Exploring the association between the 2-repeat allele of the MAOA gene promoter polymorphism and psychopathic personality traits, arrests, incarceration, and lifetime antisocial behavior

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Abstract
A line of research has revealed that a polymorphism in the promoter region of the MAOA gene is related to antisocial phenotypes. Most of these studies examine the effects of low MAOA activity alleles (2-repeat and 3-repeat alleles) against the effects of high MAOA activity alleles (3.5-repeat, 4-repeat, and sometimes 5-repeat alleles), with research indicating that the low MAOA activity alleles confer an increased risk to antisocial phenotypes. The current study examined whether the 2-repeat allele, which has been shown to be functionally different from the 3-repeat allele, was associated with a range of antisocial phenotypes in a sample of males drawn from the National Longitudinal Study of Adolescent Health. Analyses revealed that African-American males who carried the 2-repeat allele were, in comparison with other African-American male genotypes, significantly more likely to be arrested and incarcerated. Additionally, analyses revealed that African-American male carriers of the 2-repeat allele scored significantly higher on an antisocial phenotype index and on measures assessing involvement in violent behaviors over the life course. There was not any association between the 2-repeat allele and a continuously measured psychopathic personality traits scale. The effects of the 2-repeat allele could not be examined in Caucasian males because only 0.1% carried it.

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1. Introduction
A significant amount of behavioral genetic research has examined the genetic basis to antisocial behaviors (Moffitt, 2005). The results of these studies, best summarized by a number of meta-analyses, indicate that approximately 50% of the variance in measures of antisocial phenotypes is attributable to genetic factors (Ferguson, 2010; Mason & Frick, 1994; Miles & Carey, 1997; Rhee & Waldman, 2002). More recent research has begun to investigate genetic polymorphisms that might be partially responsible for producing variation in antisocial phenotypes (Caspi et al., 2002). Genes involved in neurotransmission have been identified as the most promising candidate genes for antisocial behaviors and traits (Ferguson & Beaver, 2009). Although studies have identified an association between polymorphisms in a number of neurotransmission genes and various antisocial behaviors, these associations are often plagued by the inability for follow-up studies to replicate the original findings. An important exception to the replication problem appears to be for a functional polymorphism in the monoamine oxidase A (MAOA) gene.

The MAOA gene has been mapped to the X chromosome at location Xp11.23–11.4 (Levy et al., 1989) and codes for the production of the MAOA enzyme that catabolizes certain neurotransmitters, such as dopamine and serotonin (Shih, Chen, & Ridd, 1999). The MAOA gene has a polymorphism in the promoter region that is the result of a 30 base pair (bp) variable number of tandem repeats (VNTR) in the regulatory region of the gene. This polymorphism has been shown to be functional as different alleles correspond to the production of MAOA enzymes with different activity levels (Sabol, Hus, & Hamer, 1998). Recognizing differences in transcriptional efficiency, researchers commonly pool the alleles into two groups: those that correspond to low MAOA activity and those that correspond to high MAOA functioning. In most studies, the 2-repeat allele and the 3-repeat allele are pooled together to form the low MAOA activity genotype and the 3.5-repeat allele, 4-repeat
allele, and 5-repeat allele are pooled together to form the high MAOA activity genotype (Caspi et al., 2002).

The polymorphism in the promoter region of the MAOA gene has been the source of a considerable amount of research examining whether different alleles are associated with antisocial phenotypes. In a landmark study, Caspi et al. (2002) reported a link between low MAOA activity alleles and antisocial behaviors, but only among males who had been maltreated in childhood. The results of a meta-analysis seemed to confirm the association between MAOA and antisocial outcomes for maltreated males (Kim-Cohen et al., 2006). Although most of this research has revealed that MAOA only has significant effects when paired to a criminogenic environment, there is some evidence to indicate that the low MAOA activity alleles may have effects independent of environmental factors for some antisocial behaviors (Beaver, DeLisi, Vaughn, & Barnes, 2010).

Guo and his colleagues (2008) provided evidence that the MAOA gene is related to delinquent behavior in a sample of adolescents and young adults independent of environmental factors. Unlike the vast majority of research examining the effects of the MAOA gene, Guo et al. examined the effects of the 2-repeat allele against the effects of the 3-repeat allele and 5-repeat allele and against the effects of the 3.5-repeat allele and the 4-repeat allele. The results of their analysis indicated that carriers of the 2-repeat allele were at a statistically significant greater risk for engaging in serious and violent delinquency in adolescence and early adulthood. The effects were particularly marked for males. Guo et al. also conducted a functional analysis of the alleles and found that the 2-repeat allele, in comparison with 3-repeat and 4-repeat alleles, had the lowest level of promoter activity.

The results of the study by Guo et al. suggest that pooling together the 2-repeat and 3-repeat alleles may be incorrect and that the 2-repeat allele should be examined in isolation because of its functional significance. Besides this single study, though, research has yet to fully explore this possibility and thus whether the 2-repeat allele is truly a marker for antisocial phenotypes remains to be determined. The current study examines this possibility by testing for an association between the 2-repeat allele and psychopathic personality traits, the odds of being arrested, the odds of being incarcerated, and lifetime antisocial behavior in a sample of American males.

2. Materials and methods

2.1. Participants

Data for this study were drawn from the National Longitudinal Study of Adolescent Health (Add Health; Harris, 2009). The Add Health is a four-wave prospective study of a nationally representative sample of American youth who were enrolled in middle or high school in 1994–1995. The first (N = 20,745) and second (N = 14,738) waves of data were collected when most of the respondents were adolescents. The third wave of data was collected in 2001–2002 when the subjects were young adults (N = 15,197). The fourth wave of data was collected in 2007–2008 when the subjects were 24–32 years of age (N = 15,701). More details about the data can be gathered by consulting previously published reports (Harris, Tucker Halpern, Smolen, & Haberstick, 2006; Harris et al., 2003; Resnick et al., 1997).

At wave 3, a subsample of subjects was genotyped for the MAOA-uVNTR. Respondents who had a sibling who was also participating in the Add Health study were eligible for inclusion in the DNA subsample. In total, 2574 subjects submitted usable buccal cells that were genotyped, making the Add Health one of the largest samples in the world that includes genotypic and phenotypic information. Genotyping was carried out in a coordinated effort between the Add Health team and the Institute of Behavioral Genetics in Boulder, Colorado (Harris et al., 2006). As discussed below, the analytical sample was based on Ns ranging between 167 and 174 African-American males. In the statistical analyses, missing cases were removed using listwise deletion techniques.

2.2. Genotyping procedures

Subjects were genotyped for the MAOA-uVNTR polymorphism using a variant of the assay developed previously (Sabol et al., 1998). Primer sequences were as follows: forward, 5′-ACA-GCCTGACCGTGGAGAAG-3′ (fluorescently labeled), and reverse, 5′-GAACGTACGCCCTCATTCCGA-3′. This assay produced PCR products of 291 (2-repeat allele), 321 (3-repeat allele), 336 (3.5-repeat allele), 351 (4-repeat allele), and 381 (5-repeat allele) base pairs. The genotypes were scored independently by two different raters. Subjects with the 2-repeat allele were placed into one group and subjects with the 3-repeat, 3.5-repeat, 4-repeat, and 5-repeat alleles were pooled together into another group. Because most research examining the effects of MAOA has focused only on males and because MAOA is X-linked, the current study includes only males in the analytical sample.

2.3. Measures

Four main outcome measures were employed in the current study. The first outcome measure was a psychopathic personality traits scale. Prior researchers analyzing these data have developed a 23-item five-factor model-based psychopathic personality traits scale (Beaver, Barnes, May, & Schwartz, 2011) based on wave 4 data, where higher values represent more psychopathic personality traits. This same scale was used in the current study (Cronbach’s α = 0.81). In addition, two criminal justice measures were also included as outcome variables. First, respondents were asked at wave 4 whether they had ever been arrested during their life (0 = no, 1 = yes). Second, respondents were asked at wave 4 whether they had ever been incarcerated during their life (0 = no, 1 = yes). The last outcome measure was a composite antisocial phenotype index that was constructed by combining scores on the psychopathic personality traits scale, the arrest measure, and the incarceration measures. Specifically, respondents who scored 1.5 standard deviations above the mean on the psychopathic personality traits scale were assigned a value of one (1) and all other scores were assigned a value of zero (0). Then scores on the dichotomized psychopathic personality traits variable were summed together with the binary arrest variable and the binary incarceration variable, which produced a composite antisocial phenotype with scores ranging between zero (0) and three (3).

Last, a dichotomous race variable was included in the analyses. At wave 1, interviewers were asked to indicate the race that best describes each respondent. The data were initially analyzed using respondents who were characterized as being either Caucasian or African-American.

3. Findings

Since prior research has revealed that the distribution of the 2-repeat allele varies by race (e.g., Reti et al., 2011; Widom & Brzustowicz, 2006), the analysis begins by examining the allelic distributions by race. As Table 1 shows, the 2-repeat allele was carried by 0.1% of Caucasian males and by 5.2% of African-American males. To check the consistency of these estimates, all of the analyses were recalculated using self-reported race instead of
research has revealed that self-reported race correlates almost perfectly with race identified via genetic markers (Tang et al., 2005). The results were virtually identical when using self-reports of race, where 0.1% of Caucasian males and 5.5% of African-American males were carriers of the 2-repeat allele. These estimates are directly in line with those reported in other samples (e.g., Reti et al., 2011; Widom & Brzustowicz, 2006). Because only 0.1% of Caucasian males had the 2-repeat allele, the remaining analyses were conducted using only African-American males. Missing data on some of the outcome measures reduced the final analytical sample size to between N = 167 and N = 174 and resulted in one (1) carrier of the 2-repeat allele to be dropped from the analysis.

The next set of statistical models examined the association between the 2-repeat allele and the psychopathic personality traits variables. Since the psychopathic personality traits scale was coded continuously and approximated normality, ordinary least squares (OLS) regression was estimated. Importantly, all of the analyses in this study were estimated using the "cluster" command in STATA10.0 to correct for the clustering of observations in families (any cases missing a family ID number were dropped from the analyses). The results of this model revealed a non-significant association between the 2-repeat allele and scores on the psychopathic personality traits scale (b = 0.11, SE = 0.07, p = 0.24, R² = 0.04). To check the sensitivity of the results, the analyses were recalculated using negative binomial regression as well as z-transforming the psychopathic personality traits scale. The pattern of results was identical to those reported using OLS regression with the untransformed psychopathic personality traits scale.

The next series of statistical models used the ever arrested and ever incarcerated variables as outcome measures. Binary logistic regression models were estimated because both outcome measures were coded dichotomously. The results revealed that carriers of the 2-repeat allele were significantly more likely to be arrested compared to carriers of other alleles (b = 0.13, SE = 0.08, OR = 3.85, p = 0.008, Nagelkerke R² = 0.03, N = 169). In particular, 2-repeat allele carriers were 3.85 times more likely to be arrested than carriers of other alleles. The predicted probabilities associated with being arrested were 0.80 for 2-repeat allele carriers and 0.51 for carriers of other alleles. In total, 8.6% of the subjects who had been arrested carried the 2-repeat allele compared with only 2.4% of the subjects who had never been arrested.

An additional binary logistic regression equation also revealed a statistically significant association between the 2-repeat allele and the odds of being incarcerated (b = 1.11, SE = 0.67, OR = 3.06, p = 0.096, Nagelkerke R² = 0.02, N = 174). Carriers of the 2-repeat allele were 3.06 times more likely to have been incarcerated than carriers of other alleles. Overall, the predicted probability of being incarcerated was 0.60 for 2-repeat carriers and 0.33 for carriers of other alleles. In total, 9.5% of the subjects who had been incarcerated carried the 2-repeat allele compared with only 3.4% of the subjects who had not been incarcerated.

The last main set of analyses examined the association between the 2-repeat allele and the composite antisocial phenotype index. The results of the OLS equation revealed a statistically significant and positive association, wherein carriers of the 2-repeat allele, on average, scored higher on the composite index when compared to non-carriers of this allele (b = 0.88, SE = 0.35, Beta = 0.21, p = 0.014, N = 167). To ensure that this association was not affected by the distribution of the composite index, the model was recalculated using negative binomial regression. The substantive results were identical to those garnered when using OLS regression.

3.1. Supplemental analyses

To check the robustness of the results, two lifetime antisocial behavioral outcome measures were employed. First, self-reported violence scales were created for each of the four waves of data collection. These four scales were then z-transformed, summed together, and the resulting summated scale was once again z-transformed. This scale provides an estimate of lifetime involvement in violent antisocial behaviors. An OLS regression equation was then calculated to estimate the association between the 2-repeat allele and scores on the lifetime violence scale, with the results revealing a positive and statistically significant association (b = 0.11, SE = 0.49, Beta = 0.27, p = 0.026, R² = 0.07). Importantly, the missingness across all four waves of data resulted in losing two (2) cases with the 2-repeat allele so all of these analyses (and the following one) were based on a sample size of N = 130, of which 6.2% had the 2-repeat allele.

The second sensitivity analysis was conducted by assigning all respondents who scored 1.5 standard deviations or higher on the lifetime violence scale a value of one (1) and all other scores a value of zero (0). In addition, at wave 4 respondents were asked whether they had ever been convicted or pled guilty to a crime other than a minor traffic violation. This item was then dichotomized (0 = no, 1 = yes) and summed together with the dichotomized lifetime violence scale. Scores on this lifetime antisocial behavior index ranged between zero (0) and two (2) and is similar to indexes that have been used previously (Beaver et al., 2007; Haberstick et al., 2005). An OLS regression equation revealed a positive and statistically significant association between the 2-repeat allele and this lifetime antisocial behavioral scale (b = 0.45, SE = 0.24, Beta = 0.20, p = 0.062, R² = 0.04). The pattern of results was confirmed when re-estimating the models using negative binomial regression.

In addition, we also explored the possibility that the individual MAOA alleles might have a monotonic relationship with the outcome measures. To do so, all of the alleles were disaggregated into an ordinal variable which measured each respondents’ genotype (i.e., 1 = 4-repeat allele, 2 = 3-repeat allele, and 3 = 2-repeat allele). The effects were largely consistent with those reported when MAOA was dichotomized, except that there was not an association with either of the outcome measures that were estimated using the lifetime violence scales. Follow-up analyses

### Table 1

Descriptive statistics for selected Add Health study variables and scales.

<table>
<thead>
<tr>
<th></th>
<th>African-Americans (%)</th>
<th>Caucasians (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2R</td>
<td>52.3</td>
<td>37.0</td>
</tr>
<tr>
<td>3R</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>3.5R</td>
<td>42.0</td>
<td>60.0</td>
</tr>
<tr>
<td>5R</td>
<td>0.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52.6</td>
<td>47.4</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incarceration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65.0</td>
<td></td>
</tr>
<tr>
<td>Composite index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>45.1</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Psychopathic personality traits</td>
<td>Mean = 53.93</td>
<td>SD = 9.62</td>
</tr>
</tbody>
</table>

Note: except for MAOA, the descriptive statistics are not presented for Caucasians because none of the analyses using the antisocial variables/scales include data from Caucasians.
revealed that there were not any significant differences between the 3-repeat allele and the 4-repeat allele on any of the outcome measures, strongly suggesting that the 2-repeat allele was driving the significant associations with the outcome measures.

4. Discussion

Studies examining the potential link between MAOA and antisocial phenotypes typically divide alleles into a high MAOA activity group and a low MAOA activity group, with the latter being associated with an increase in antisocial phenotypes for males who were maltreated as children (Caspi et al., 2002; Kim-Cohen et al., 2006). There is limited research indicating that there may be heterogeneity in the functionality of the low MAOA activity alleles with the 2-repeat allele being related to lower promoter activity in comparison with all of the other alleles (Guo et al., 2008). As a result, pooling together the 2-repeat and 3-repeat alleles into a single group may mask differential effects that exist for each of these alleles. Here, we addressed this possibility by examining whether the 2-repeat allele was associated with psychopathic personality traits, the odds of being arrested, the odds of being incarcerated, and lifetime antisocial behavior. Analysis of African-American males drawn from the Add Health sample revealed that carriers of the 2-repeat allele were at much greater risk for being arrested during their lifetime and for being incarcerated during their lifetime. Although there was no evidence linking the 2-repeat allele to scores on the continuously measured psychopathic personality traits scale, there was evidence linking the 2-repeat allele to an antisocial phenotype index that included a dichotomized measure of psychopathic personality traits as well as to scales measuring involvement in acts of serious violence across the life course. These findings suggest that future MAOA research may benefit from examining the effects of the 2-repeat allele separately from other alleles.

The potential association between the 2-repeat allele and antisocial phenotypes in Caucasian males could not be explored in the current study because only 0.1% of Caucasian males carried the 2-repeat allele. This is not unique to the current study as the frequencies of the 2-repeat allele in the Add Health paralleled those detected in other studies, wherein less than 1% of Caucasian males carry the 2-repeat allele and approximately 5–6% of African-American (or minority) males carry the 2-repeat allele (Retti et al., 2011; Wisdom & Brunstrom, 2006). If the 2-repeat allele does indeed have an effect on antisocial phenotypes, then future studies need to collect much larger samples of both Caucasians and African-Americans to include a sufficient number of 2-repeat allele carriers to be examined in statistical analyses.

The limited available evidence suggests that the 2-repeat allele may have an independent effect on antisocial phenotypes. This finding, if replicated in future studies, is unique in that most of the MAOA research that pools together the 2-repeat and 3-repeat alleles has indicated that these genotypes only confer a risk to antisocial phenotypes when paired with environmental risk factors (Caspi et al., 2002; Kim-Cohen et al., 2006). Whether the effect of the 2-repeat allele could be amplified or blunted by environmental conditions is an important avenue for future research, but the low base-rate of 2-repeat allele carriers prevented an exploration of gene-environment interaction in the current study.

The results of the current study should be interpreted with caution in light of a number of limitations that need to be addressed in replication studies. First, the measures of psychopathic personality traits, ever arrested, and ever incarcerated were based on self-reports, not official data. Although self-reports have been shown to be reliable and valid instruments for assessing antisocial phenotypes (Krueger et al., 1994; Sutton, 2010), it is possible that official crime data would have produced differing results. Second, the measures of criminal justice outcomes did not delineate between different types of offenders, such as violent predatory offenders versus non-violent property offenders. Perhaps the 2-repeat allele would have varying effects on different subcategories of offenders. Third, the sample analyzed in the current study is the same as the one analyzed in Guo et al.’s (2008) study. While we examined different outcome measures and focused only on African-American males, it is important that future studies estimate the association between the 2-repeat allele and antisocial phenotypes in other samples. Last, although the frequency of the 2-repeat allele is similar to prior research, only about 5% of the final analytical sample carried the 2-repeat allele. Future research needs to examine much larger samples in order to include more 2-repeat allele carriers. Until these limitations are addressed, it would be premature to hypothesize how the 2-repeat allele may impact criminal activity patterns in society.

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