Child Abuse and Neglect, *MAOA*, and Mental Health Outcomes: A Prospective Examination

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Background: Studies have examined the interaction of *MAOA* genotype with childhood maltreatment in relation to depressive symptomatology and alcohol abuse with conflicting findings. Both high- and low-activity allele combinations have been shown to be protective for maltreated children with direction of findings varying by study methodology and participants' sex.

Methods: Participants in a prospective cohort design study involving court-substantiated cases of child abuse and neglect and a matched comparison group were followed up into adulthood and interviewed ($N = 802$). Eighty-two percent consented to provide blood, 631 gave permission for DNA extraction and analyses, and 575 were included in the final sample. This sample included male, female, white, and nonwhite (primarily black) participants. Symptoms of dysthymia, major depression, and alcohol abuse were assessed using the National Institutes of Mental Health Diagnostic Interview Schedule-III-R.

Results: Significant three-way interactions, *MAOA* genotype by abuse by sex, predicted dysthymic symptoms. Low-activity *MAOA* genotype buffered against symptoms of dysthymia in physically abused and multiply-maltreated women. Significant three-way interactions, *MAOA* genotype by sexual abuse by race, predicted all outcomes. Low-activity *MAOA* genotype buffered against symptoms of dysthymia, major depressive disorder, and alcohol abuse for sexually abused white participants. The high-activity genotype was protective in the nonwhite sexually abused group.

Conclusions: This prospective study provides evidence that *MAOA* interacts with child maltreatment to predict mental health outcomes. Reasons for sex differences and race findings are discussed.

Key Words: Alcohol abuse, child abuse and neglect, depression, dysthymia, *MAOA* genotype, prospective longitudinal design

Research has shown that adults who were abused, neglected, or both as children are at increased risk for a variety of negative consequences, including depression, alcohol abuse, and violent and criminal behavior (1–19). At the same time, several scholars have called attention to a group of children who appear resilient despite histories of childhood adversities including maltreatment (20–27).

Researchers have begun to examine gene by environment interactions to understand differences in outcomes for children exposed to early adversities. Studies have focused on monoamine oxidase A (*MAOA*) genotype as a moderator between the environmental stressor of child maltreatment and subsequent outcomes. *MAOA* is a gene located on the X chromosome (Xp11.23–11.4) that encodes the MAOA enzyme, which breaks down neurotransmitters serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (28). Variability in *MAOA* genotype is due to a polymorphism of the *MAOA* gene with a variable number of tandem repeats (VNTR). The variability has been shown to correlate with transcription with shorter, 3-repeat allele, being less active than the longer, 4-repeat allele (29–31). *MAOA* has been implicated in affective functioning in knockout mice, suggesting that normal *MAOA* activity is important for anger expression (32). Neurotransmitters 5-HT, NE, and DA that MAOA metabolizes have been linked to depressive and substance abuse symptomatology (33), which are also outcomes predicted by child maltreatment (2,3,10,34–36).

Caspi *et al.* (37) found that *MAOA* genotype moderated the relationship between child maltreatment and antisocial and violent offences in males, with high-activity *MAOA* protecting maltreated children. This research has since been replicated (38–40), replicated in part (41–43), or not replicated (44,45). A recent meta-analysis showed a significant effect of the interaction of *MAOA* genotype and child maltreatment on antisocial behaviors (46). Most these studies have been conducted with white males. However, some research (47,48) with females reported that low-activity allele was protective, opposite to Caspi *et al.* (37), and one study that examined these relationships separately in blacks and whites found different results (41).

Although the MAOA enzyme metabolizes neurotransmitters implicated in depressive symptomatology and alcohol abuse, few studies have examined whether *MAOA* interacts with child maltreatment to predict these outcomes. Cicchetti *et al.* (49) reported a significant interaction of *MAOA* genotype and level of maltreatment in the prediction of depressive symptomatology using a sample of low-income adolescents. Children who were more severely maltreated and had low *MAOA* activity displayed more symptoms of depression than those with high-activity *MAOA* and severe levels of maltreatment. A study of white adults (50), using retrospective self-reports of physical and sexual abuse, found that *MAOA* genotype interacted with abuse to predict major depressive disorder symptoms in men and women, but in the opposite direction to Cicchetti *et al.* (49). Abuse and high-activity *MAOA* were associated with more depression symptoms, compared with those with low-activity *MAOA* and abuse histories (50).

Research on alcohol abuse to date has also produced conflicting results. In a sample of Native American adult women, Ducci *et al.* (51) found that *MAOA* genotype interacted with self-reported childhood sexual abuse to predict alcohol abuse: individuals with low levels of *MAOA* and abuse histories reported a higher number of symptoms, compared with those with high levels of *MAOA* and

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abuse histories. Studies with adolescents in Sweden (52,53) found a clear difference between boys and girls in the interaction of family adversity and genotype predicting alcohol-related problem behaviors and risky alcohol consumption. Boys with the low-activity and girls with high-activity *MAOA* genotype were at increased risk if they were also exposed to family adversity (54).

In summary, several studies have reported interactions of the *MAOA* genotype and child maltreatment to predict a variety of outcomes. However, the direction of these relationships has varied considerably, with differences in the operationalization of maltreatment, study design (cross-sectional vs. longitudinal), sex, race/ethnicity, and outcome assessed. Some studies have used documented cases of childhood abuse and neglect, whereas others have relied on retrospective self-reports. Thus, it is difficult to draw firm conclusions about these relations.

The current research builds on previous studies by examining the interaction of child maltreatment and *MAOA* genotype using a prospective cohort design with court documented cases of childhood physical abuse, sexual abuse, and neglect and matched control subjects who were followed up into adulthood and assessed. This study offers several advantages for testing the gene (*MAOA*) by environment (child abuse and neglect) interaction. First, this study involves a clear operationalization and lack of ambiguity about the child maltreatment in our sample by using documented cases of child abuse and neglect. Second, there is a comparison group matched on the basis of age, sex, race/ethnicity, and approximate social-class background (55). Third, we use a structured diagnostic interview to assess psychiatric disorders. Fourth, we have a diverse sample with males, females, whites, and nonwhites. Finally, we have followed our participants into adulthood so that we can compare risks beyond adolescence and into adulthood.

This article examines the interaction of child maltreatment and the *MAOA* genotype in relation to three adult mental health outcomes—major depressive disorder (MDD); dysthymia (DD); which has been shown to have a common genetic underpinning to MDD (56), and alcohol abuse (AA). We ask two basic questions: 1) Does child maltreatment interact with *MAOA* genotype to predict MDD, DD, and AA? 2) Does the interaction between childhood maltreatment and *MAOA* genotype in predicting outcomes of MDD, DD, and AA differ by race, sex, or type of maltreatment experienced?

Methods and Materials

Participants

This research is based on a specialized cohort design study in which abused and neglected children were matched with nonabused and nonneglected children and followed prospectively into young adulthood (18). Only court-substantiated cases of child abuse and neglect were included. Cases were drawn from the records of county juvenile and adult criminal courts in a metropolitan area in the Midwest during the years 1967 through 1971. To avoid potential problems with ambiguity in the direction of causality and to ensure that temporal sequence was clear (that is, child neglect or abuse led to subsequent outcomes), abuse and neglect cases were restricted to those in which children were 11 years of age or less at the time of the abuse or neglect incident.

The abuse and neglect group includes three types: physical abuse, sexual abuse, and neglect. Physical abuse cases included injuries such as bruises, welts, burns, abrasions, lacerations, wounds, cuts, bone and skull fractures, and other evidence of physical injury. Sexual abuse charges varied from relatively nonspecific charges of "assault and battery with intent to gratify sexual desires" to more specific charges of "fondling or touching in an obscene manner," sodomy, incest, rape, and so forth. Neglect cases reflected a judgment that the parents' deficiencies in child care were beyond those found acceptable by community and professional standards at the time. These cases represented extreme failure to provide adequate food, clothing, shelter, and medical attention to children.

A critical element of the design was the establishment of a comparison group, matched to the maltreatment group as closely as possible on the basis of sex, age, race, and approximate family socioeconomic status during the time period under study (1967 through 1971). To accomplish this matching, the sample of abused and neglected cases was first divided into two groups on the basis of their age at the time of the abuse or neglect incident. Children who were under school age at the time of the abuse or neglect were matched with children of the same sex, race, date of birth ($\pm$1 week), and hospital of birth through the use of county birth record information. For children of school age, records of more than 100 elementary schools for the same time period were used to find matches with children of the same sex, race, date of birth ($\pm$6 months), and same class in same elementary school during the years 1967 through 1971. Overall, there were matches for 74% of the abused and neglected children (55).

This research began in 1986 as an archival study focused on the "cycle of violence" (18). A second phase located and interviewed 1196 individuals between 1989 and 1995, and 896 of the study participants were reinterviewed in 2001–2002. Data for this study were collected during 2003–2005 in the context of a medical status examination (including blood collection through venipuncture) and interview of 806 participants. Of those interviewed, 638 (82%) consented to provide blood, and 631 gave permission for DNA extraction and analyses. Internal review board regulations that define prisoners as a vulnerable population requiring additional protections prevented the collection of blood from 31 incarcerated participants.

Although there was attrition associated with death, refusals, and our inability to locate individuals over the various waves of the study, the composition of the samples at the four time points has remained about the same. The abuse and neglect group represented 56% to 58% at each time period, whites were 62% to 66%, and males were 48% to 51% of the samples. There were no significant differences across the samples on these variables or in mean age across the four phases of the study.

The average age of participants is 41 years (SD = 3.85; range 31–51). Approximately half the sample is female (48.7%), and 60.8% is white, non-Hispanic. Using participant-reported race/ethnicity, the nonwhite/minority group includes blacks (35.1%) and Hispanics (4.1%). The average highest grade of school completed for the sample was 11.47 (SD = 2.19), and the median occupational level (57) was semiskilled workers (only 11.3% were in the professions). Thus, the overall sample is skewed toward the lower end of the socioeconomic spectrum. Maltreatment was divided into types: physical abuse (7%), sexual abuse (9%), neglect (72%), and multiple maltreatment (12%).

The interviewers and participants were blind to the purpose of the study, to the inclusion of an abused and/or neglected group, and to the participants' group membership. Participants were told that they had been selected as part of a large group of individuals who grew up in that area during the late 1960s and early 1970s. Institutional review board approval was obtained for the procedures, and participants signed a consent form acknowledging that they understood the conditions of their participation and were participating voluntarily.