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Moderation of 5-HTTLPR and MAOA Effects on Alcohol Dependence Differs by Type of Childhood Abuse

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Background
• 5-HTTLPR is a variable-number-of-repeats region in the gene SLC6A4 located on chromosome 17.
• The two versions are Long and Short, with the Short allele associated with reduced transcription of serotonin transporter mRNA.
• Previous gene-environment interaction (GxE) studies indicated the presence of one or two Short alleles to be related to greater increases in substance use in adolescents from families low on involved-supportive parenting (Brody et al., 2000) and greater risk of early alcohol use in adolescents who were malnurtured as children (Kaufman et al., 2007).
• MAOA is a variable-number-of-repeats gene on the X-chromosome that codes for an enzyme (also MAOA) which degrades neurotransmitters.
• Number of repeats that result in Low MAOA activity have been linked to increased rates of delinquency and violence (Guo et al., 2008).
• The relationship between Low MAOA and violence, conduct disorder, and antisocial personality disorder is especially strong in individuals who experienced childhood maltreatment or physical abuse (Caspi et al., 2002; Kim-Cohen et al., 2006).

Current Study
• Previous studies of GxE interactions in childhood abuse and externalizing behaviors tend to collapse across the broad range of childhood maltreatment.
• We explored moderation of the effect of MAOA and 5-HTTLPR genotypes on alcohol dependence symptoms at age 25 by type of childhood abuse experienced (Physical and/or Sexual) prior to age 18.

Participants
• Minnesota Twin and Family Study (MTFS) community-sampled twin participants who were assessed for alcohol dependence at age 25 (N=2063, 44.9% female) were included in our sample.
• Of these, 1949 (44.1% female) had childhood abuse status data available.
• 1203 (45.1% female) were genotyped for 5-HTTLPR.
• 978 (27.4% female) were genotyped for and homozygous on MAOA.
• Females who were heterozygous for the High-Low activity genotype (N=227) were dropped from our genetic analyses due to uncertain MAOA activity level (see Kim-Cohen et al., 2006).

Measures
• Abuse status: Childhood Physical and Sexual abuse were assessed at either age 21 or age 29.
• 54.3% of those assessed for abuse were asked two Yes/No questions about physical and sexual assault respectively as part of a broader Life Events Inventory, as well as the first age at which they experienced that type of assault.
• 74.1% received a more extensive abuse assessment, including:
  • 4 items on severe Physical abuse if they were ever hit leaving a mark, hit with an object, assaulted with a weapon, or injured in another way by an adult responsible for them, and
  • 9 items on Sexual abuse (ranging from being propositioned to intercourse, whether in an unwanted situation prior to age 18 or with anyone more than 5 years older prior to age 13).
• For those assessed on both measures (N=1551) reliability was good as indicated by cross-measure correlations of r=0.72 for Physical abuse and r=0.73 for Sexual abuse. Discrepancies tended to favor abuse endorsement on the second, more specific measure.
• Abuse status was aggregated across measures separately for Physical and Sexual abuse.
• Proportion reporting Physical abuse was 22.4%, while 6.2% reported Sexual abuse.
• For each abuse type, exposure before age 18 was coded as 1, while non-exposure was coded 0.

Measures, continued
• Alcohol dependence symptoms: Participants were assessed for DSM-IV criteria alcohol dependence symptoms at age 25 covering approximately the past 4 years.
• Each individual received a count of symptoms which had definitely been met.
• The sample mean was 1.3 symptoms, with a standard error of 0.12 and a range of 0 to 10.
• 5-HTTLPR was assessed from participants’ peripheral blood samples or buccal swabs as described in Anchordoqui et al. (2003).
• Number of repeats was coded into Short (S, 4/5bp) and Long (L, 5/2bp).
• Proportions of each genotype were: LS=32.3%, LL=48.9%, SS=18.8%.
• 5-HTTLPR was in Hardy-Weinberg Equilibrium, with a Minor Allele (S) Frequency of 0.43, \(\chi^2(0.02) = 0.87\).
• Individuals were coded for number of Short alleles they possessed (0, 1, or 2).
• MAOA was assessed from participants’ peripheral blood samples or buccal swabs as described in Haberstick et al. (2005).
• Individuals were dichotomized for MAOA activity level, with high activity indicated by 3.5 or 4 repeats of the MAOA gene and Low activity indicated by 2, 3, or 5 repeats (as described in Caspi et al., 2002).
• The Low activity genotype was less frequent (31.4% of the sample), which is similar to previous reports (e.g. 43.3% males, 19.7% females, Guo et al., 2008).
• MAOA was coded as ‘O’ for High activity, ‘T’ for Low activity.

Analyses
• Multiple regressions were conducted in Mplus (Muthén & Muthén, 1997-2008), taking into account the non-independent nature of the twin data.
• Alcohol dependence symptom counts were modeled on a zero-inflated Poisson distribution.

Table 1. Regression Results

<table>
<thead>
<tr>
<th>MAOA</th>
<th>5-HTTLPR</th>
<th>Next</th>
<th>Beta</th>
<th>Z</th>
<th>Beta</th>
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<tr>
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<td></td>
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<td>-0.066</td>
<td>-1.931</td>
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<tr>
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<td></td>
<td>MAOA</td>
<td>0.080</td>
<td>1.863</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>-0.345</td>
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<tr>
<td></td>
<td></td>
<td>Physical</td>
<td>1.110</td>
<td>2.514</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Figure 1. Moderation of 5-HTTLPR effect by sexual abuse status

Figure 2. Moderation of MAOA effect by sexual abuse status

Conclusions
• There was a significant interaction between exposure to childhood Sexual abuse and genetic status in predicting adult alcohol dependence symptoms for both 5-HTTLPR and MAOA. Similar to previous findings (Caspi et al., 2002; Kim-Cohen et al., 2006; Kaufman et al., 2007; Brody et al., 2009), the Short allele in 5-HTTLPR (p=0.001) and Low MAOA activity (p<0.01) increased number of alcohol dependence symptoms in individuals who had experienced childhood Sexual abuse.

• Physical abuse did not interact with either gene in predicting alcohol dependence symptoms, though there was a significant main effect in the 5-HTTLPR model (p=0.04) and a suggestive main effect in the MAOA model (p=0.05), indicating that physical abuse in childhood is predictive of increased alcohol dependence symptoms in adulthood regardless of genetic status on MAOA or 5-HTTLPR.

• Sex was a significant (p<0.001) covariate in each model, although the current models did not examine interactions separately by sex.

References

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