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Does *MAOA* Increase Susceptibility to Prenatal Stress in Young Children?

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Abstract

Background—We previously demonstrated a gene-by-prenatal-environment interaction whereby the monoamine oxidase A gene (*MAOA*) modified the impact of prenatal tobacco exposure (PTE) on adolescent disruptive behavior (DB), with the *MAOA* risk genotype varying by sex. We extend this work by examining whether this mechanism is evident with another common adversity, prenatal stress exposure (PSE), and whether sex differences are present earlier in development in closer proximity to exposure.

Methods—Participants were 281 mothers and their 285 children derived from a prenatal cohort with in-depth prospective measures of PSE and PTE. We assessed DB at age 5 via dimensional developmentally-sensitive measurement. Analyses were stratified by sex based on prior evidence for sex differences.

Results—Concurrent stress exposure predicted DB in children (β=.310, p=.001), while main effects of prenatal exposures were seen only in boys. We found a three-way interaction of *MAOA*xPSExsex on DB (β=.813, p=.022). Boys with *MAOA-H* had more DB as a function of PSE, controlling for PTE (β=.774, p=.015), and as a function of PTE, controlling for PSE (β=.362, p=.037). Boys with *MAOA-L* did not show this susceptibility. *MAOA* did not interact with PSE (β=−.133, p=.561) nor PTE (β= −.144; p=.505) in predicting DB in girls. Examination of gene-environment correlation (rGE) showed a correlation between paternal *MAOA-L* and daughters' concurrent stress exposure (r=−.240, p=.013).

Discussion—Findings underscore complex mechanisms linking genetic susceptibility and early adverse exposures. Replication in larger cohorts followed from the pregnancy through adolescence is suggested to elucidate mechanisms that appear to have varying developmental expression.

Keywords

monoamine oxidase A; pregnancy smoking; early adversity; disruptive behavior; gene x environment interaction; sex differences

1. Introduction

The monoamine oxidase A gene untranslated variable number of tandem repeats marker, referred to herein, as *MAOA*, influences the degradation of monoamines, thus may critically regulate risk for aggression and related phenotypes (Buckholtz & Meyer-Lindenberg, 2008, Sabol *et al.*, 1998). In their seminal study nearly 15 years ago, Caspi and colleagues demonstrated how *MAOA* moderated the impact of childhood maltreatment on later aggressive antisocial behavior in adult males (Caspi *et al.*, 2002). Since this time, at least 34 empirical papers and 3 reviews of the *MAOA*-adversity-antisocial behavior mechanism have followed (Buades-Rotger & Gallardo-Pujol, 2014, Byrd & Manuck, 2014, Goldman & Rosser, 2014, Kim-Cohen *et al.*, 2006). Since the most recent meta-analysis published in 2014, an additional 8 papers have linked the MAOA x adversity interaction to a range of adult problem behaviors including criminal behavior (Lu & Menard, 2016), aggression

(Hohmann *et al.*, 2016, Rehan *et al.*, 2015, Schlüter *et al.*, 2016, Zhang *et al.*, 2016), cigarette smoking (Huang *et al.*, 2015), drug use (Harro & Oreland, 2016), and alcohol use (Cervera-Juanes *et al.*, 2015). Yet very few studies to date have examined *MAOA* x adversity interactions in regards to the developmental expression of these patterns in young children (Enoch *et al.*, 2010, Hill *et al.*, 2013, Kim-Cohen *et al.*, 2006).

Furthermore, despite accruing evidence of *MAOA* x adversity interactions, the direction of these patterns has been inconsistent. Results have been most robust regarding antisocial behavior in male offenders with the low-activity *MAOA* variant (*MAOA-L*) who were exposed to childhood maltreatment (Byrd & Manuck, 2014). However, a number of studies in offender and non-offender male samples have suggested instead, that the *high* activity variant (*MAOA-H*) confers greater antisocial risk (Gorodetsky *et al.*, 2014, Lee, 2011, Prichard *et al.*, 2008, Tikkanen *et al.*, 2011, Tikkanen *et al.*, 2010, Tikkanen *et al.*, 2009, Van Der Vegt *et al.*, 2009). Moreover, evidence from a growing number of studies that include female subjects suggests that *MAOA* interacts with environmental adversity in a sex-specific manner. To date there are 15 studies that have included females. Of these, 10 have suggested that females with the *high*-activity variant are at greater risk for antisocial behavior following exposure to childhood adversity or maltreatment (Åslund *et al.*, 2011, Kim-Cohen *et al.*, 2006, Kinnally *et al.*, 2009, Mcgrath *et al.*, 2012, Nikulina *et al.*, 2012, Nilsson *et al.*, 2011, Prom-Wormley *et al.*, 2009, Sjöberg *et al.*, 2007), while 5 studies suggest that the *low*-activity variant is associated with risk (Beach *et al.*, 2010, Enoch *et al.*, 2010, Hohmann *et al.*, 2016, Kim-Cohen *et al.*, 2006, Rehan *et al.*, 2015). Thus, there is substantial evidence for sex differences in patterns, but the risk (or susceptibility) variant in each sex remains unclear.

Limitations of candidate gene-by-environment studies could contribute to observed discrepancies regarding *MAOA*. Behavioral phenotypes are associated with numerous genes, each of which accounts for a very small percentage of behavioral variability (Geschwind & Flint, 2015), while individual genes associated with specific behavioral phenotypes also affect multiple other traits (Plomin & Deary, 2015). In light of this concern, the field has largely shifted towards genome-wide approaches involving tens of thousands of individuals (Chabris *et al.*, 2015, Dick *et al.*, 2015, Gratten *et al.*, 2014). Yet, GWAS approaches are not without limitations. Large epidemiologic samples offer significantly more power to detect small effect sizes, but are limited by the depth of measurement of environmental exposures. Poor measurement of environmental factors, then, could introduce error similar to measuring the wrong gene (Dick *et al.*, 2015). In this way, candidate gene studies involving functional variants implicated in developmental pathways that utilize precise measures of environmental exposures can offer unique insights that much larger studies cannot. This may be especially true regarding environmental exposures that occur *in utero,* given the relative paucity of studies involving pregnant women (Wisner, 2012). While there is growing evidence to support the role of the intrauterine environment in shaping developmental trajectories (Babenko *et al.*, 2015), how the prenatal environment may be modulated by *MAOA* has just begun to be explored (Hill *et al.*, 2013, Hohmann *et al.*, 2016, Wakschlag *et al.*, 2010a).

Two environmental adversities commonly experienced concomitantly during the prenatal period are prenatal tobacco exposure (PTE) and prenatal stress exposure (PSE) (Flemming *et al.*, 2013). PTE still affects some 1 in 10 births in the United States and has been linked to a wide range of adverse child outcomes including antisocial behaviors and their precursor phenotypes (U.S. Department of Health and Human Services, 2014). In a prior independent sample, we demonstrated moderation of vulnerability to PTE by *MAOA* in a sex-specific manner (Wakschlag *et al.*, 2010a) with patterns similar to those previously observed for childhood maltreatment (Byrd & Manuck, 2014, Caspi *et al.*, 2002). Specifically, adolescent boys with PTE and *MAOA-L* exhibited increased conduct disorder symptoms, compared to boys with *MAOA-H*. In adolescent girls, however, it was *MAOA-H* that interacted with PTE to predict conduct disorder symptoms, and also hostile attribution bias patterns on a face-processing task (Wakschlag *et al.*, 2010a). The only other study to our knowledge that examined *MAOA* x PTE on antisocial behavior did not find sex-specific patterns (Hohmann *et al.*, 2016), but assessed PTE by maternal report at 3 months postpartum, whereas we previously assessed PTE prospectively using a combination of interviews and biomarkers (Wakschlag *et al.*, 2010a).

This discrepancy in results supports the notion that different ways of measuring environmental exposures could lead to different results (Dick *et al.*, 2015). Indeed, as maternal cigarette smoking during pregnancy is an increasingly stigmatized behavior, under-reporting leading to misclassification of exposed versus non-exposed children is a well-established source of error (Estabrook *et al.*, 2015, Pickett *et al.*, 2005, Pickett *et al.*, 2003). Moreover, as frequency, patterns, and topography of cigarette smoking are known to fluctuate significantly across gestation, prospective measurement of PTE that includes biomarker confirmation of reports is needed to most accurately capture this environmental exposure (Dukic *et al.*, 2007, Estabrook *et al.*, 2015, Pickett *et al.*, 2005). Yet, even with ideal measurement of PTE, disentangling this particular exposure from the concomitant exposures is critical (Chiarella *et al.*, 2015). As rates of cigarette smoking in the general population decline, PTE is increasingly intertwined with psychosocial stress during pregnancy (Flemming *et al.*, 2015) but studies of PTE, including our previous study on *MAOA* x PTE (Wakschlag *et al.*, 2010a), lack adequate control of PSE. More recently, we have shown that *jointly* accounting for PSE and PTE significantly enhances the prediction of behavioral disinhibition (Clark *et al.*, 2015). In particular, PSE and PTE independently predicted higher levels of early childhood disruptive behavior, with the effect of PSE mediated by early difficult temperament and executive control.

Finally, the biological impact of environmental adversity could vary as a function of developmental timing (Dick *et al.*, 2015). Advances in developmentally based measurement has increasingly enabled fine-grained characterization of disruptive behavior in very young children, (Wakschlag *et al.*, 2014) in whom conduct disorder symptoms are impossible (i.e. truancy in preschool-aged children) or improbable (i.e. stealing while confronting a victim) (Wakschlag *et al.*, 2010b). To our knowledge, the *MAOA* x prenatal adversity interaction has rarely been examined in close proximity to exposure in the first years of life (Byrd & Manuck, 2014, Enoch *et al.*, 2010, Hill *et al.*, 2013). In the current study, we extend our prior work by examining commonly co-occurring forms of prenatal adversity and their interaction with *MAOA*, independent of one another, utilizing in-depth prospective measurement of

each of these exposures. Specifically, we tested the moderating effect of *MAOA* on PSE and PTE in predicting disruptive behavior in five-year-old children, probing for previously observed sex-effects in these gene x environment interactions, controlling for other prenatal exposures, postnatal exposures and parenting. We hypothesized that *MAOA* genotype would interact independently with both PSE and PTE to contribute to preschool disruptive behavior, with sex differences in the risk variant.

One of the primary challenges of causal modeling of prenatal exposures is the potential for genetic confounding (D'onofrio *et al.*, 2010, D'onofrio *et al.*, 2012, D'onofrio *et al.*, 2008, Estabrook *et al.*, 2015). In the present case, associations among PSE, PTE and disruptive behavior could result from underlying genetic factors that simultaneously influence parental traits, and by association, parental behaviors that influence the prenatal intrauterine environment, postnatal environment, and child traits (Gaysina *et al.*, 2013, Harold *et al.*, 2013, Jaffee & Price, 2007). Thus, using available data on parental *MAOA* genotype, we provided a partial test for genotype-environment correlation (*r*GE).

2. Material and Methods

2.1 Sample

Participants were 281 mothers and their 285 children (4 sets of twins; 141 boys, 144 girls) from the Midwest Infant Development Study - Preschool Phase (MIDS-P). In the initial phase of MIDS, mothers were recruited in early pregnancy (nearly three-quarters of women enrolled prior to 16 weeks gestation) using flyers distributed over a 4.5-year period to all obstetric clinics in two Midwestern cities. Smoking was oversampled (56% smokers at the start of the study), and women reporting binge drinking (> 2 drinks in any one sitting) or any illicit drug use were excluded. Non-smokers were matched broadly to smokers by demographic factors known to be associated with cigarette smoking (educational attainment, race, ethnicity, and Medicaid status). The sample was predominantly low-income women (56.8% non-Hispanic Caucasian; 43.2% other races and ethnicities) with a mean age of 25.7 years and a mean educational attainment of 13.1 years. Sixty percent of participants were unmarried, and 53% reported another smoker in the home during the pregnancy (Espy *et al.*, 2011). In MIDS-P, children were assessed for disruptive behavior around age 5. (Descriptive statistics are shown in Table 2).

2.2 Measures

2.2.1 Prenatal and concurrent stress exposure—In contrast to prior work examining maltreatment, in this study we examined intrauterine and preschool exposure to a range of normative psychosocial stressors. We assessed mothers using the Life Stressors and Social Resources Inventory (LISRES) (Moos *et al.*, 1988) at 28 weeks of gestation (PSE), and again at the preschool follow-up when disruptive behavior was assessed, termed concurrent stress exposure (CSE). The LISRES is a 200-item structured interview that provides an integrated picture of an individual's life context over the past 12 months. By assessing both life stressors (9 scales) and social resources (7 scales) available to manage these stressors, this unified framework recognizes the interdependence between the two (Moos & Moos, 1994).

The 9 Stressors Scales and sample questions are: physical health (Have you had asthma or allergies?); home/neighborhood (Is there enough heat in the winter? Has your home been burglarized?); financial (Do you have enough money to afford furniture or household equipment that needs to be replaced?); work (Did you find out that you were not going to get an expected promotion at work?); spouse/partner (Did your relationship change for the worse in the last year?); child (How often do any of your children get on your nerves?); extended family (When you spend time with your mother/stepmother, how often is she critical or disapproving of you?); friends & social activities (Have you had a serious conflict with a friend in the past year?); and negative life events (Did you lose your home through fire, flood, disaster, or major catastrophe?). The 7 Social Resources Scales and sample items are: financial (Has your financial situation improved?); work (Did you have a significant success at work?); spouse/partner (Did you start seeing someone exclusively?); children (Do you share mutual interests or activities with one or more of your children?); extended family (When you spend time with your mother can you count on her help when you need it?); friends (Do you confide in any of your friends?); and positive life events (Did you move to a better home?).

The LISRES scales have high internal reliability (α = .83 – .84) and test-retest reliability (r = .67 – .70). Raw scores on the 16 scales, which fell into the ‘average’ range, relative to normative samples (Moos & Moos, 1994), were converted into continuous factor scores using confirmatory factor analysis. These factor scores, representing PSE and CSE, were controlled in all regression models.

2.2.2 Prenatal and concurrent tobacco exposure—Smoking was assessed at each prenatal study visit (mean of 2.93 ± 0.70 visits; range = 1 − 4 visits) by self-report using timeline follow-back methodology (Sobell & Sobell, 1996), combined with repeated prospective blood and urine cotinine radioimmunoassays (Wang *et al.*, 1997). Smoking patterns were established via a ‘best-estimate’ approach such that non-disclosure, under-reporting, and over-reporting were corrected based on serum cotinine values, employing statistical methods previously described (Dukic *et al.*, 2007). Based on this calculation, 77.3% of women in this sample reported a lifetime smoking history and 69.4% of women smoked during pregnancy. Among pregnancy smokers, mean daily smoking after learning of the pregnancy was approximately one cigarette (M = 0.8; SD = 2.4; range = 0–16.7); 2.6% of women smoked an average of more than 10 cigarettes (half pack)/day. A continuous corrected mean serum cotinine measure of average cigarettes per day across pregnancy was used as the measure of PTE. Concurrent tobacco exposure (CTE) from mothers’ reported cigarettes/day smoked at the time of the preschool assessments was included as a covariate in all regression models.

2.2.3 Disruptive Behavior—Disruptive behavior was assessed with the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB), which utilizes a dimensional approach to differentiate normative misbehavior from facets of disruptive behavior (i.e., aggression, noncompliance, temper loss and low concern for others) within a developmental context (Wakschlag *et al.*, 2014). Item Response Theory (IRT) modeling (Hambleton *et al.*,

1991) was utilized to generate a continuous unidimensional total disruptive behavior score as the outcome measure (M = −.076; SD = 0.95; range = −2.60 2.510).

2.2.4 Covariates—Maternal parenting quality (responsiveness) was assessed by direct observation in the home at child age 5 using the responsivity subscale of the Early Childhood Home Observation for Measurement of the Environment (EC-HOME) (Totsika & Sylva, 2004). Additional covariates were child age, prenatal alcohol exposure, parent antisocial behavior (from mother and fathers'/partners' reports) (Zoccolillo, 2000), concurrent stress exposure (CSE) (Moos & Moos, 1994), and concurrent tobacco exposure (CTE).

2.3 Genotyping

Participant saliva samples were collected with DNA Genotek Oragene Self-Collection Kits. DNA was extracted and quantified with Quanti-iT Pico Green dsDNA assay. Following Polymerase Chain Reaction, products were separated on a 3730 Genetic Analyzer (Wakschlag *et al.*, 2010a). As *MAOA* is an X-linked gene, boys have one allele, and are classified as either *MAOA-H* or *MAOA-L*. With two alleles, girls are either homozygous or heterozygous. Previous investigators concur that variants with 4 repeats should be classified as *MAOA-H* and 3 repeats as *MAOA-L*. There is some discrepancy in the classification of the 5-repeat variant (Deckert *et al.*, 1999, Sabol *et al.*, 1998). Consistent with the approach of Sabol and Kim-Cohen (Kim-Cohen *et al.*, 2006, Sabol *et al.*, 1998), we classified variants with 5 repeats as *MAOA-L*. In girls, heterozygotes with 3.5/4 were classified as MAOA-H, along with 4/4 homozygotes. All other genotypes in girls were classified as low.

The distribution of *MAOA* genotypes for boys and girls by population are shown in Table 1. To test for Hardy-Weinberg Equilibrium, Likelihood Ratio tests were conducted with *MAOA* classified as multi-allelic with five possible alleles of 2, 3, 3.5, 4, and 5 repeats in unrelated females only. Allele frequencies met Hardy-Weinberg equilibrium (HWE) for each of the following populations: European American: $\chi^2 = 0.427$, $df = 3$, 2p = .934; Latino: $\chi^2 = 2.085$, $df = 3$, 2p = .555; African-American: $\chi^2 = 5.183$, $df = 6$, 2p = .521. HWE was not calculated for the remaining children due to small numbers (classified as "other" in Table 1). These populations were: Hispanic black (3 boys, 3 girls); Hispanic Native American (5 girls); Hispanic other (2 boys); non-Hispanic Asian (2 girls); and non-Hispanic other (1 boy, 3 girls). In the total sample of 285, there were 129 children (79 boys, 50 girls) with *MAOA-H* genotype and 156 children (62 boys, 94 girls) with *MAOA-L* genotype. For subsequent analyses, *MAOA* genotype was coded as 1 = low activity, 2 = high activity.

2.4 Inference of paternal genotype from maternal and female child genotype

Maternal, but not paternal genotypes were directly assessed in this cohort. Girls receive one *MAOA* allele from each parent. Mothers can transmit either of their two alleles, while fathers can only transmit their single allele. In this way, if mothers and daughters' *MAOA* genotype is known, paternal genotype can be inferred in families in which daughters possess an allele that is not possessed by her mother. This allele, then, must have been transmitted from her father who is hemizygous. For example, in a daughter who is 3/4, if her mother is 4/4, her father must be 3/-. Paternal genotype can also be inferred in families in which

daughters are homozygous. For example, if a daughter is 4/4 and her mother is 4/4, her father must be 4/-. If her mother is, instead, 3/4, her mother must have transmitted a 4 allele; the daughter's other allele is also 4, which means her father must be 4/-. In families in which mothers and heterozygous daughters have the same *MAOA* genotype, paternal genotype cannot be inferred – here, one cannot discern which allele has been transmitted by the mother. Using this technique, we inferred paternal genotypes where possible (n = 107, or 74% of girls) for use in tests of gene-environment correlation.

2.5 Analysis

We evaluated variables for normality prior to use in regression models. PTE was left-skewed and thus log transformed after adding 1 to all values to obtain continuous values > 0. All interaction covariates were calculated by first mean-centering each covariate, then calculating the product terms.

2.5.1 Tests for G x E x sex—Linear regression analysis was used to test *MAOA* x PSE x sex on disruptive behavior, controlling for PTE and covariates, and *MAOA* x PTE x sex on disruptive behavior controlling for PSE and covariates. Based on previous literature showing differential effects of these interactions by sex, analyses were also conducted separately for boys and girls. Statistical significance of the interaction terms were tested using a Wald test.

2.5.2 Tests for rGE—To examine the possibility that findings regarding *MAOA* x PSE resulted from a relationship between parental genotype and environmental exposures, we used bivariate correlation analysis to examine relationships between parental genotypes and environmental exposures (PSE, PTE, CSE, CTE and maternal responsiveness).

3. Results

Descriptive characteristics for the total sample and for boys and girls separately are shown in Table 2. Due to hemizygosity in males, significantly more boys were classified as the *MAOA-H* genotype (56.0%) than girls (34.7%) ($\chi^2 = 13.053$, $p < .001$). Other variables did not significantly differ between boys and girls. Of the 94 girls (65.3%) classified as *MAOA-L,* 64 (68.1%) were heterozygotes with intermediate phenotypes (2/4, 3/4 or 4/5) (Table 1).

3.1 Main effects

CSE showed a main effect on disruptive behavior in the full sample ($\beta = .310$; $p = .001$) (Table 3). In models stratified by sex (Table 4), main effects were observed in boys with respect to PSE ($\beta = -.676$; $p = .031$), prenatal alcohol exposure ($\beta = .185$; $p = .043$), and CSE ($\beta = .446$; $p < .001$). A trend for PTE on was observed ($\beta = .193$; $p = .057$). In girls, we observed a main effect of *MAOA* (high) genotype on disruptive behavior ($\beta = .215$; $p = .047$).

3.2 MAOA x PSE x sex on disruptive behavior

We found a significant 3-way interaction of *MAOA* x PSE x sex on disruptive behavior ($\beta = .813$; 95% CI: .096 to 1.231; $p = .022$) (Table 3). Figure 2 illustrates the interaction of *MAOA* x PSE on disruptive behavior in boys (left) versus girls (girls). In conditions of low

PSE, boys with *MAOA-H* exhibited lower disruptive behavior symptoms compared with boys with *MAOA-L*. However, in conditions of high PSE, boys with *MAOA-H* had greater disruptive behavior, whereas those with *MAOA-L* appeared to be buffered. These patterns were not observed in girls.

3.3 MAOA x PTE on disruptive behavior

For PTE, the three-way interaction of *MAOA* x PTE x sex was not significant (β = .135, p = .598). However, in the analyses stratified by sex, *MAOA* x PTE predicted disruptive behavior in boys (β = .362, p = .037), but not in girls (β = −.144, p = .505). Boys with *MAOA-H* exposed to more PTE exhibited more disruptive behaviors.

3.4 Passive rGE

Evidence of gene-prenatal environment correlation was not found. Correlations were as follows: maternal genotype and PSE (r = .056, p = .347), maternal genotype and PTE (r = .037, p = .538), paternal genotype (for girls only) and PSE (r = −.105, p = .284), paternal genotype and PTE (r = −.057, p = .567). We did observe a correlation between paternal *MAOA* genotype and CSE—girls whose fathers had the low activity *MAOA* genotype were exposed to higher concurrent stress (r = −.240, p = .013). No correlations were found between maternal genotype and CSE (r = .090, p = .130), maternal genotype and CTE (r = −.013; p = .827), paternal genotype and CTE (r = −.045, p = .643), maternal genotype and maternal responsiveness (r = −.081, p = .184), or paternal genotype and maternal responsiveness (r = .096, p = .329).

4. Discussion

There is increasing support for the role of early life adversity, in particular, prenatal adversity, in shaping disruptive behavior pathways (Aizer *et al.*, 2015, Chiarella *et al.*, 2015, Clark *et al.*, 2015, Hanson *et al.*, 2015, Ronald *et al.*, 2010). How (and whether) these pathways are modulated by child *MAOA* genotype is just beginning to be examined (Hill *et al.*, 2013, Hohmann *et al.*, 2016, Wakschlag *et al.*, 2010a). Adding to this small but growing subset of the *MAOA* literature (Byrd & Manuck, 2014), we found that the impact of two common prenatal adversities, PSE and PTE, like childhood maltreatment, may also be modulated by *MAOA*. We additionally present preliminary evidence for a gene-environment correlation between paternal *MAOA-L* and girls' preschool stress exposure. We take a very cautious approach to making sense of these findings for several reasons. First, there are discrepancies in these results from our own earlier findings in an independent adolescent sample (Wakschlag *et al.*, 2010a). Next, studies of preschool-aged children with measures of PSE and PTE with which these results could be compared are lacking. Finally, as alluded to in the introduction, *MAOA* has proved to be consistently inconsistent in its effects on behavior.

4.1 Association of MAOA-H with disruptive behaviors – susceptibility to prenatal adversity seen boys, but not in girls

Boys possessing the high-activity variant exhibited higher levels of disruptive behavior as a function of increasing prenatal adversity; PSE and PTE appeared to interact independently

with *MAOA*. Girls with *MAOA-H* also showed more disruptive behaviors relative to *MAOA-L* girls, but this association was independent of the level of prenatal adversity. In fact, direct effects of prenatal exposures (tobacco, alcohol, stress) on boys' disruptive behavior were not seen in girls. Taken together, girls appeared comparatively resilient to measured prenatal adversities. In our earlier study in an independent sample, we found *MAOA* x PTE interactions on conduct disorder symptoms in both sexes, but the low activity variant was associated with risk in adolescent boys, whereas the high-activity variant was associated with risk in adolescent girls (Wakschlag *et al.*, 2010a). A potential explanation to consider in future work would be whether increasing testosterone levels associated with the pubertal transition in boys alters the function or influence of *MAOA* on behavior. Indeed, we have previously shown that testosterone levels in cerebrospinal fluid interact with *MAOA* to predict antisocial behavior in adult males, and have proposed a mediating effect of testosterone on gene transcription (Sjöberg *et al.*, 2008). Ultimately, understanding the influence of *MAOA* across developmental periods could be enhanced by measuring hormones and their interactions.

4.2 MAOA x adversity interactions in young children

There is only one other study to our knowledge that examined the effect of *MAOA* x prenatal stress on disruptive patterns in pre-pubertal children. Hill and colleagues found that infants (of both sexes) with *MAOA-L* whose mothers reported more negative life events and more neighborhood deprivation during pregnancy exhibited greater negative emotionality at 5 weeks of age (Hill *et al.*, 2013). We found that 5-year-old boys (but not girls) with the *high*- not low-activity variant, and greater PSE, exhibited more disruptive behavior. While different outcomes (negative emotionality versus disruptive behavior), different measures of prenatal stress (life history calendar versus LISRES interview), and different ages of children (5 weeks versus 5 years) could explain these discrepancies, both studies also show discrepancies with the predominant *MAOA-L*-maltreatment-antisocial behavior pattern observed in adolescent and adult males (Byrd & Manuck, 2014). Could the *MAOA* x adversity interaction vary as a function of developmental timing?

Indeed, the few studies that have examined G x E processes with other genes in preadolescent children are less consistent with the diathesis-stress model (Alexandra Burt *et al.*, 2013, Burt & Klump, 2014b, Kim-Cohen *et al.*, 2006). Rather, following a bioecological G x E model (Burt & Klump, 2014a), genetic influences may be most strongly expressed in average environments (Scarr, 1992), whereas deleterious environments could amplify environmental exposures (Pennington *et al.*, 2009, Raine, 2002). Relatedly, we have recently shown that early life exposure to normative stressors is uniquely associated with higher regional homogeneity of resting state fMRI in prefrontal areas that underlie disruptive behavior pathways, after accounting for extreme violence exposure (Demir *et al.*, under review). Clearly much more work is needed to confirm the modulation of the prenatal environment by *MAOA*. The present study provides clues that investigation of how adverse environments shape development and adaptation should to take genetic susceptibility and gene-environment correlations into account.

4.3 MAOA x PTE only in boys, and less robust than anticipated

While we had previously found a 3-way *MAOA* x PTE x sex interaction in the prediction of adolescent conduct disorder (Wakschlag *et al.*, 2010a), here, we observed a *MAOA* x PTE interaction only in boys; the 3-way interaction of *MAOA* x PTE x sex in the full sample was not significant. This may be due to comparatively low levels of prenatal smoking in the current sample (0.8 cigarettes/day versus 12.8 cigarettes/day in our previous sample). Relatedly, PSE was not assessed in our previous study, but was, and was controlled for, in the current study. This difference could have further attenuated the independent effect of PTE. We also considered that detection of patterns in girls might have been hampered by lower rates of disruptive behavior at this young age (Schaeffer *et al.*, 2006), but disruptive behavior scores did not differ significantly between boys and girls (Table 2). Finally, about two thirds of the girls characterized as *MAOA-L* in this sample possessed functionally intermediate phenotypes (2/4, 3/4 or 4/5). Hill and colleagues (2013) noted that their findings did not differ, however, whether they omitted or included heterozygote females, nor did outcomes differ among hetero- and homozygous females (Hill *et al.*, 2013). Nonetheless, more information is needed on the molecular functionality of *MAOA* alleles of different repeat lengths in relevant cellular contexts.

4.4 Paternal MAOA-L – girls' CSE correlation

Perhaps the most intriguing, albeit unexpected finding was that daughters whose fathers had the *MAOA-L* genotype had significantly higher concurrent stress exposure (CSE) as reported by their mothers, suggesting the possibility of a passive gene-environment correlation. The impact of this correlation in the current sample, however, is unclear. CSE showed a main effect on disruptive behavior in the full sample (Table 3; $\beta = .310$; $p = .001$), but seems to be driven by the effect of CSE in boys (Table 4; $\beta = .446$; $p < .001$) rather than girls ($\beta = .154$; $p = .270$). Moreover, while girls with *MAOA-L* fathers had more CSE, girls with *MAOA-H* actually exhibited higher disruptive behavior, regardless of prenatal stress or tobacco exposure (Table 4). It would be important to confirm this apparent paternal *MAOA* – preschool stress correlation using path analysis, and in a sample in which paternal genotypes were assessed directly. Comparison of genetically-related and genetically-unrelated parent-child dyads could further elucidate this correlation (Harold *et al.*, 2013, Rice *et al.*, 2013, Roos *et al.*, 2016).

4.5 Limitations

There are additional limitations of this study not already mentioned that are worthy of consideration. First, the sample size may raise questions about adequate power to test for 3-way interactions. We conducted a post-hoc power analysis of the regression model used to test the *MAOA* x PSE x sex interaction and conclude that statistical power was in fact adequate (power = .999; $R^2 = .252$, 14 predictors, probability level of .05, N = 285). Moreover, the depth of exposure and outcome measures in this study relative to large epidemiologic studies could have further increased our power to detect effects. Second, while we controlled for a number of prenatal and postnatal confounders including parenting quality (maternal responsiveness), there are undoubtedly still unmeasured factors, for example, the quality of the parent-child relationship, that could have influenced children's

disruptive behaviors (Kochanska & Kim, 2014). Third, as this cohort was oversampled for smokers to examine PTE, we cannot rule out the possibility that allele frequencies of *MAOA* are different from samples that are more normative – a tendency toward antisocial behavior could be over-represented (Wakschlag *et al.*, 2003). Finally, the racial and ethnic diversity on the sample could have affected results—larger subpopulations met HWE, while very small subpopulations were not tested.

5. Conclusions

We provide preliminary evidence for the modulation of maternal psychosocial stress and maternal smoking during pregnancy by child *MAOA* genotype for preschool-aged boys in a racially and ethnically diverse population oversampled for smokers. It would be important to confirm these patterns in larger more representative samples. A longitudinal study that follows children across developmental periods and accounts for how the monoamine system may interact with the changing environmental and hormonal milieu would be ideal. We posit that transitions across the prenatal period to early childhood and across pubertal development could critically influence the function of apparently well-established G x E interactions.

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Highlights

- Whether and how *MAOA* moderates susceptibility to prenatal adversity is unclear.
- Here *MAOA* moderated susceptibility to prenatal stress and tobacco exposure in boys.
- Preliminary evidence for passive gene-environment correlation was found.
- Girls whose fathers had *MAOA-L* genotype experienced higher stress at age 5.
- Future research to elucidate developmental variation in mechanisms is recommended.

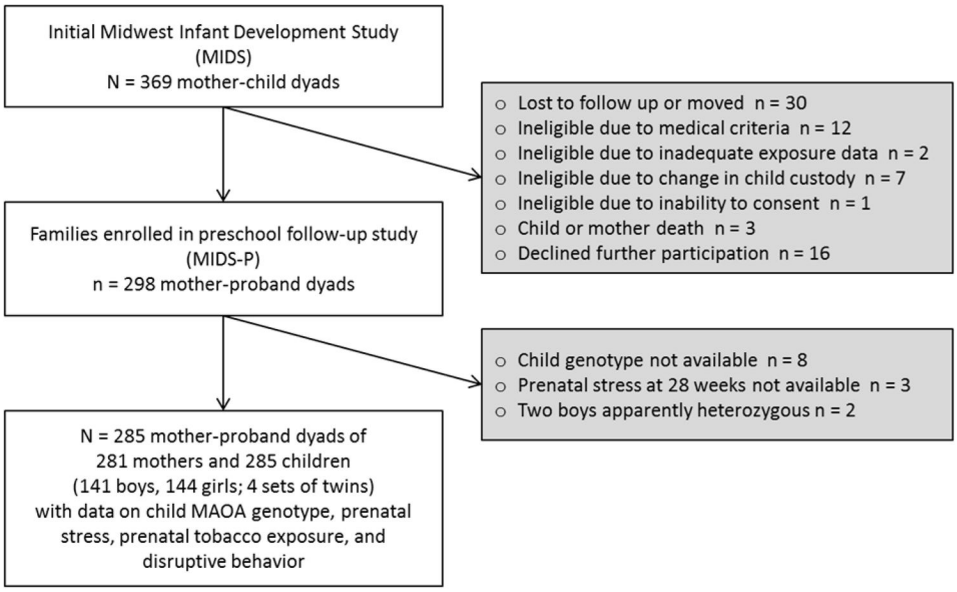

Figure 1.
Flow chart showing derivation of the analytic sample.

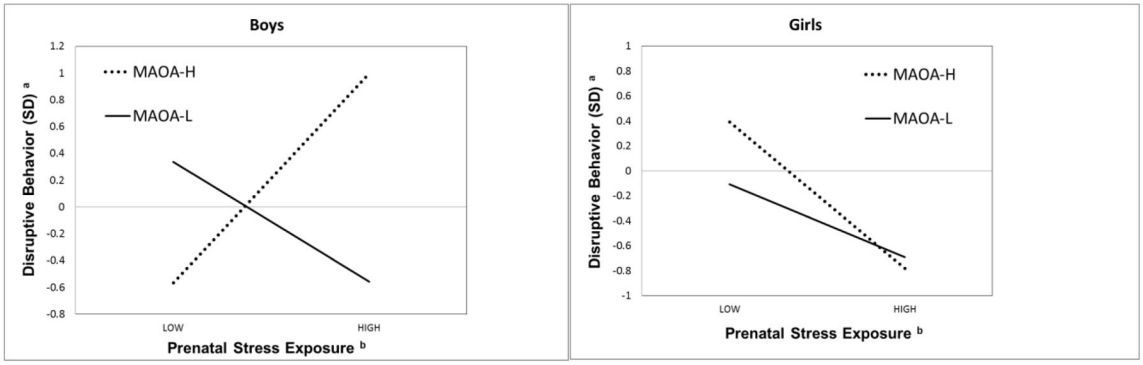

Figure 2.

MAOA x prenatal stress exposure in boys versus girls.*

*Covariates: Child age, *MAOA* genotype, prenatal tobacco exposure, prenatal alcohol exposure, parent antisocial behavior, concurrent stress exposure, and concurrent tobacco exposure, maternal responsiveness

SD = standard deviations

[a]Multidimensional Assessment Profile of Preschool Disruptive Behavior, unidimensional IRT score

[b]Life Stressors and Social Resources Scale (LISRES) assessed at 28 weeks gestation, factor score

Table 1

Distribution of *MAOA* genotypes for boys and girls by population (N = 285)

	Boys		Girls	
Population	***MAOA* Genotype**	**Freq (%)**	***MAOA* Genotype**	**Freq (%)**
European American (Non-Hispanic whites)	3/-	36 (43.9%)	3/3	12 (15.0%)
		0	3/3.5	1 (1.3%)
		0	3/4	36 (45.0%)
		0	3.5/4	1 (1.3%)
	4/-	46 (56.1%)	4/4	30 (37.5%)
	MAOA-High	46 (56.1%)	*MAOA*-High	31 (39.7%)
	MAOA-Low	36 (43.9%)	*MAOA*-Low	49 (61.3%)
	Total	82 (100%)	Total	80 (100%)
Latino (Hispanic whites)	3/-	1 (11.1%)	3/3	4 (28.6%)
		0	3/4	5 (35.7%)
	4/-	8 (88.9%)	4/4	4 (28.6%)
		0	4/5	1 (7.1%)
	MAOA-High	8 (88.9%)	*MAOA*-High	4 (28.6%)
	MAOA-Low	1 (11.1%)	*MAOA*-Low	10 (71.4%)
	Total	9 (100%)	Total	14 (100%)
African American (Non-Hispanic blacks)	2/-	2 (4.7%)	2/2	1 (2.9%)
		0	2/3	3 (8.6%)
		0	2/4	1 (2.9%)
	3/-	17 (39.5%)	3/3	8 (22.9%)
		0	3/3.5	1 (2.9%)
		0	3/4	12 (34.3%)
	4/-	23 (53.5%)	4/4	9 (25.7%)
	5/-	1 (2.3%)	5/5	0
	MAOA-High	23 (53.5%)	*MAOA*-High	9 (25.7%)
	MAOA-Low	20 (46.5%)	*MAOA*-Low	26 (74.3%)
	Total	43 (100%)	Total	35 (100%)
Other (Includes Asian, Pacific Islander, Native American, and mixed race/ethnicity)	3/-	4 (57.1%)	3/3	0
		0	3/4	8 (53.3%)
		0	3/5	1 (6.7%)
	4/-	3 (42.9%)	4/4	5 (33.3%)
		0	4/5	1 (6.7%)
	MAOA-High	3 (42.9%)	*MAOA*-High	5 (33.3%)
	MAOA-Low	4 (57.1%)	*MAOA*-Low	10 (66.7%)

	Boys		Girls	
Population	***MAOA* Genotype**	**Freq (%)**	***MAOA* Genotype**	**Freq (%)**
	Total	7 (100%)	Total	15 (100%)
Total all populations	2/-	2 (1.4%)	2/2	1 (0.7%)
		0	2/3	3 (2.1%)
		0	2/4	1 (0.7%)
	3/-	58 (41.1%)	3/3	24 (16.7%)
		0	3/3.5	2 (1.4%)
		0	3/4	61 (42.4%)
		0	3/5	1 (0.7%)
		0	3.5/4	1 (0.7%)
	4/-	80 (56.7%)	4/4	48 (33.3%)
		0	4/5	2 (1.4%)
	5/-	1 (0.7%)	5/5	0
	MAOA-High	80 (56.0%)	*MAOA*-High	50 (34.7%)
	MAOA-Low	61 (44.0%)	*MAOA*-Low	94 (65.3%)
	Total	141 (100%)	Total	144 (100%)

Table 2

Sample characteristics for total sample (N = 285) and by sex

	Total		Boys n = 141	Girls n = 144	
	Mean (SD)	**Range**	**Mean (SD)**	**Mean (SD)**	**p**
Predictors					
Prenatal stress exposure [a]	50.1 (5.8)	37.3–69.6	50.2 (6.1)	50.0 (5.6)	.789
Prenatal tobacco exposure [b]	0.8 (2.2)	0–16.7	0.7 (2.0)	0.8 (2.1)	.730
Outcome					
Disruptive behavior [c]	61.0 (50.1)	0 – 267	66.5 (53.3)	55.7 (46.3)	.069
Covariates					
Child age in years	5.1 (0.3)	4.6–6.0	5.1 (0.2)	5.1 (0.2)	.382
Percentage male	49.5%				
Percentage MAOA-L	54.7%		44.0%	65.3%	<.001
Prenatal alcohol exposure [d]	.03 (.05)	0 –.33	.04 (.06)	.03 (.05)	.298
Parent antisocial behavior [e]	5.2 (4.1)	0–17	5.2 (4.3)	5.1 (4.0)	.814
Concurrent life stress [f]	50.1 (6.2)	37.3–68.4	50.0 (5.9)	50.3 (6.4)	.456
Concurrent tobacco exposure [g]	4.2 (6.6)	0–30.0	3.4 (5.9)	4.8 (7.0)	.066
Maternal responsiveness [h]	3.61 (1.9)	0–7.00	3.7 (1.7)	3.6 (1.9)	.661

[a] Life Stressors and Social Resources Scale, assessed at 28 weeks gestation

[b] Cotinine-corrected mean cigarettes per day across pregnancy

[c] Multidimensional Assessment Profile of Preschool Disruptive Behavior raw score

[d] Average number of drinks per day reported across each trimester of pregnancy

[e] Antisocial Behavior Questionnaire, sum of maternal and paternal scores

[f] Life Stressors and Social Resources Scale, assessed at child age 5, raw score

[g] Maternal smoking in cigarettes/day at child age 5

[h] Early Childhood Home Observation for Measurement of the Environment, Responsivity subscale, raw score

Table 3

Three-way interaction of *MAOA* genotype x prenatal stress exposure x sex on disruptive behavior in preschoolers [a] (N = 285)

	B	SE	β	95% CI	t	Sig.
Child age	−.296	.239	−.086	−.768 − .176	−1.237	.218
Sex [b]	.609	.419	.323	−.220 − 1.437	1.451	.149
MAOA genotype [c]	.355	.187	.189	−.013 − .724	1.902	.059
Prenatal stress exposure (PSE) [d]	.035	.050	.213	−.065 − .135	.694	.489
Prenatal tobacco exposure [e]	.041	.032	.094	−.023 − .104	1.264	.208
Prenatal alcohol exposure [f]	1.881	1.156	.112	−.402–4.163	1.627	.106
Parent antisocial behavior [g]	.005	.018	.024	−.029 − .040	.306	.760
Concurrent stress exposure [h]	.047	.013	.310	.020 − .073	3.474	.001
Concurrent tobacco exposure [i]	.011	.011	.081	−.010 − .033	1.045	.297
Maternal responsiveness	−.001	.040	−.002	−.079 − .077	−.032	.975
MAOA x sex	−.220	.268	−.202	−.749 − .309	−.822	.412
MAOA x PSE	−.212	.216	−.335	−.638 − .215	−.981	.328
PSE x sex	−.797	.426	−.587	−.1.638 − .045	−1.870	.063
MAOA x PSE x sex	.664	.287	.813	.096–1.231	2.309	.022

[a] Multidimensional Assessment Profile of Preschool Disruptive Behavior, unidimensional IRT score

[b] Boys coded as 1; girls coded as 0

[c] Child *MAOA* genotype (*MAOA-L* = 1; *MAOA-H* = 2)

[d] Life Stressors and Social Resources Scale (LISRES) assessed at 28 weeks gestation, factor score

[e] Mean maternal cotinine during pregnancy, natural log-transformed

[f] Mean reported drinks per day during pregnancy

[g] Antisocial behavior questionnaire, sum of maternal and paternal scores

[h] Life Stressors and Social Resources Scale (LISRES) assessed at child age 5, factor score

[i] Maternal smoking in cigarettes/day at child age 5

[j] Early Childhood Home Observation for Measurement of the Environment , responsivity subscale

Table 4

Interaction of *MAOA* genotype x prenatal stress exposure (PSE) in predicting disruptive behavior [a] in boys (n = 141) versus girls [b] (n = 144)

	Boys		***Girls***	
Predictors	**β [95% CI]**	***p***	**β [95% CI]**	***p***
Child age	−.059 [−.907 − .463]	.521	−.099 [−.972 − .357]	.360
Child *MAOA* [c]	.071 [−.245 − .523]	.472	.215 [.005 − .787]	.047
Prenatal stress exposure [d]	−.676[−.221 − .010]	.031	.173 [−.080 − .135]	.610
Prenatal tobacco exposure [e]	.193 [−.001 − .164]	.053	−.012 [−.109 − .252]	.922
Prenatal alcohol exposure [f]	.185 [.085–5.589]	.043	−.045 [−.266 − .168]	.678
Parent antisocial behavior [g]	−.048 [−.057 − .036]	.660	.156 [−.151 − .299]	.196
Concurrent stress exposure [h]	.446 [.034 − .110]	< .001	.154 [−.045 − .425]	.270
Concurrent tobacco exposure [i]	.180 [−.002 − .059]	.069	.025 [−.212 − .221]	.838
Maternal responsiveness [j]	.068 [−.074 − .154]	.483	−.139 [−.180 − .040]	.207
MAOA x PSE	.774 [.089 − .799]	.015	−.133 [−.555 − .365]	.561

[a] Multidimensional Assessment Profile of Preschool Disruptive Behavior, unidimensional IRT score

[b] Boys coded as 1; girls coded as 0

[c] Child *MAOA* genotype (*MAOA-L* = 1; *MAOA-H* = 2)

[d] Life Stressors and Social Resources Scale (LISRES) assessed at 28 weeks gestation, factor score

[e] Cotinine-corrected mean cigarettes per day across pregnancy, log-transformed

[f] Mean reported drinks per day during pregnancy

[g] Antisocial behavior questionnaire, sum of maternal and paternal scores

[h] Life Stressors and Social Resources Scale (LISRES) assessed at child age 5, factor score

[i] Maternal smoking in cigarettes/day at child age 5

[j] Early Childhood Home Observation for Measurement of the Environment , responsivity subscale