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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., 2009) and greater risk of early alcohol use in adolescents who were maltreated 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*=2093, 44.9% female) were included in our sample.
- Of these, 1949 (44.1% female) had childhood abuse status data,
- 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.
  - 54.2% 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*=551) reliability was good as indicated by cross-measure correlations of *r*=0.27 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 Anchordoquy et al. (2003).
  - Number of repeats was coded into Short (S, 484bp) and Long (L, 528bp).
  - Proportions of each genotype were: LL=32.3%, LS=48.9%, SS=18.9%.
  - 5-HTTLPR was in Hardy-Weinberg Equilibrium, with a Minor Allele (S) Frequency of 0.43, $\chi^2(1)=0.02$, $p=0.87$.
  - 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 '0' for High activity, '1' for Low activity.

Analyses

- Multiple regressions were conducted in Mplus (Muthèn & Muthèn, 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

Model: $AD\_Sx^A = \beta_0 + \beta_1 Sex^B + \beta_2 Physical^C + \beta_3 Sexual^D + \beta_4 genotype^{EF} + \beta_5 Physical*Sexual + \beta_6 Physical*genotype + \beta_7 Sexual*genotype + \beta_8 Physical*Sexual*genotype$

MAOA	*β*	*Z*	*p*
Sex[B]	**-0.858**	**-3.341**	**0.001**
Physical[C]	0.257	1.948	0.051
Sexual[D]	-0.656	-1.931	0.053
MAOA[E]	-0.003	-0.026	0.980
Physical* Sexual	0.879	1.863	0.063
Physical* MAOA	-0.085	-0.345	0.730
Sexual* MAOA	**1.110**	**2.514**	**0.012**
Physical* Sexual* MAOA	-0.057	-0.991	0.321

5-HTTLPR	*β*	*Z*	*p*
Sex[B]	**-0.462**	**-3.715**	**<0.001**
Physical[C]	**0.311**	**2.063**	**0.039**
Sexual[D]	-0.227	-1.053	0.292
5HTT[F]	-0.064	-0.911	0.362
Physical* Sexual	0.269	0.713	0.476
Physical* 5HTT	-0.060	-0.438	0.661
Sexual* 5HTT	**0.515**	**3.438**	**0.001**
Physical* Sexual* 5HTT	-0.153	-0.545	0.585

[A]Count of alcohol dependence symptoms
[B]Sex: male=0, female=1
[C]Physical abuse before age 18: 0=no, 1=yes
[D]Sexual abuse before age 18: 0=no, 1=yes
[E]MAOA activity: 0=high, 1=low
[F]5-HTTLPR genotype: 0=LL, 1=LS, 2=SS

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

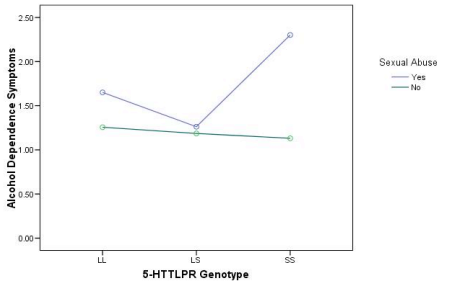
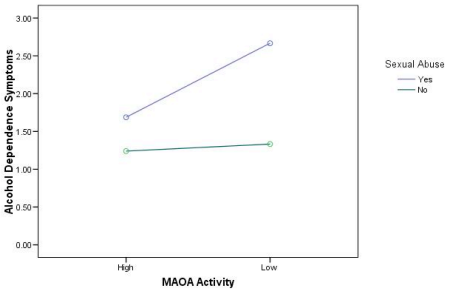


Figure 2. Moderation of MAOA effect by sexual abuse status



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 ($p\leq0.001$) covariate in each model, although the currents models did not examine interactions separately by sex.

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