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Parental care moderates the influence of *MAOA-uVNTR* genotype and childhood stressors on trait impulsivity and aggression in adult women

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Abstract

Objectives—Adverse childhood experiences are associated with poor mental health outcomes, including vulnerability to mood disorders and/or antisocial behavior. A functional polymorphism in the regulatory region of the monoamine oxidase A gene (monoamine oxidase A untranslated variable nucleotide tandem repeat, *MAOA-uVNTR*) may moderate the degree of risk conferred by early trauma. Experiential factors may mitigate or exacerbate the effects of trauma on individuals at genetic risk. We examined the association among *MAOA-uVNTR* genotype, early stress (family death, family separation, parents' divorce, physical and/or sexual abuse), quality of parental care, and disadvantageous outcomes (trait impulsivity/aggression and depression severity) in adult women.

Methods—Diagnostic assessments were completed for 159 female participants. All were either healthy or were diagnosed with major depressive disorder or bipolar disorder. Participants were assessed for lifetime trait aggression and impulsiveness and current severity of depression, and were genotyped for the *MAOA-uVNTR* polymorphism. Participants rated the level of parental care they experienced, and were asked to report specific childhood stressors and abuse.

Results—High perceived parental care mitigated the effect of a childhood stressor on impulsivity scores in low-expressing *MAOA-uVNTR* allele carriers, but level of perceived care had no effect in the group homozygous for the high-expressing *MAOA-uVNTR* allele. Gene–environment interactions did not influence depression severity in the mood disorder group, indicating that the effects of parenting we observed in our participants were independent of depression status.

Conclusion—These results suggest that gene–environment interactions influence not only disadvantageous outcomes, but also sensitivity to features of the environment that could alleviate these outcomes.

Keywords

childhood stress; gene–environment interaction; impulsivity; *MAOA-uVNTR*; parental care

Introduction

The experience of childhood trauma has been associated with risk for poor mental health outcomes that persist across the lifespan. Such disadvantageous outcomes include an increased likelihood of exhibiting antisocial and impulsive behavior in adulthood (Grilo *et al.*, 1999; Roy, 2002). Genetic factors may play a moderating role in risk conferred by early stress (Caspi *et al.*, 2002; Foley *et al.*, 2004; Huang *et al.*, 2004; Haberstick *et al.*, 2005; Huizinga *et al.*, 2006; Kim-Cohen *et al.*, 2006; Nilsson *et al.*, 2006; Widom and Brzustowicz, 2006; Young *et al.*, 2006; Cicchetti and Rogosch, 2007; Frazzetto *et al.*, 2007; Nilsson *et al.*, 2007; Vanyukov *et al.*, 2007; Ducci *et al.*, 2008; Weder *et al.*, 2008). In particular, the low expressing allele of the X-linked monoamine oxidase A (*MAOA*) untranslated variable nucleotide tandem repeat (*MAOA-uVNTR*) upstream promoter polymorphism is associated with reduced transcription of the *MAOA* gene (Sabol *et al.*, 1998). This allele is associated with a greater propensity for antisocial behavior and impulsivity in males who experience early stress (Caspi *et al.*, 2002; Huang *et al.*, 2004; Kim-Cohen *et al.*, 2006). This gene $\times$ environment effect may extend to broader mental health outcomes, including conduct disorder, emotion dysregulation, and aggressiveness (Foley *et al.*, 2004; Kim-Cohen *et al.*, 2006; Cicchetti and Rogosch, 2007).

The gene–environment interaction involving the low-expressing *MAOA-uVNTR* allele has been replicated in the presence of various types of childhood stressors. There have typically been two strategies for defining early adversity: some have defined adversity as self-reported physical and/or sexual abuse (Huang *et al.*, 2004), observed or confirmed physical or emotional maltreatment (Caspi *et al.*, 2002), or other measures of deprivation such as parental neglect and poor socioeconomic conditions (Foley *et al.*, 2004; Cicchetti and Rogosch, 2007). Studies have generally, although not universally, supported the notion that the low-expressing *MAOA-uVNTR* allele confers risk in individuals who experienced early stress (Caspi *et al.*, 2002; Foley *et al.*, 2004; Huang *et al.*, 2004; Kim-Cohen *et al.*, 2006; Nilsson *et al.*, 2006; Widom and Brzustowicz, 2006; Young *et al.*, 2006; Cicchetti and Rogosch, 2007; Frazzetto *et al.*, 2007; Nilsson *et al.*, 2007; Vanyukov *et al.*, 2007; Ducci *et al.*, 2008; Weder *et al.*, 2008; although see Haberstick *et al.*, 2005; Huizinga *et al.*, 2006). However, there is evidence that multiple stressors compound the risk for poorer mental health outcomes. For example, parental neglect could put children at greater risk for a wide range of early stressors (Jaffee and Price, 2007) or exacerbate the effect of abuse on mental health outcomes. In contrast, the experience of an early stressor in the context of a positive family or social environment may be associated with a lower risk for adverse mental health outcomes. The impact of protective factors may vary as a function of genetic variation (Kaufman *et al.*, 2004, 2006), parallel to earlier reports of differential sensitivity to negative experiences. No study that we are aware of has examined the impact of *MAOA-uVNTR* genotype on sensitivity to early stress in the context of ameliorating experiences.

Finally, the importance of *MAOA-uVNTR*–early stress interactions in women is not well understood. *MAOA-uVNTR* is an X-linked gene, and half of all female X chromosomes are inactivated. The functional status of *MAOA-uVNTR* alleles in females is therefore unknown. Investigation of *MAOA-uVNTR*–environment interactions influencing behavior has therefore often focused on males (Caspi *et al.*, 2002; Foley *et al.*, 2004; Kim-Cohen *et al.*, 2006; Vanyukov *et al.*, 2007), although some have examined female populations (Huang *et al.*, 2004; Sjöberg *et al.*, 2007; Ducci *et al.*, 2008). As females may be at greater risk for developing mental health problems, understanding the contributing processes in females is necessary. In this study, we determined whether the experience of an early stressor such as physical or sexual abuse, family death, divorce, or separation interacted with *MAOA-uVNTR* genotype to influence impulsive personality traits and depression severity in adulthood in females. We further assessed the potential moderating role of parental care on these gene–environment interactions. We hypothesized that if parental care moderated *MAOA-uVNTR*–early stress

interactions, that individuals who experienced both low parental care and an early stressor would exhibit the highest impulsivity/aggression of all groups, and that high parental care would mitigate somewhat the influence of an early stressor on adult impulsivity/aggression.

Materials and methods

Participants

One hundred and fifty-nine ($n = 159$) unrelated female participants were included in this study. Participants had lifetime diagnoses of major depressive disorder ($n = 106$), bipolar disorder ($n = 34$), or were healthy controls ($n = 19$). Within the clinical population, 25 participants had been diagnosed with disorders linked with impulsivity: borderline personality disorder ($n = 20$), antisocial personality disorder ($n = 3$), and conduct disorder ($n = 2$, designated as remitted at interview). In addition, of the 140 individuals in our pool diagnosed with a mood disorder, 53 were designated as remitted at interview. Our sample was predominantly Caucasian ($n = 97$), but included Asians ($n = 9$), African Americans ($n = 36$), individuals of more than one race ($n = 9$), and missing or not reported race ($n = 8$). A subset of these reported Hispanic ethnicity ($n = 13$). Age ranged from 19 to 64 years, with a mean age of 38.6 years. The highest occupational level attributed to the parents of our participants, on average, was middle-high (described as small business ownership, farm ownership, managing positions or minor professional positions). All patients gave written informed consent to participate in this study, per our approved institutional review board approved protocol.

Structured clinical interview

All participants underwent semistructured clinical interviews for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition to obtain axis I and II diagnoses (Spitzer *et al.*, 1992). Interviews were conducted by clinical psychologists or nurses with a master's degree or PhD. During the interview, sex and self-reported race were recorded for each participant. Family histories of depression, substance use disorders and/or alcohol abuse in all first-degree relatives was also recorded. Socioeconomic status was assessed by asking the participant to rate the highest level of occupational achievement by either parent. A more detailed description of the interview process is available elsewhere (Mann *et al.*, 1999).

Parental bonding instrument—Participants were asked to rate their experience with the parent with whom they spent the most time using the parental bonding instrument (PBI) (Parker, 1979). Sample statements included: 'Spoke to me with a warm and friendly voice', 'Appeared to understand my problems and worries', 'Seemed emotionally cold to me', and 'Made me feel I was not wanted'. Ratings were on a scale of 1–4; '1' meant the sentence is 'very like' their experience, '2' meant 'moderately like' their experience, '3' meant 'moderately unlike' their experience, and '4' meant 'very unlike' their experience. Earlier studies have yielded a two-factor or three-factor structure underlying response to parental care questions (Parker, 1979). After this work, a parental 'care' scale has been validated in multiple populations and with other measures of parental neglect (Parker, 1981). The parental 'care' subscale was therefore calculated for each of our participants. Care scale scores were z-scored to ensure normal distribution. The mean of these scores was calculated for these participants, and scores were generated for each individual by reverse scoring raw parental care scores: individuals who scored above the mean were designated as 'high parental care', and those who scored below the mean were designated as 'low parental care'.

Early life stressors—During the clinical assessment interview, participants were asked about their early life experiences; whether and the age at which they experienced the death of a close family member (mother, father, or sibling), separation from their family, and/or divorce of their parents. They were also asked whether they had experienced sexual or physical abuse

(or both) in their lifetime and whether that abuse occurred before the age of 15. Individuals who experienced any of these stressors before the age of 15 were categorized within the early family stressor or abuse group. Participants who reported physical or sexual abuse were asked to detail the type of abuse, ages at which the abuse occurred, and whether the perpetrator of the abuse was a parent, step-parent, sibling, or another person known or unknown to the participant.

Impulsivity/aggression trait measures—Participants were administered by the Brown–Goodwin Aggression Inventory (Brown *et al.*, 1979), the Barratt Impulsivity Scale (Barratt, 1965), and the Buss–Durkee Hostility Inventory (Buss and Durkee, 1957). For the Brown–Goodwin scale, answers were given for three life stages: early childhood (ages 0–12 years), adolescence (ages 13–18 years), and adulthood (18 years and above). Individuals' scores on the Brown–Goodwin Aggression Inventory, Barratt Impulsivity Scale, and Buss–Durkee Hostility Inventory were found to have high reliability (Cronbach's $\alpha = 0.75$). Principal components analysis with mean replacement for missing values was computed to generate one impulsivity/aggression factor score for each participant as described earlier (Mann *et al.*, 1999).

MAOA-uVNTR genotyping

DNA was obtained from blood samples or from squamous epithelium collected from buccal mucosa using cheek swabs (Puregene Kit, Gentra Systems, Minneapolis, Minnesota, USA). DNA was then extracted from lymphocytes using our previously published method (Huang *et al.*, 2004) and from squamous epithelial cells according to the manufacturer's standard recommended procedure. PCR was performed in a volume of 20 μ l containing 100–200 ng DNA; 25 mmol/l $MgCl_2$; 1% of dimethyl sulfoxide or BSA; 1 times PCR buffer; 10 mmol/l dATP, dGTP, dCTP, and dTTP; 100 ng/l of two primers, *MAOA-uVNTR*Pr-3 (5'-TGCTCCAGAAACATGAGCAC-3') and *MAOA-uVNTR*Pr-4 (3'-TAGACTTGGGGATCCGACTG-5'); and 1U RedTaq polymerase (Sigma, St Louis, Missouri, USA). The samples were preheated at 94°C for 5 min, denatured at 94°C for 35 cycles of 30 s each, annealed at 55°C for 30 s, with extension at 72°C for 40 s in a Stratagene Robocycler 96 PCR system (Stratagene Inc., La Jolla, California, USA). Products were electrophoresed on a 1.8% NuSieve 3:1 agarose gel (BMA, Rockland, Maine, USA) and stained with ethidium bromide. They were then visualized under UV light and sizes were determined by comparison with a 100 bp DNA sequencing ladder. Individuals with 2 or 3 repeat alleles were categorized as low expressing, with 3.5 or 4 repeat alleles as high expressing, and one of each were categorized as 'heterozygotes'. As the expressing of the 5-repeat allele has not been determined, these were removed from analysis. *MAOA-uVNTR* genotype frequencies were as follows: low-expressing allele (22.7%), high-expressing allele (48.8%), and 'heterozygotes' (28.5%).

Statistical analysis

Analysis of variance was used to analyze the two models, the first of which used impulsivity/aggression factor scores (among all participants) as an outcome variable and the second of which used Hamilton depression scores (in major depressive disorder and bipolar participants) as an outcome variable. Three predictors were included in each model: presence or absence of an early family stressor (family death, separation, or divorce) or abuse before the age of 15, quality of perceived parental care (high or low), and *MAOA-uVNTR* genotype (high expressing, low expressing or high/low expressing 'heterozygote'). Interactions between these three factors, when significant, were also included in the model. Separate analyses of variance were conducted to evaluate the potential effect of demographic and life history factors (presence of personality disorder, remission status, presence of parental depression, parental substance abuse, parental alcohol abuse, and number of additional stressors) on the relationship of early

stress, perceived parental care, and *MAOA-uVNTR* genotype on impulsivity/aggression factor scores and Hamilton depression scores. When analysis of variance models yielded a significant result, post-hoc tests were conducted using independent samples *t*-tests.

Results

Sample characteristics

Demographic composition of genotype/experience groups was comparable (Table 1). Groups did not differ in age, education history, race, or socioeconomic status. Remission status of clinical participants, the number of additional stressors experienced, personality disorder incidence, parental history of depression, alcoholism, or substance use disorder did not differ among genotype/experience groups (Table 2).

MAOA-uVNTR and early experience

To address the potential role of gene–environment correlations influencing the results, we determined whether *MAOA-uVNTR* genotype was associated with the experience of early stress, abuse, or parental care ratings. *MAOA-uVNTR* genotype was not associated with parental care ratings ($P > 0.05$). However, high-expressing/low-expressing *MAOA-uVNTR* ‘heterozygotes’ were more likely to be categorized in the early stress group [having reported either an early family stressor (family death, separation or divorce) or abuse] ($\chi^2 = 4.07$, $P = 0.016$) compared with low-expressing or high-expressing *MAOA-uVNTR* homozygotes, though the total number of stressors reported did not differ among genotype groups ($P > 0.05$).

Effects of *MAOA-uVNTR* and early experience on trait impulsivity/aggression and depression scores

High parental care mitigated the association between the experience of an early stressor and impulsivity/aggression factor scores in low-expressing *MAOA-uVNTR* allele carriers and ‘heterozygotes’ but not in high-expressing *MAOA-uVNTR* allele carriers. A significant three-way interaction among perceived parental care, experience of an early family stressor (family death, separation, divorce, and/or abuse) and *MAOA-uVNTR* genotype predicted impulsivity/aggression factor scores [$F(2,150) = 3.17$, $P = 0.048$; Fig. 1]. The effect was such that individuals with low-expressing *MAOA-uVNTR* alleles who experienced an early stressor exhibited lower impulsivity/aggression factor scores when they reported high parental care than low parental care [$t(1,12) = 2.64$, $P = 0.021$]. The same pattern was observed in ‘heterozygotes’ [$t(1,50) = 3.86$, $P = 0.0001$], but not in high-expressing *MAOA-uVNTR* carriers [$t(1,35) = 0.96$, $P = 0.342$]. Notably, individuals who experienced low care and an early stressor did not differ in impulsivity/aggression scores between high and low-expressing *MAOA-uVNTR* genotype groups [$t(1,31) = 1.05$, $P = 0.304$], indicating that the compounded risk associated with low parental care and a stressor did not differ between genotypes. A main effect in the model indicated that individuals who reported less parental care exhibited higher impulsivity/aggression scores [$F(1,147) = 10.19$, $P = 0.002$]. Individuals who reported an early stressor tended to show higher impulsivity/aggression scores as well [$F(1,147) = 2.98$, $P = 0.086$]. There was no main effect of genotype, nor any two-way interactions among independent variables in the model.

Hamilton depression scores were highest in individuals who experienced an early stressor, with the exception of ‘heterozygotes’. A two-way interaction between *MAOA-uVNTR* genotype and the experience of an early stressor predicted depression severity [$F(2,124) = 7.94$, $P = 0.001$; Fig. 2]. ‘Heterozygote’ *MAOA-uVNTR* females who did not experience an early stressor exhibited higher depression scores than ‘heterozygote’ females who experienced an early stressor ($t = 2.50$, $P = 0.015$), whereas both high-expressing *MAOA-uVNTR*

'homozygotes' ($t = 2.02$, $P = 0.049$) and low-expressing 'homozygotes' ($t = 2.47$, $P = 0.023$) showed higher depression scores following an early stressor.

No potential confounding factor that we assessed (presence of personality disorder, remission status, presence of parental depression, parental substance abuse, parental alcohol abuse, and number of additional stressors) interacted significantly with genotype, early stress, or parental care to influence impulsivity/aggression scores or Hamilton depression scores (all $P > 0.05$).

Finally, our categorization of individuals who experience either abuse or other types of early life stressors into one 'early stress' group did not significantly impact our findings. First, individuals who experienced early abuse versus family, death, separation, or divorce were not distributed differently across genotype/experience groups ($\chi^2 = 7.11$, d.f. = 2, $P = 0.213$). Individuals who experienced abuse versus family death, separation, or divorce alone did not differ significantly in Hamilton depression scores ($P > 0.05$) or trait impulsivity/aggression scores ($P > 0.05$).

Discussion

This study highlights the importance of developmental context for gene–environment interactions that may contribute to psychological and behavioral dysfunction. Although early adversity was associated with more severe trait impulsivity/aggression in adulthood in all groups in this study, better perceived parental care offset the effects of childhood adversity in low-expressing *MAOA-uVNTR* carriers, but not in high-expressing *MAOA-uVNTR* carriers. This effect did not generalize to depression severity in individuals with mood disorders, indicating that this finding was specific to trait impulsivity and aggression. Earlier studies have indicated that low-expressing *MAOA-uVNTR* carriers are at greater risk for poor outcomes following early abuse (Caspi *et al.*, 2002; Foley *et al.*, 2004; Huang *et al.*, 2004; Haberstick *et al.*, 2005; Huizinga *et al.*, 2006; Kim-Cohen *et al.*, 2006; Nilsson *et al.*, 2006; Widom and Brzustowicz, 2006; Young *et al.*, 2006; Cicchetti and Rogosch, 2007; Frazzetto *et al.*, 2007; Nilsson *et al.*, 2007; Vanyukov *et al.*, 2007; Ducci *et al.*, 2008; Weder *et al.*, 2008). Consistent with recent reports (Kaufman *et al.*, 2004, 2006), we suggest that gene–environment interactions influence not only risk for poor outcomes, but also the capacity for resilience in response to positive experiences.

Our results may explain discrepancies in the *MAOA-uVNTR* gene–environment interaction literature. Results from earlier studies targeting childhood adversity–*MAOA-uVNTR* interactions have been somewhat inconsistent (Caspi *et al.*, 2002; Foley *et al.*, 2004; Huang *et al.*, 2004; Haberstick *et al.*, 2005; Kim-Cohen *et al.*, 2006; Frazzetto *et al.*, 2007; Nilsson *et al.*, 2007; Vanyukov *et al.*, 2007), although a recent meta-analysis showed that the gene–environment interaction is robust when data from multiple studies are assessed (Kim-Cohen *et al.*, 2006). One obstacle to replicating the *MAOA-uVNTR*–early stress interaction may be that early adversity groups in other studies included individuals who experienced varying levels of parental care or other positive proximal events. We note that our 'low care' groups correspond more closely to the pattern in which low-expressing *MAOA-uVNTR* allele carriers who report early adversity exhibit more severe trait impulsiveness/aggression as adults (Fig. 1; Caspi *et al.*, 2002; Huang *et al.*, 2004; Kim-Cohen *et al.*, 2006). It is possible that studies including a large proportion of individuals who experience low parental care are more likely to detect a gene–environment interaction.

Examination of *MAOA-uVNTR*–environment interactions influencing behavior has often focused on males (Caspi *et al.*, 2002; Foley *et al.*, 2004; Kim-Cohen *et al.*, 2006; Vanyukov *et al.*, 2007), although some have examined female populations (Huang *et al.*, 2004; Sjöberg *et al.*, 2007; Ducci *et al.*, 2008). Separate analyses of males and females are desirable because

MAOA-uVNTR is an X-linked gene, and half of all female X chromosomes are inactivated. The functional status of *MAOA-uVNTR* alleles in females is therefore unknown. Further, the functional outcome of ‘heterozygosity’ for high-expressing and low-expressing alleles (only possible in females) is unknown. Presumably for this reason, earlier studies examining the association of *MAOA-uVNTR* with depressive symptoms in females have excluded individuals with one high-expressing and one low-expressing *MAOA-uVNTR* allele (Cicchetti and Rogosch, 2007). Our finding that female ‘heterozygotes’ show the opposite pattern of association of early adversity with depression severity to high-expressing and low-expressing ‘homozygotes’ is therefore novel, and must be replicated with a larger sample size. It is possible that this finding is related to the fact that female ‘heterozygotes’ were more likely to report a childhood stressor in our population, and a possible artifact. Our second set of results is somewhat consistent with other *MAOA-uVNTR* × early adversity studies focusing on females. Our results indicate that women with low-expressing *MAOA-uVNTR* alleles are more sensitive to ameliorating experiences in childhood. In parallel, one earlier study showed that the low-expressing *MAOA-uVNTR* allele carriers have a lower propensity for antisocial outcomes in the context of poor family relationships and early adversity in females (Sjöberg *et al.*, 2007). However, other studies suggest that females who experience early abuse and possess the low-expressing *MAOA-uVNTR* allele are at greater risk for antisocial personality disorder and alcoholism (Ducci *et al.*, 2008), a finding that aligns with data available for males (Caspi *et al.*, 2002; Huang *et al.*, 2004). Still others suggest that the association of *MAOA-uVNTR* genotype with experience is weak or null in females (Eley *et al.*, 2004; Huang *et al.*, 2004; Widom and Brzustowicz, 2006; Frazzetto *et al.*, 2007). As such, the findings presented here should be replicated. If true, however, our results suggest that any copy of the low-expressing *MAOA-uVNTR* allele confers sensitivity to the ameliorating effects of high parental care in females, as high-expressing and low-expressing allele ‘heterozygotes’ showed a similar pattern of association between early experiences and adult impulsivity/aggression to low-expressing *MAOA-uVNTR* carriers. Sex differences in sensitivity to ameliorating features of the childhood environment, however, remain to be elucidated.

We considered the possibility that *MAOA-uVNTR* genotype affects behavior in the child and increases the risk for certain types of adversity. We examined the association between genotype and experiences to confirm that our data were not confounded by such gene–environment correlations. Earlier studies in males (Caspi *et al.*, 2002; Foley *et al.*, 2004; Huang *et al.*, 2004) as well as females (Huang *et al.*, 2004; Sjöberg *et al.*, 2007; Ducci *et al.*, 2008) have typically failed to detect an association between *MAOA-uVNTR* genotype and the experience of early stress and/or abuse. Our results differ from these earlier studies in that individuals with one high-expressing and one low-expressing *MAOA-uVNTR* allele were more likely to have reported a childhood stressor or abuse. It is possible that this finding resulted from a type I error, as our previous work with a larger sample failed to detect this association (Huang *et al.*, 2004). Further, a lack of association between genotype and the number of childhood stressors experienced undermines the notion that genotype–environment correlations are present in our dataset. However, this finding should be replicated in a larger sample before inferences can be drawn.

The mechanisms of *MAOA-uVNTR*–early stress interactions influencing behavior have not yet been conclusively demonstrated. There are several possible mechanisms whereby *MAOA-uVNTR* genotype might influence vulnerability to mood disorders and impulsivity in adulthood. The MAOA enzyme is associated with the rate of oxidation/inactivation of monoamines serotonin, dopamine, and norepinephrine in the central nervous system. Thus, *MAOA-uVNTR* genotype is thought to predict psychiatric vulnerability through alterations to the monoamine systems, as genotype has been shown to impact MAOA enzyme levels *in vitro* (Sabol *et al.*, 1998) and *in vivo* (in men, Williams *et al.*, 2003; in women, Jönsson *et al.*, 2000; Manuck *et al.*, 2000; Zalsman *et al.*, 2005; although see Jönsson *et al.*, 2000; Ducci *et*

al., 2008). Other neural systems influenced by *MAOA-uVNTR* genotype, such as the hypothalamic pituitary adrenal axis, (Jabbi *et al.*, 2007) or prefrontal cortex (Meyer-Lindenberg *et al.*, 2006; Passamonti *et al.*, 2006) may also be involved in the observed association with behavioral traits.

Limitations

An important potential confound in our data was that better perceived parental care may have merely been a correlate of fewer additional childhood stressors. Others have reported that risk associated with *MAOA-uVNTR*–environment interactions increases with the number of stressors experienced (Foley *et al.*, 2004; Cicchetti and Rogosch, 2007). We were able to rule out this possibility because the genotype/experience groups did not differ in the average number of additional stressors (beyond the minimum of one required to be categorized in early stress groups). Another potential limitation to this study is a possible recall bias for parental care attributable to the level of adult psychopathology in our participants; individuals who are more depressed or impulsive as adults may tend to perceive their childhood experiences more negatively. However, the PBI has been validated against other standardized measures of neglect (Lancaster *et al.*, 2007), across cultures and clinical and healthy populations (Parker, 1993; Reti *et al.*, 2002; Heider *et al.*, 2006; Uji *et al.*, 2006), do not change after recovery from major depressive episodes (Lizardi and Klein, 2005), and has been correlated with both parental self-ratings as well as with independent observations of parental care (Parker, 1981). These studies support the notion that the PBI reflects actual parental care. A final limitation to our data is that our sample included relatively few normal controls compared with participants with mood disorders. Future studies should confirm the potential for amelioration of impulsivity and aggression by high parental care in a larger sample of healthy adults.

Conclusion

Although replication of our results is necessary, this study suggests that genotype may further moderate the association of positive early experiences with resiliency to childhood stress. This finding implies that the ‘risk’ attributed to the low-expressing *MAOA-uVNTR* allele may be more aptly described as sensitivity to early life events. As such, low-expressing *MAOA-uVNTR* carriers may be at greater risk for poor outcomes but may also be more responsive to intervention strategies. In summary, considering the interactions among genes and multiple types of early life experiences, may lend additional insight both to behavioral dysfunction and its underlying processes.

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Fig. 1.

Parenting quality moderates the influence of *MAOA-uVNTR* genotype and childhood stress on impulsivity/aggression scores in clinical and healthy participants.

Fig. 2.

The effects of *MAOA-uVNTR* genotype, childhood stressors, and parenting quality on Hamilton depression scores in clinical participants.

Table 1
Demographic factors by genotype/experience groups

Genotype/experience group	n	Age (years)	Education (years)	Race	SES
Low expressing					
MAOA- <i>uVNTR</i> genotype					
High care/no stressor	11	39.18	16.00	C	High
High care/stressor	6	31.00	16.00	AA	High
Low care/no stressor	4	43.75	16.25	C	Low
Low care/stressor	8	42.12	13.62	C	Low
Heterozygote					
MAOA- <i>uVNTR</i> genotype					
High care/no stressor	10	41.50	16.00	C	High/low
High care/stressor	19	36.79	15.58	C	High
Low care/no stressor	7	38.86	15.43	C	High
Low care/stressor	34	38.45	15.21	C	High/low
High expressing					
MAOA- <i>uVNTR</i> genotype					
High care/no stressor	18	36.61	16.33	C	High
High care/stressor	12	35.83	14.58	C	Low
Low care/no stressor	9	39.44	15.78	C/AA	High
Low care/stressor	25	40.76	14.76	C	High
Total	163	38.56	15.38	C	High

Means are presented for age and education. Modes are presented for race (C and AA) and SES.
AA, African American; C, Caucasian; SES, socioeconomic status.

Risk factors/diagnoses by MAOA-u VNTR genotype/experience groups

Genotype/experience group	n	Additional stressors	Parent depression	PD (%)	MD (%)	Remitted (%)
Low expressing						
MAOA-uVNTR genotype						
High care/no stressor	11	NA	0	18.2	72.7	50.0
High care/stressor	6	1	1	16.7	50.0	00.0
Low care/no stressor	4	NA	0	25.0	100.0	25.0
Low care/stressor	8	2	2	37.5	100.0	50.0
Heterozygote						
MAOA-uVNTR genotype						
High care/no stressor	10	NA	0	20.0	66.7	16.7
High care/stressor	19	1	1	26.3	94.7	61.1
Low care/no stressor	7	NA	0	57.1	100.0	14.3
Low care/stressor	34	1	1	26.5	100.0	40.6
High expressing						
MAOA-uVNTR genotype						
High care/no stressor	18	NA	0	11.1	62.5	53.8
High care/stressor	12	2	2	50.0	100.0	25.0
Low care/no stressor	9	NA	0	00.0	88.9	37.5
Low care/stressor	25	1	1	44.0	96.0	20.8
Total/mean/mode	163	1	1	33.0	88.1	37.1

Medians are presented for number of additional stressors and number of first degree relatives diagnosed with depression. Percentage of group members diagnosed with any PD is presented. Percentage of group members diagnosed with a MD and percentage of individuals diagnosed with remitted mood disorders are also presented. MD, mood disorder; NA, not applicable; PD, personality disorder.