Official Record; P, Parent; PN, Prenatal; PR, Parent-Report; r, age range; SR, Self-Report; sx, Symptom Count; TR, Teacher-Report.

[a] "Positive" indicates a significant ($P<.05$) interaction effect with the low-activity MAOA variant, as presented in the original study report, "Negative" indicates no interaction effect ($P>.05$), and "Opposite" indicates a significant ($P<.05$) interaction with the high-activity MAOA variant. "Partial" indicates a significant interaction effect for one or more, but not all, measures tested in a study with multiple dependent variables.

[b] One-tailed *P*-value, with smaller values ($P<.50$) indicating greater sensitivity among low-activity MAOA subjects and larger values ($P>.50$) indicating greater sensitivity among high-activity MAOA subjects.

* Denotes a weighted mean P-value created when multiple dependent variables and/or multiple environmental moderators were analyzed separately in the published report.

** From footnoted observations that were not a component of primary analyses in Caspi et al,(1) 2002.

Table 2

Studies Included in the All Male Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed P Value	Fisher P Value After Study Exclusion
Caspi et al,(1) 2002	442	0.0050	1.02×10^{-2}
Foley et al,(12) 2004	514	0.0200	9.32×10^{-3}
Haberstick et al,(13) 2005	772	0.1423	7.15×10^{-3}
Huizinga et al,(14) 2006	277	0.7794	3.50×10^{-3}
Kim-Cohen et al,(15) 2006	975	0.0145	1.73×10^{-2}
Nilsson et al,(16) 2006	79	0.0078	5.11×10^{-3}
Frazzetto et al,(18) 2007	82	0.0020	5.27×10^{-3}
Vanyukov et al,(27) 2007	144	0.6517	4.10×10^{-3}
Hart et al,(28) 2009	672	0.0250	1.08×10^{-2}
van der Vegt et al,(19) 2009	239	0.9000	3.28×10^{-3}
Beach et al,(20) 2010	244	0.0300	6.14×10^{-3}
Beaver et al,(29) 2010	420	0.0694	6.73×10^{-3}
Derringer et al,(21) 2010	595	0.3520	4.65×10^{-3}
Edwards et al,(22) 2010	186	0.0675	5.44×10^{-3}
Enoch et al,(30) 2010	3182	0.3936	2.48×10^{-6}
Wakschlag et al,(31) 2010	78	0.0160	4.95×10^{-3}
Aslund et al,(23) 2011	780	0.0048	1.78×10^{-2}
Lee,(32) 2011	672	0.9641	1.28×10^{-3}
Cicchetti et al,(24) 2012	312	0.1190	5.61×10^{-3}
Fergusson et al,(25) 2012	399	0.0192	8.05×10^{-3}
Total	11064		
Average Sample Size	553		.0044

Table 3

Studies Included in the All Male, Maltreatment Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed P Value	Fisher P Value After Study Exclusion
Caspi et al,(1) 2002	442	0.0050	8.59×10^{-6}
Foley et al,(12) 2004	514	0.0200	5.63×10^{-6}
Haberstick et al,(13) 2005	772	0.1423	8.20×10^{-7}
Huizinga et al,(14) 2006	277	0.7794	3.40×10^{-7}
Kim-Cohen et al,(15) 2006	975	0.0145	8.59×10^{-6}
Nilsson et al,(16) 2006	79	0.0183	1.23×10^{-6}
van der Vegt et al,(19) 2009	239	0.9000	2.70×10^{-7}
Beach et al,(20) 2010	244	0.0300	2.25×10^{-6}
Derringer et al,(21) 2010	595	0.3520	3.80×10^{-7}
Edwards et al,(22) 2010	186	0.0675	1.51×10^{-6}
Aslund et al,(23) 2011	780	0.0048	2.24×10^{-5}
Cicchetti et al,(24) 2012	312	0.1190	1.59×10^{-6}
Fergusson et al,(25) 2012	399	0.0051	7.46×10^{-6}
Total	5814		
Average Sample Size	447		.0000008

Table 4

Studies Included in the All Female, Maltreatment Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed P Value	Fisher P Value After Study Exclusion
Caspi et al,(1) 2002	229	0.1285	9.88×10^{-3}
Sjoberg et al,(26) 2007	117	0.9494	2.85×10^{-2}
Ducci et al,(37) 2008	187	0.0002	3.73×10^{-3}
Prom-Wormley et al,(36) 2009	721	0.9750	1.39×10^{-1}
Beach et al,(20) 2010	294	0.0240	3.98×10^{-3}
Derringer et al,(21) 2010	246	0.1057	8.54×10^{-3}
Aslund et al,(23) 2011	882	0.9995	9.68×10^{-1}
McGrath et al,(38) 2012	192	0.9066	3.08×10^{-2}
Total	2868		
Average Sample Size	359		.02