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MAOA, maltreatment, and gene–environment interaction predicting children's mental health: new evidence and a meta-analysis

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Previous research on adults has shown that a functional polymorphism in the promoter region of the monoamine oxidase A (*MAOA*) gene moderates the impact of childhood maltreatment on risk for developing antisocial behavior. Thus far, attempts to replicate this finding have been mixed. The current study (i) presents new data investigating this finding in a sample of 975 seven-year-old boys, and (ii) evaluates the extant data by conducting a meta-analysis of published findings. We replicated the original finding by showing that the *MAOA* polymorphism moderates the development of psychopathology after exposure to physical abuse, we extended the finding to childhood closer in time to the maltreatment experience, and we ruled-out the possibility of a spurious finding by accounting for passive and evocative gene–environment correlation. Moreover, meta-analysis demonstrated that across studies, the association between maltreatment and mental health problems is significantly stronger in the group of males with the genotype conferring low vs high *MAOA* activity. These findings provide the strongest evidence to date suggesting that the *MAOA* gene influences vulnerability to environmental stress, and that this biological process can be initiated early in life.
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Introduction

Children who experience familial adversity such as physical abuse and inter-parental violence show wide variability in their mental health outcomes.[1,2] Many of these children develop behavioral and emotional difficulties, but many others are resilient and exhibit better functioning than predicted given their exposure to adversity. Recent findings[3] suggest that one explanation for variability in outcomes among maltreated individuals relates to a gene–environment interaction (G × E) involving a functional polymorphism in the promoter region of the monoamine oxidase A (*MAOA*) gene. Specifically, maltreated children with the *MAOA* genotype conferring low levels of the *MAOA* enzyme more often developed conduct disorder, antisocial personality, and violent criminality in adulthood than maltreated children with a high-activity *MAOA* genotype. *MAOA* selectively degrades serotonin, norephinephrine, and dopamine following reuptake from the synaptic cleft, and, therefore, plays a key role in regulating behavior.[4,5] Thus far, efforts to replicate Caspi *et al.*'s[3] results have met with mixed results[6–9] indicating that, as yet, accepting the *MAOA* by maltreatment G × E hypothesis would be premature without further investigation. The present study tested whether Caspi *et al.*[3] original finding would replicate in a representative birth cohort sample of 7-year-old boys.

Previous studies have examined the moderating influence of the *MAOA* polymorphism on psychopathology years after the exposure to adversity. Mental health outcomes as a consequence of childhood adversity have been measured at mean ages ranging from 13 to 26 years.[3,6,7] Whether the moderating effect of *MAOA* activity might be present in early life and closer in time to the stressful experience is unknown, yet this information is crucial for understanding the role that G × E might play in developmental processes. The present study asked whether *MAOA* gene activity moderates the impact of maltreatment on mental health outcomes in childhood.

A downward extension of the G × E hypothesis to young children requires a developmentally informed approach for assessing mental health.[10] Based on evidence from animal[5,11] and human[12,13] studies that linked *MAOA* enzyme deficiency with increased

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aggression, Caspi *et al*.'s[3] original G × E investigation of an adult sample targeted antisocial behavior as the hypothesized outcome. Subsequent studies[6–9] using adolescent samples did the same. However, longitudinal data have indicated that adolescent and adult violence and criminality have childhood origins often of the same kind (i.e., antisocial behavior), but also of a different type (e.g., anxiety, hyperactivity).[14] This is because early in development, psychopathology tends to be less differentiated than in later years, when broad behavioral and emotional difficulties develop into more stable and differentiated patterns of maladaptation.[15] Moreover, physical maltreatment is known to elevate risk for a variety of mental health outcomes, including but not limited to antisocial behavior.[16] In childhood, the most common domains of mental health problems include antisocial behavior such as aggression and destructiveness, attention deficits, impulsivity, and hyperactivity, and emotional problems such as anxiety and social withdrawal.[17] More often than not, these domains tend to co-occur in the same child[18] and when they do, this signals greater severity of psychopathology as well as a poorer long-term prognosis.[19] Accordingly, the combination of these mental health problems in 7-year-old boys was the focus of the present investigation.

In order to apply a rigorous test of a G × E, there must be evidence that the risk factor of interest and the outcome are linked via true environmental causation.[10] Otherwise, the association between a putative 'environmental' pathogen and a disorder could be mediated by an unknown third variable, which could reflect unidentified genetic influences. Such a correlation between genetic susceptibility and an environmental risk variable is referred to as a genotype–environment correlation (rGE).[20] The association between familial adversity and mental health outcomes might be explained by rGE of two different kinds.[21] First, aggressive parents may transmit to their children both an adverse rearing environment and a genetic susceptibility toward developing psychopathology (passive rGE). Second, a child with a particular genotype may behave in ways that elicit harsh treatment (evocative rGE). With respect to maltreatment and children's antisocial behavior, evidence of a causal association exists,[22] which argues against rGE as the only mediating mechanism. However, it is desirable to account for possible rGE and so far, only one G × E study involving *MAOA* activity and familial adversity has done so.[6] In the present study, we tested for the presence of passive rGE by controlling for mothers' antisocial personality and evocative rGE by testing whether boys' *MAOA* genotype predicted their exposure to maltreatment.

An extension of the replication strategy is to use meta-analysis systematically to aggregate results over multiple studies, which with regard to this particular G × E hypothesis remains mixed. One possible reason for discrepancy is across-study variability in conceptualizing and measuring the putative environmental risk factor. For instance, in a positive replication by Foley *et al*.,[6] 'family adversity' was measured prospectively as parental neglect, domestic violence, and harsh discipline. In the study by Haberstick *et al*.,[7] a partial failure to replicate, maltreatment was assessed retrospectively using different indicators. Meta-analysis is one tool for ascertaining whether a finding transcends such differences across studies. Meta-analysis is an increasingly valuable method in the field of psychiatric genetics, which in recent years has been plagued by non-replications,[23] leaving questions about gene effects on behavior in doubt. By pooling data from several studies, meta-analysis maximizes power to detect effects and avoids overemphasizing estimates from any single study.[24] The present investigation evaluated the current state of the cumulative evidence regarding *MAOA* activity, childhood adversity, and G × E via a meta-analysis.

Materials and methods

Sample

Participants are members of the Environmental Risk (E-Risk) Longitudinal Twin Study. The E-Risk sampling frame was two consecutive birth cohorts (1994 and 1995) in a birth register of twins born in England and Wales.[25] Of the 15 906 twin pairs born in these 2 years, 71% joined the register. Bias from non-response was corrected as follows.

The E-Risk Study probability sample was drawn using a high-risk stratification sampling procedure. High-risk families were those in which the mother had her first birth when she was 20 years of age or younger. We used this sampling (a) to replace high-risk families who were selectively lost to the register via non-response and (b) to ensure sufficient base rates of children growing up in at-risk environments. Age at first childbearing was used as the risk-stratification variable because it was recorded for virtually all families in the register, it is relatively free of measurement error, and early childbearing is a known risk factor for children's problem behaviors.[26,27] The sampling strategy resulted in a final sample in which one-third of Study mothers (younger only; $N = 314$) constitute a 160% oversample of mothers who were at high risk based on their young age at first birth (15–20 years). The other two-thirds of Study mothers ($N = 802$) accurately represent all mothers in the general population (aged 15–48) in England and Wales in 1994–1995 (estimates derived from the General Household Survey[28]). To provide unbiased statistical estimates that can be generalized to the population of British families with children born in the 1990s, the data reported in this article were corrected with weighting to represent the proportion of young mothers in that population.

The E-Risk Study sought a sample size of 1100 families to allow for attrition in future years of the longitudinal study while retaining statistical power. An initial list of families who had same-sex twins was drawn from the register to target for home visits. Of

the families from the initial list, 1116 (93%) participated in home-visit assessments when the twins were aged 5 years, forming the base sample for the study: 4% of families refused and 3% could not be reached after many attempts. Written informed consent was obtained from mothers. With parent's permission, questionnaires were posted to the children's teachers, and teachers returned questionnaires for 94% of cohort children.

A follow-up home visit was conducted 18–24 months after the children's age-5 assessment. Follow-up data were collected for 98% of the 1116 E-Risk Study families. At this follow-up, teacher questionnaires were obtained for 91% of the 2232 E-Risk Study children (93% of those taking part in the follow-up). The E-Risk Study has received ethical approval from the Maudsley Hospital Ethics Committee.

The present study includes 975 of the 1092 total boys in the E-Risk Study who are of Caucasian ancestry and for whom genotypic data were available. (DNA was not available for 36 boys. These boys did not differ significantly from the rest of the sample on risk for physical abuse exposure or level of mental health problems. Genotyping failure occurred in 23 cases.) Boys' single X chromosome yields two straightforwardly characterized *MAOA* promoter genotypes: high activity (66.3% in this sample) and low activity (33.7%).[3] Girls were excluded because, having two copies of the X chromosome, they fall into two homozygous groups, 'high–high' (39.1% in this sample) and 'low–low' (15.1%), and a third heterozygous group, 'high–low' (45.8%). Based on presently available evidence, girls' status on *MAOA* gene expression cannot be characterized with certainty because of conflicting findings regarding the inactivation status of the *MAOA* locus on the X chromosome.[29,30] In other words, whether the level of *MAOA* transcription in female subjects results from one or both copies of the *MAOA* gene is presently unknown and therefore, inferences about high or low *MAOA* activity in girls cannot be made.

DNA extraction and genotyping

At ages 5 and 7 years, DNA samples were obtained from study members via buccal swabs and extracted using a procedure described by Freeman *et al*.[31] Primer sequences are described by Sabol *et al*.,[4] namely *MAO APT1* (5′-ACAGCCTGACCGTGGA GAAG-3′) and *MAO APB1* (5′-GAACGGACGCTC CATTCGGA-3′). *MAO APT1* was 5′-labeled with the FAM fluorophore. Polymerase chain reaction (PCR) was carried out on a PTC-225 DNA engine (MJ Research, Hercules, CA, USA), using the following cycling conditions: initial 2 min denaturing step at 95°C, followed by 35 cycles of 94°C for 1 min, 55.5°C for 1 min and 72°C for 2 min, and a final extension phase of 72°C for 5 min. Reactions contained 1 × reaction Buffer IV (Abgene, Epsom, UK), 1.5 mM $MgCl_2$, 50 ng of genomic DNA, 5 pmols of each primer, 0.3 mM dNTPs, and 1.5 U of Native *Taq* (Promega, Madison, WI, USA) in a volume of 10 μl. PCR products were denatured in highly deionized formamide and analyzed by electrophoresis on an Applied Biosystems 3100 genetic analyzer (Applied Biosystems, Foster City, CA, USA), set up in genotyping mode, using a POP4 polymer and ROX-labeled GS500 size standard (Applied Biosystems). Results were analyzed using GeneScan v3.7 and Genotyper v3.6 software (Applied Biosystems).

Physical abuse exposure

Children's physical abuse exposure was assessed separately for each twin at the first and follow-up assessments by interviewing mothers with the standardized clinical interview protocol from the *Multi-Site Child Development Project*.[32] The interview protocol was designed to enhance mothers' comfort with reporting valid child maltreatment information, while also meeting researchers' legal and ethical responsibilities for reporting. Under the UK Children Act,[33] our responsibility was to secure intervention if maltreatment was current and ongoing. Such intervention on behalf of E-Risk families was carried out with parental cooperation in all but one case.

The protocol included standardized probe questions such as, 'Do you remember any time when (boy's name) was disciplined severely enough that he may have been hurt?' and 'Did you worry that you or someone else may have harmed or hurt (boy's name)?' Questions were carefully worded to avoid implying that the mother was the perpetrator, so mothers might feel more willing to report that a child had been maltreated. In cases where mothers reported any maltreatment, interviewers probed for details about the incident and recorded notes. Based on the mothers' narrative, interviewers coded if the boy had definitely been physically maltreated ($N = 34$). Examples of such maltreatment included being a victim of adjudicated assault by a teenaged sibling, punished by being burned with matches, had injuries (e.g., fractures or dislocations) from neglectful or abusive parental care, and/or were formally registered with a social services child protection team for physical abuse.

A further 147 boys were designated as 'probable maltreatment.' The 'probable maltreatment' category does not represent a milder form of abuse compared to the 'definite maltreatment' category. Instead, this group includes children who could only be suspected of having experienced maltreatment. In these probable cases, the boy had been reported by concerned schools, neighbors, and/or family members to child protective services but the case was not resolved or registered, he seemed afraid of his father during our home visit, the mother reported that he received frequent physical discipline, or she said he had been smacked harder than intended, leaving a mark or bruise. Some of these boys will not have experienced maltreatment, whereas a subset of them has been maltreated but our coding had to remain uncertain. To enhance certainty, we used information about

intimate partner violence to re-classify children in the probable category who were at greatest likelihood of having been maltreated. Researchers have documented the high correlation between intimate partner violence and child maltreatment.[34,35]

Intimate partner violence in the home was assessed by inquiring about 12 acts of physical violence (e.g., kicking a partner, threatening a partner with a knife) following the protocol of the *Conflict Tactics Scale – Form R*.[36] Mothers were asked about their own violence toward a partner and about any partner's violence toward them in the years of the child's life before the age-5 and the age-7 assessments. A methodological study demonstrated strong reliability and validity for the partner violence scale (i.e., 0.89 internal consistency and 75% inter-partner agreement).[37]

Children in the 'probable' maltreatment category were classified as having physical abuse exposure if their families were in the top 5% of the distribution of partner violence at either the age-5 or age-7 assessments. This method resulted in 28 boys from the 'probable maltreatment' group being added to the group of children we classified for this article as having been exposed to physical abuse. The resulting group totaled 62 boys (6.4% of the cohort unweighted; 4.7% weighted to represent the population) who were exposed to physical abuse.

Children's mental health outcomes

At the age-7 assessment, children's behavior problems were assessed with the *Child Behavior Checklist*[38] and the *Teacher Report Form*,[39] supplemented with items from the Rutter Child Scale[40] and additional items measuring *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*[41] criteria for attention deficit hyperactivity disorder (ADHD). The CBCL cutoff for the clinical range (top 2% of the standardization sample) was exceeded by 7% of E-Risk cohort boys. Symptoms and behaviors were reported for the preceding 6 months and each item was scored as (0) 'not true,' (1) 'somewhat true,' and (2) 'very often true.' Sample items from the *Antisocial Behavior Scale* include 'physically attacks people,' 'lying or cheating,' and 'destroys things that belong to others' ($M = 21.57$, s.d. = 18.02). Sample items from the *Attention Deficit Hyperactivity Scale* include 'very restless,' 'cannot concentrate,' and 'impulsive or acts without thinking' ($M = 16.25$, s.d. = 12.40). Sample items from the *Emotional Problems Scale* include 'too fearful or anxious,' 'unhappy, sad, or depressed,' and 'withdrawn from social interaction' ($M = 11.08$, s.d. = 8.23). Following recommendations from the test manual,[42] we used mother interviews and teacher reports of children's behavior in combination to maximize reliability and validity. Mother and teacher reports of the same behaviors were moderately correlated and alpha reliabilities for all scales exceeded 0.85. Because simple combinatorial rules work as well, or better, than more complicated ones,[43] mothers' and teachers' reports were averaged to create scales of antisocial behavior, attention-deficit hyperactivity, and emotional problems. Principal Components Analysis (PCA) of the three subscales identified a single *Composite Mental Health Problem Scale* that accounted for 64.1% of the variance. Each of the component scales loaded adequately on the factor, with factor loadings ranging from 0.61 to 0.90. All scale scores were standardized with a mean of 0 and a standard deviation of 1.

Maternal antisocial personality symptoms

Mothers reported on their own lifetime antisocial history. Questions were derived from the *Diagnostic Interview Schedule*,[44] supplemented by items from the *Young Adult Behavior Checklist*.[45] The items covered illegal behavior, deceitfulness, impulsivity, aggressiveness, recklessness, and irresponsibility. A symptom was considered to be present if the mother reported behavioral items representing the symptom as being 'very true or often true.' Symptom counts in this study ranged from 0 to 6 ($M = 0.61$, s.d. = 1.07).[46]

Statistical analyses

First, we used ordinary least-squares regression to test the main effect associations of boys' physical abuse exposure and *MAOA* genotype in predicting mental health problems. Second, we tested for an interaction between *MAOA* activity and physical abuse exposure in predicting boys' mental health problems. Third, we tested whether boys' *MAOA* genotype was associated with risk for physical abuse exposure (i.e., evocative rGE). Fourth, we controlled for a possible passive rGE by adjusting for the effect of maternal antisocial personality symptoms in the regression analyses. Analyzing two boys in each family creates dependence in the data, and thus all regression results are based on the sandwich or Huber/White variance estimator,[47] a method available in *STATA 9.0*,[48] which adjusts estimated standard errors to account for that dependence and provides statistical tests that are robust to model assumptions.[49] Fifth, we conducted a meta-analysis pooling results from previous G × E studies of the *MAOA* polymorphism, physical maltreatment, and mental health with findings from the present study.

Results

Allele frequencies

Genotypes in the sample consisted of five variants of the 30-bp repeat sequence: 2- (0.2%), 3- (31.9%), 3.5- (2.1%), 4- (64.2%), and 5-repeats (1.6%). These allele frequencies matched closely the frequencies reported in other Caucasian samples.[31] In terms of expression, all studies agree on the functional classification of the two most common alleles, that is, 3-repeats (low activity), and 4-repeats (high activity). Of rare alleles, both Sabol *et al*.[4] and Deckert *et al*.[50] assayed the 3.5-repeat with the same result (high activity), whereas a discrepancy resulted for the 5-repeat. We chose the classification of Sabol *et al*.[4] (i.e., 5-repeat equals low

activity) as they assayed three cell lines as opposed to one. The rare 2-repeat, of which only two cases exist in our sample, was classified as low activity based upon precedence in previous studies. Dropping the 18 boys with the 2- or 5-repeat alleles did not alter the pattern of findings nor their significance.[3,6,7]

Predicting composite mental health problems

Sample sizes, group means, and effect size comparisons are presented in Table 1. As expected, there was a significant main effect of physical abuse exposure on children's mental health problems (Table 2). In addition, we found a significant main effect of *MAOA* activity ($P=0.017$), such that boys with the high activity allele had a higher level of mental health problems. The test for the interaction between *MAOA* activity and physical abuse exposure revealed a significant G × E ($b=-0.84$, s.e. = 0.40, $t=2.09$, $P=0.037$). This interaction showed that the effect of physical abuse exposure was significantly weaker among boys with high *MAOA* activity ($b=0.61$, s.e. = 0.22, $t=2.83$, $P=0.005$) than among boys with low *MAOA* activity ($b=1.45$, s.e. = 0.33, $t=4.40$, $P<0.001$) (see Figure 1).

Next, we examined whether there might be evidence of a rGE in two ways. First, we tested for the possibility that a child's genotype might be involved in evoking or eliciting physical abuse exposure. We found that it did not. Boys' *MAOA* activity was not significantly associated with likelihood of exposure to physical abuse (low-activity *MAOA* 3.5%; high-activity *MAOA* 5.3%; $F_{(1,974)}=1.89$, $P=0.170$). Second, we tested whether a child's *MAOA* genotype might be related to the likelihood of experiencing physical abuse indirectly via an association with

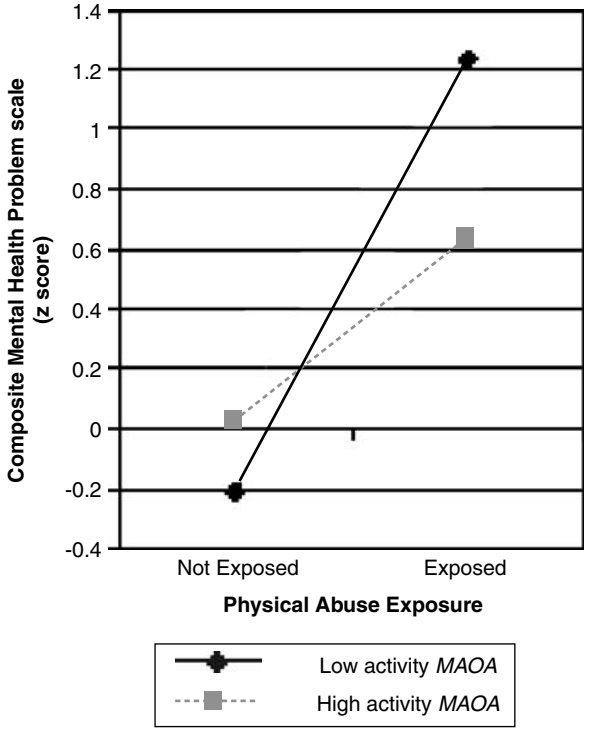

Figure 1 Gene-by-physical abuse exposure interaction predicting children's composite mental health problems.

Table 1 Sample sizes, means, standard deviations, and effect size (Cohen's *d*) comparisons of age-7 mental health outcomes in boys by *MAOA* genotype and physical abuse exposure

Children's mental health outcomes	*Physical abuse exposure*	*MAOA genotype*	
		Low activity	*High activity*
Sample sizes	Not exposed	$N=313$	$N=600$
	Exposed	$N=16$	$N=46$
		M (s.d.)	M (s.d.)
Composite mental health problem scale	Not exposed	−0.21 (0.91)	0.02 (0.97)
	Exposed	1.24 (1.38)	0.63 (1.04)
		$d=1.55$	$d=0.63$
Component mental health subscales			
Antisocial behavior subscale	Not exposed	−0.19 (0.90)	0.02 (0.98)
	Exposed	1.07 (1.61)	0.68 (1.02)
		$d=1.33$	$d=0.67$
Attentional problems and hyperactivity subscale	Not exposed	−0.17 (0.89)	0.04 (1.01)
	Exposed	1.02 (1.13)	0.45 (1.18)
		$d=1.32$	$d=0.40$
Emotional problem subscale	Not exposed	−0.13(0.90)	−0.03 (0.99)
	Exposed	0.92 (1.10)	0.37 (1.01)
		$d=1.15$	$d=0.40$

Abbreviations: MAOA, monoamine oxidase.

parental characteristics that increase environmental risk exposure. Maternal antisocial personality symptoms were significantly correlated with children's likelihood of physical abuse exposure ($b = 1.22$, s.e. = 0.26, $t = 4.79$, $P < 0.001$). However, when the model was adjusted for the main effects of physical abuse exposure, *MAOA* genotype, and maternal antisocial personality symptoms, the interaction between *MAOA* activity and physical abuse exposure remained significant (Table 2).

Do results hold for component mental health subscales?

We repeated the analyses separately predicting each of the component mental health subscales to examine whether the G × E interaction finding would be robust across multiple outcomes. All subscale findings of the interaction were in the predicted direction (Figure 2a–c) and mirrored the findings reported for the composite mental health measure. However, only the ADHD subscale yielded clear statistical significance ($b = -0.78$, s.e. = 0.35, $t = 2.26$, $P = 0.024$) (Table 2). This G × E finding remained significant ($P = 0.014$) after controlling for maternal antisocial personality symptoms.

Meta-analysis

We included studies in our meta-analysis if they fulfilled four criteria. First, the study had to be published in a peer-reviewed journal. Second, the study had to include genotypic information on the variable number tandem repeat polymorphism in the promoter region of the *MAOA* gene. Third, the study had to include a measure of serious familial adversity in childhood that was significantly associated in a main effect fashion with the outcome measure. Fourth, the sample had to be drawn from a non-clinical population. In addition to the present study, we know of four previous studies that meet all criteria.[3,6–8] A study by Young *et al*.[9] was excluded

Table 2 Results of regression analyses testing gene-by-physical abuse exposure interaction effects on children's mental health outcomes

Children's mental health outcomes	*Test for main effects*[a]				*Test for interaction term*				*Test for passive rGE*			
	b	*s.e.*	t	P	b	*s.e.*	t	P	b	*s.e.*	t	P
Composite mental health problem scale												
Constant	−0.19	0.07	2.83	0.005	−0.21	0.07	3.18	0.002	−0.31	0.07	4.56	0.001
Physical abuse exposure	0.83	0.19	4.44	0.001	1.45	0.33	4.41	0.001	1.25	0.30	4.12	0.001
MAOA genotype	0.19	0.08	2.40	0.017	0.23	0.08	2.81	0.005	0.22	0.08	2.86	0.004
Physical abuse exposure × *MAOA* genotype					−0.84	0.40	2.09	0.037	−0.85	0.39	2.19	0.029
Maternal antisocial personality symptoms									0.18	0.05	3.76	0.001
Component mental health subscales												
Antisocial behavior subscale												
Constant	−0.18	0.06	2.73	0.007	−0.19	0.06	3.01	0.003	−0.30	0.07	4.49	0.001
Physical abuse exposure	0.81	0.18	4.55	0.001	1.26	0.39	3.27	0.001	1.05	0.38	2.77	0.006
MAOA genotype	0.19	0.08	2.34	0.019	0.21	0.08	2.66	0.008	0.21	0.08	2.72	0.007
Physical abuse exposure × *MAOA* genotype					−0.61	0.44	1.38	0.169	−0.63	0.45	1.40	0.163
Maternal antisocial personality symptoms									0.18	0.05	3.84	0.001
ADHD subscale												
Constant	−0.15	0.06	2.42	0.016	−0.17	0.06	2.73	0.007	−0.26	0.06	4.07	0.001
Physical abuse exposure	0.62	0.18	3.37	0.001	1.20	0.27	4.49	0.001	1.01	0.23	4.35	0.001
MAOA genotype	0.18	0.08	2.23	0.026	0.21	0.08	2.57	0.010	0.21	0.08	2.62	0.009
Physical abuse exposure × *MAOA* genotype					−0.78	0.35	2.26	0.024	−0.80	0.32	2.48	0.014
Maternal antisocial personality symptoms									0.16	0.04	3.90	0.001
Emotional Problem Subscale												
Constant	−0.11	0.06	1.92	0.055	−0.13	0.06	2.20	0.028	−0.17	0.06	2.60	0.010
Physical abuse exposure	0.57	0.16	3.44	0.001	1.05	0.29	3.67	0.001	0.97	0.27	3.56	0.001
MAOA genotype	0.08	0.07	1.07	0.283	0.10	0.07	1.41	0.159	0.10	0.07	1.38	0.168
Physical abuse exposure × *MAOA* genotype					−0.65	0.35	1.85	0.065	−0.65	0.35	1.89	0.059
Maternal antisocial personality symptoms									0.06	0.04	1.65	0.099

[a]*N*s range between 954 and 959 across models because of missing data on boys' mental health measures or maternal antisocial personality symptoms.

Abbreviations: ADHD, attention deficit hyperactivity disorder; MAOA, monoamine oxidase A; rGE, gene–environment correlation.

The table presents final models with main effects and interactions entered simultaneously.

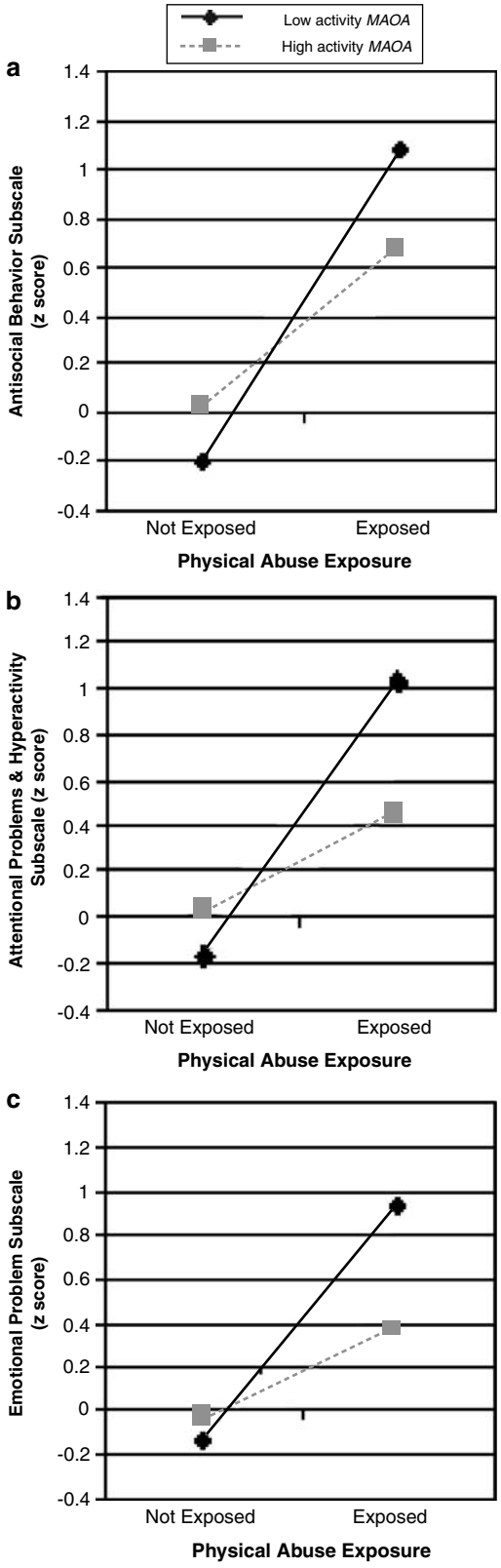

Figure 2 Gene-by-physical abuse exposure interaction predicting subscales of children's (**a**) antisocial behavior, (**b**) attentional problems and hyperactivity, and (**c**) emotional problems.

because their entire sample consisted of adolescents in clinical treatment for serious conduct problems, no matched control group was included, and their measure of lifetime conduct disorder symptoms places the temporal ordering of the risk and outcome variables in question.

Standard methods for effect size conversion were used to translate the results of the different studies into a common metric of correlations.[51,52] The correlations of interest were those reported between family adversity and antisocial behavior within each *MAOA* genotype group. If papers reported more than one outcome measure, we chose the most general measure of antisocial behavior (e.g., composite measures). Where necessary, authors were contacted for additional results in order to calculate effect sizes. All correlations were z-transformed and their standard errors derived.

Heterogeneity across studies was assessed using the χ^2-based Q statistic, as well as the I^2 measure of the percentage of across-study variation attributable to heterogeneity.[53,54] Using meta-analysis programs available in *STATA 9.0*,[48,55] fixed- and random-effects estimates and results were consistent across all analyses; we report only results from the more conservative random-effects model. Meta-analysis of the interaction effect was carried out using the difference in the transformed correlations across the *MAOA* groups within each study.

Figure 3 depicts results of the meta-analysis conducted in two ways. First, panel a presents a forest plot of the correlations between maltreatment and antisocial behavior by *MAOA* activity group for all studies. Within the high-activity *MAOA* group, there was no evidence of significant heterogeneity across studies ($\chi^2_{df=4} = 0.79$, $P = 0.940$, $I^2 = 0.0\%$), but there was mild–moderate heterogeneity across studies in the low-activity *MAOA* group as indicated by the I^2 measure ($\chi^2_{df=4} = 6.29$, $P = 0.179$, $I^2 = 36.4\%$). The random effects pooled estimates within *MAOA* activity groups were as follows: low *MAOA* activity, 0.32 (95% CI: 0.23, 0.40; $P < 0.001$); high *MAOA* activity, 0.12 (95% CI: 0.08, 0.17; $P < 0.001$).

Second, panel b presents a forest plot of the meta-analysis of the interaction effect based on the differences in correlations by *MAOA* activity group. No significant heterogeneity was detected across the studies ($\chi^2_{df=4} = 3.79$, $P = 0.440$, $I^2 = 0.0$). The pooled random-effects estimate of the change in correlations from the high- to low-activity *MAOA* groups indicated a significant effect of 0.18 (95% CI: 0.10, 0.26; $P < 0.001$).

We carried out two additional sensitivity analyses on the meta-analysis results. First, we removed the study by Caspi *et al*.[3] and re-estimated the pooled effects to rule-out potential bias contributed by the first published study of this hypothesis.[24,56] This resulted in a significant but reduced pooled difference in correlations of 0.16 (95% CI: 0.07, 0.25; $P = 0.001$). Second, we removed the Nilsson *et al*.[8] study, which reported an effect size larger in

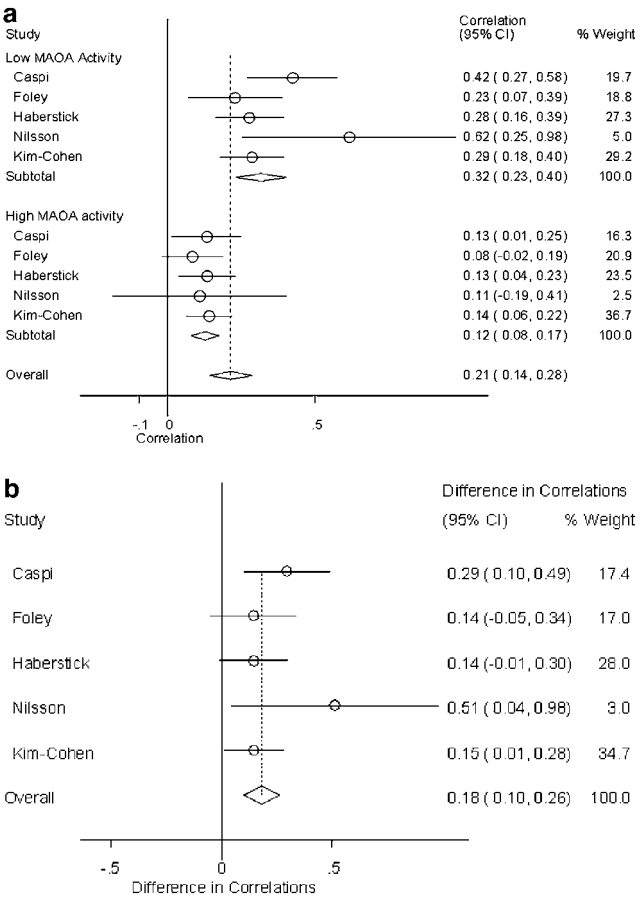

Figure 3 Meta-analysis pooling results across studies. Summary correlations between measures of childhood maltreatment and mental health are presented separately in the low- vs high-activity *MAOA* genotype groups. CI indicates confidence interval. Squares and % weight indicate the size of each study's contribution to the summary correlations indicated by diamonds. (**a**) Forest plot of correlations between childhood maltreatment and mental health, as a function of *MAOA* genotype group in five independent studies. (**b**) Forest plot of the interaction effect based on differences in correlations between childhood maltreatment and mental health observed in low- vs high-activity MAOA genotype groups in five independent studies.

magnitude than the original study by Caspi *et al*.[3] After both studies were removed, results showed a pooled effect of 0.15 (95% CI: 0.05, 0.24; $P=0.002$) (Meta-analysis using effect sizes for children's antisocial behavior from the Kim-Cohen *et al*. study resulted in the same pattern of significant findings. Details are available from first author.).

Discussion

Since 2002 when evidence first appeared that an *MAOA* polymorphism moderates the impact of childhood maltreatment on risk for antisocial behavior,[3] scientists have awaited supporting data through replication. The present investigation evaluated this G × E hypothesis in two ways. First, using data from a representative birth cohort sample of 7-year-old boys, we replicated and extended Caspi *et al*.'s[3] original results. Among children who were exposed to physical maltreatment, boys with the low-activity *MAOA* allele had mental health problem scores that were half a standard deviation higher than boys with the high-activity allele. Second, our preliminary meta-analysis found supportive evidence of this G × E effect. Pooling estimates from five studies, we found that the association between early familial adversity and mental health was significantly stronger in the low-activity *MAOA* vs the high-activity *MAOA* groups. If replication is the '*sine qua non* for accepting a hypothesis' (p. 627),[57] then evidence from the present study brings the field closer toward confirming that *MAOA* activity is meaningfully involved in explaining variability in developmental outcomes as a consequence of maltreatment.

Beyond replication and meta-analysis, this study contributes novel information in several additional ways. First, we extended the findings downward to a sample of 7-year-old boys, indicating that variability in young children's mental health is explained significantly by differences in vulnerability to stress as indexed by a genetic polymorphism. This finding suggests that one mechanism by which maltreatment leads to the development of psychopathology relates specifically to *MAOA* functioning, and that this biological process can be initiated early in life. Eventually, such evidence can inform not only what treatments might help prevent psychopathology in physically maltreated children but also when such intervention might be most successful. Second, we evaluated *MAOA* activity in relation to children's global mental health outcomes in addition to their antisocial behavior. In the Dunedin sample of adult males, the *MAOA* polymorphism did not moderate stress effects in predicting depression,[58] suggesting that in adults, *MAOA* activity moderates the impact of stress specifically towards an antisocial outcome. In childhood, the G × E involving *MAOA* appears to influence ADHD-related symptoms as well as a broader phenotype comprising several domains of mental health that together signal the beginning of a maladaptive trajectory toward the development of adult antisocial behavior. Third, we ruled-out the possibility that the G × E might be explained spuriously by a passive or evocative rGE.

One unexpected finding of the present study was that the *MAOA* polymorphism predicted children's mental health outcomes in a main effect fashion. Boys with the genotype conferring high *MAOA* activity had slightly but significantly elevated levels of global mental health problems as well as antisocial behavior and attention-deficits/hyperactivity relative to boys with the low-activity genotype. This finding is not inconsistent with previously published results of a significant main effect of the high-activity *MAOA* genotype on increasing risk for antisocial behavior and ADHD.[59–61] Moreover, closer inspection of other

G × E studies involving the *MAOA* polymorphism reveals similar findings, albeit at marginally significant levels.[3,6,7] For instance, Foley *et al*.[6] found a nonsignificant trend ($P < 0.14$) for the high-activity *MAOA* allele increasing risk for conduct disorder; after adjusting for the interaction between the *MAOA* polymorphism and maltreatment, the main effect became significant ($P = 0.04$). However, two recent studies found contradictory results with positive prediction from the low-activity *MAOA* genotype to ADHD.[62,63] Further research to resolve these discrepancies is needed to understand the direction of gene effects on conferring risk for psychopathology in the absence or presence of risk exposure.

Strengths of this study include a meta-analysis as well as an original analysis of data from a large, nonselected sample of boys at a young age when early emerging psychopathology predicts continuing difficulties in later life. Genotype, phenotype, and physical abuse exposure were measured using independent methods. The findings, however, should be interpreted in light of several limitations. First, our sample comprised Caucasian twins living in England and Wales. However, allele frequencies for the *MAOA* promoter polymorphism[3,4] and base rates of physical abuse exposure in our sample are comparable to those reported elsewhere.[34] Future research should test whether our findings replicate in singleton children and in non-Caucasian samples. Second, official records of maltreatment history were not available. However, unlike many large-scale studies that rely upon self-complete questionnaires, we interviewed caregivers face-to-face about violence exposure, a method having evidence of good validity.[22] Third, because girls' *MAOA* genotype cannot be characterized with confidence, our findings and the findings of previous studies are informative only about males. More progress toward understanding X-chromosome inactivation and *MAOA* gene expression is needed before the relevance of this finding to female subjects can be evaluated. Fourth, our meta-analysis contained only four studies in addition to Caspi *et al*.'s[3] original study. Therefore, our meta-analysis results should be re-evaluated once further tests of the hypothesis are published.

Ultimately, the goal of genomics research is to prevent mental disorder[57] and to refine treatment strategies.[64] Reliable G × E findings have considerable potential for informing such efforts.[10] However, a statistical interaction between a genotype and an environmental risk factor requires further research to uncover the biological mechanisms involved in the interaction.[65] Because the *MAOA* enzyme selectively metabolizes serotonin, norepinephrine, and dopamine,[4,5] which are involved in multiple brain functions associated with stress regulation,[66] it is likely to be one of myriad factors involved in the development of biological sensitivity to stress and the social context.[67] A statistical G × E involving *MAOA* thus represents an important launching pad for developmental neuroscience research into the underlying causal mechanisms involved in the etiology of psychopathology.[10,64,68–70] Moreover, it is possible that the *MAOA* gene may simply be a marker for a behavioral trait, which itself moderates the association between maltreatment and children's mental health.

Eradicating child maltreatment is clearly the preferred way to combat risk for psychiatric problems, and yet large numbers of children in Western societies are abused and exposed to family violence each year.[35] Once an adverse experience touches off an otherwise 'silent' genetic vulnerability and triggers a cascade of biological events toward atypical development, what can be done to halt or reverse the process? In addition to possible pharmacological interventions, recent research on the serotonin transporter polymorphism suggests that social support can protect even genetically vulnerable children from the negative sequelae of maltreatment.[71] As evidence for significant G × E in predicting mental health continues to emerge,[70] both scientists and the public are becoming increasingly aware that like many developmental processes,[72] the nature of gene effects on behavior, too, is often contingent upon experience.

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