Interactions Between the COMT Val108/158Met Polymorphism and Maternal Prenatal Smoking Predict Aggressive Behavior Outcomes

Patricia A. Brennan, Emory University
Constance Hammen, University of California
Patrick Sylvers, Emory University
William Bor, Mater Misericordiae Children’s Hospital
Jake Najman, University of Queensland
Penelope Lind, Queensland Institute of Medical Research
Grant Montgomery, Queensland Institute of Medical Research
Alicia K Smith, Emory University

Journal Title: Biological Psychology
Volume: Volume 87, Number 1
Publisher: Elsevier | 2011-04, Pages 99-105
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.biopsycho.2011.02.013
Permanent URL: http://pid.emory.edu/ark:/25593/cdt8s

Final published version: http://dx.doi.org/10.1016/j.biopsycho.2011.02.013

Copyright information:
© 2011 Elsevier B.V. All rights reserved.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Accessed January 31, 2020 9:42 AM EST
Interactions Between the COMT Val108/158Met Polymorphism and Maternal Prenatal Smoking Predict Aggressive Behavior Outcomes

Patricia A. Brennan, Ph.D., Emory University
Constance Hammen, Ph.D., University of California, Los Angeles
Patrick Sylvers, Ph.D., Emory University
William Bor, M.B.B.S., F.R.A.N.Z.C.P., Mater Misericordiae Children's Hospital, South Brisbane, Australia
Jake Najman, Ph.D., University of Queensland, Australia
Penelope Lind, Ph.D., Queensland Institute of Medical Research, Brisbane, Australia
Grant Montgomery, Ph.D., and Queensland Institute of Medical Research, Brisbane, Australia
Alicia K. Smith, Ph.D., Emory University

Abstract

The purpose of the current study is to examine the moderating influence of the catechol O methyltransferase gene (COMT) on the maternal prenatal smoking/offspring externalizing disorder relationship. The sample consisted of 430 young adults born between 1981 and 1984 at the Mater Misericordiae Mother’s Hospital in Brisbane, Australia, as well as their mothers and peers. Mothers reported their prenatal smoking status during pregnancy, and genetic data was obtained from the youth at a later follow-up in adulthood. The outcome measures in this study were mother and teacher reports of youth attention problems and aggression at age 15, and youth, mother and peer reports of youth attention problems and aggression at age 20 (combined to create latent factors of attention problems and aggression at each age). The COMT Val108/158Met polymorphism (rs4680) significantly interacted with maternal cigarette smoking during pregnancy to predict youth aggressive behavior at ages 15 and 20. This gene-environment interaction was not significant for youth attention problems.

© 2011 Elsevier B.V. All rights reserved.
Correspondence to: Patricia Brennan, Ph.D., Department of Psychology, 36 Eagle Row, Emory University, Atlanta, GA 30322. Tel: 404-727-7458. FAX: 404-727-0372. pbren01@emory.edu.
Publisher’s Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Maternal smoking during pregnancy has been associated with both attention deficit hyperactivity disorder (ADHD; Linnet et al., 2003), antisocial outcomes (Wakschlag et al., 2002) in offspring. This association has been found to be consistent across several phases of offspring development including early childhood, adolescence, and adulthood. The strength of the association between maternal prenatal smoking and offspring externalizing disorder appears to increase as the severity level of the antisocial problems increases (Wakschlag et al., 2002). For example, maternal smoking during pregnancy was related to life course persistent offending (arrests occurring during adolescence and adulthood), but not to adolescent limited offending in males in a Danish birth cohort study (Brennan et al., 1999). Associations between prenatal smoking and offspring externalizing disorders have remained significant when potentially confounding environmental risks of poverty, parenting deficits and low maternal age at birth are controlled (Fergusson et al., 1998; Thapar et al., 2003; Wakschlag & Keenan, 2001).

Twin studies have also been used to assess whether the relationship between maternal prenatal smoking and offspring externalizing behavior remain significant when controlling for genetic influences. In one such study, the association between maternal smoking and offspring ADHD was found to persist after controlling for genetic influences (Thapar et al., 2003). In a separate twin study researchers found that genetic effects explained about half of the association between maternal prenatal smoking and child conduct problems; in this study, controls for both genetic influences and parent psychopathology accounted for the initial association in its entirety (Maughan et al., 2004). Familial risk for externalizing problems has also been found to interact with maternal smoking in pregnancy in the prediction of inattentive behaviors in offspring, with positive associations between high levels of maternal prenatal smoking and child inattention only being evident in cases of concomitant familial risk (Buschgens et al., 2009).

A novel design strategy has recently been used to evaluate outcomes for siblings discordant for maternal prenatal smoking (D’Onofrio et al., 2010; Lindblad & Hjern, 2010). Results from studies using this design suggest that familial background factors, rather than environmental exposure effects, explain associations between maternal prenatal smoking and externalizing problems. However, as acknowledged by their authors, these sibling discordant design studies did not test for gene by environment interactions, leaving open the possibility that prenatal exposure to maternal smoking may result in externalizing behavior outcomes for offspring at particular genetic risk. For example, Kahn and colleagues (2003) noted an interaction between a DAT1 genotype and maternal prenatal smoking in the prediction of oppositional and hyperactive symptoms in young children. This finding was replicated in an adolescent sample, however the G × E effect was specific to hyperactive-impulsive symptoms in males (Becker et al., 2008). Other studies have failed to replicate this effect for DAT1 and other dopamine related genotypes (e.g., Brookes et al., 2006; Langley et al., 2008). Overall, findings in the literature to date suggest that tests of gene-by-environment (G × E) interactions may be a fruitful avenue to pursue in terms of the offspring behavioral risks associated with maternal prenatal smoking.

**Catechol O-methyltransferase (COMT)** is a key modulator of extracellular dopamine levels in the prefrontal cortex. A common G/A polymorphism produces a valine-to-methionine amino acid substitution at codons 108 and 158 (Val108/158Met; rs4680), which results in a 3- to 4-fold variation in COMT activity whereby the Val and Met alleles confer high and
low activity, respectively (Lachman et al., 1996). The Met allozyme results in a substantially decreased immunoreactive protein (Shield, Thomae, Eckloff, Wieben & Weinshilboum, 2004). This well-characterized, functional polymorphism has been associated with atypical neural processing and connectivity in healthy individuals (Dennis et al., 2010), deficits in executive functioning abilities (Tunbridge et al., 2006), and with aggression and serious antisocial behavior in individuals with ADHD (Caspi et al., 2008).

Prenatal exposure to nicotine also leads to persistent abnormalities in neurotransmitter functioning in the cerebrocortical areas of the rat brain (Slotkin et al., 2007). Furthermore, both maternal prenatal smoking and COMT associations with conduct disorder appear to be specific to aggressive behavior, rather than covert antisocial behavior (Monuteaux et al., 2006, 2009). Taken together, these findings suggest that the combination of the Val/Val genotype and prenatal exposure to maternal smoking may lead to neural processing deficits that increase vulnerability for aggression and ADHD in adolescence and adulthood.

One previous study examining the interaction of prenatal risk and COMT variation in the prediction of externalizing problems found that birth weight interacted with Val108/158Met to predict antisocial behavior in an ADHD sample (Thapar et al., 2005); however, this finding has had at least one failure to replicate (Sengupta et al., 2006). Although Thapar and colleagues (2005) stated that Val108/158Met did not interact with maternal prenatal smoking to predict antisocial behavior in their sample, specific methodological details (e.g., how maternal smoking was measured) are unclear. Moreover, their examination was focused on the prediction of antisocial behavior in individuals with ADHD, rather than the population as a whole. Further, no study that we are aware of has examined the interaction between the Val108/158Met genotypes and maternal smoking during pregnancy to predict ADHD related outcomes.

The goal of the current study is to test for associations or interactions between Val108/158Met genotypes and maternal prenatal smoking in the prediction of both aggressive and attentional behavior problems in adolescence and young adulthood. Specifically, we predict that offspring who were exposed to maternal cigarette smoking during pregnancy, and who carry the Val/Val genotype will be at increased risk for evidencing externalizing behavior problems. We further predict that these findings will persist from adolescence to adulthood, and that they will not be explained by the potential confound of offspring birth weight.

Methods

Participants

Participants in this study consisted of women and their young adult offspring selected from a prospective birth cohort study of children (N=7,223) born between 1981 and 1984 at the Mater Misericordiae Mother’s Hospital in Brisbane, Australia (Keeping, Najman, Morrison, Western, Andersen & Williams, 1989). The birth cohort was predominantly Caucasian and of lower middle and working class socioeconomic status (SES). The Mater-University of Queensland Study of Pregnancy (MUSP) was originally devised to investigate the children’s physical, cognitive, and psychological health as a function of pregnancy, obstetric and psychosocial conditions as well as to predict health, development, and behavior at age 5.

Participants were selected from the larger birth cohort based on continued residency in the Brisbane area and on women’s self-reports of depression on the Delusions-Symptoms-States Inventory (DSSI; Bedford & Foulds, 1978) obtained at 4 times prior to child’s age 5 including pregnancy. Details are provided in Hammen and Brennan (2001, 2003). Families were selected to include a range of chronicity and severity of maternal depression, later
confirmed by diagnostic interviews of lifetime depression on the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995). Of the 815 mothers recruited 458 reported no lifetime history of depression, and 357 reported a lifetime history of major depression or dysthymic disorder. The sample studied at youth age 15 was 92% Caucasian and 8% minority (Asian, Pacific Islander, and Aboriginal), and largely lower middle class in family income, making it demographically representative of the original birth cohort.

Of the original 815 subjects studied at age 15, 747 of them also participated in a follow up focused on young adult behavioral outcomes collected at youth ages 20–21. In addition, 777 were eligible for inclusion in a genetic study conducted when they were between 22 and 25 years of age (others had withdrawn from further follow-ups, were deceased or had major medical problems). Five hundred and twelve of the 777 participants were located and provided blood samples for genotyping (227 males, 285 females). The others could not be located (n = 63), were unavailable (e.g., lived abroad: n = 29), or refused actively or passively (e.g., agreed but did not complete procedures; n = 173).

The youth and their mothers were included in the current study if the mother provided a prospective report of smoking during pregnancy, if the family participated in the age 15 follow up, if either the mother or the youth provided reports of youth externalizing problems at age 20–21, and if the youth Val108/158Met polymorphism was successfully genotyped at youth ages 22–25. These inclusion criteria resulted in a sample of 470 youth. In comparison to the community birth cohort from which they were originally drawn, the youth included in this study were more likely to be female (57% vs. 47%; \( \chi^2(1, 7223) =17.98, p < .001 \)). They did not differ from the original birth cohort in terms of Caucasian ethnicity (92% vs. 89%; \( \chi^2(1, 7223) = 2.56, p = .11 \)), mother age at delivery \((t(1,7221)=1.75, p=.08)\) or mother education level \((t(1,7164)=1.55, p=.11)\).

**Procedures**

Mothers completed a questionnaire during pregnancy, and the youth and their mothers completed interviews and questionnaires separately and privately in their homes when the youth turned 15. Subsequently, youth and/or their peers and mothers completed questionnaires about the youth when he or she was 20–21 years of age, and as noted above, the youth were recontacted for the DNA collection in 2006 when they were between the ages of 22–25. Participants gave informed consent for each procedure, and protocols were approved by the institutional review boards of the University of Queensland, Queensland Institute for Medical Research, UCLA, and Emory University.

**Measures**

**Maternal smoking during pregnancy**—In a questionnaire completed during their first prenatal clinic visit (occurring at pregnancy week: \( M=18.14, SD=5.85 \)) women were asked if they smoked cigarettes in the past week, and if so, how many they had smoked. For the purposes of this study, maternal smoking was coded as a categorical (yes/no) variable, and 164 mothers (35%) in the sample reported that they were smoking during pregnancy at the first clinic visit. It is important to note that retrospective reports after birth indicated that 96 percent of these women continued to smoke through their third trimester.

**Youth attentional and aggressive behavior problems**—At the age 15 follow up, mothers completed the Achenbach Child Behavior Checklist (CBCL), teachers completed the Achenbach Teacher Report Form (TRF), and youth completed the Achenbach Youth Self Report (YSR) measures (Achenbach, 1991). At the age 20–21 follow up, mothers and peers completed the Adult Behavior Checklist (ABCL) and youth completed the Adult Self
Report (ASR; Achenbach & Rescorla, 2003). Raw scores on Attention Problem and Aggressive Behavior scales were used in this study. Means and standard deviations of Achenbach scale scores are presented in Table 1. Data from youth, mother, and teacher reports were combined to form latent variables of Aggressive Behavior and Attention Problems at age 15. Missing data from each reporter at age 15 was as follows: youth 0.4%; mother 1.9%; and teacher 21.5%. Similarly, data from youth, mother and peer reports were combined to form latent variables of Aggressive Behavior and Attention Problems at age 20–21. Missing data from ages 20–21 was as follows: youth 3.8%; mother 4.9%; and peer 28.3%.

Genotyping—Participants who agreed to the blood collection follow up were mailed consent forms, a blood collection pack, and questionnaires, and were instructed to have the blood drawn at a local pathology lab. The blood samples were picked up by courier from the individual and transported to the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research, where the DNA was extracted and genotyped. The assay for the \( \text{COMT} \) Val108/158Met (rs4680) polymorphism was designed using MassARRAY Assay Design software (version 3.0; Sequenom Inc., San Diego, CA) and typed using iPLEX chemistry on a Compact MALDI-TOF Mass Spectrometer (Sequenom). Forward and reverse PCR primers and a primer extension probes were purchased from Bioneer Corporation (Daejeon, Korea). Genotyping was carried out in standard 384-well plates with 12.5 ng genomic DNA used per sample. A modified Sequenom protocol was followed, using half reaction volumes in each of the PCR, SAP and iPLEX stages giving a total reaction volume of 5.5 \( \mu \)L. The iPLEX reaction products were desalted by diluting samples with 18 \( \mu \)L of water and 3 \( \mu \)L SpectroCLEAN resin (Sequenom) and then were applied to a SpectroChip (Sequenom), processed and analyzed on a Compact MALDI-TOF Mass Spectrometer by MassARRAY Workstation software (version 3.3) (Sequenom). Allele calls for 384-well plates were reviewed using the cluster tool in the SpectroTYPER software (version 3.3; Sequenom) to evaluate assay quality. The genotype frequencies for Val108/158Met were consistent with Hardy-Weinberg Equilibrium (HWE) using Chi-square tests. Observed allele frequencies were as follows: Val/Val - 24.0%, Val/Met - 51.1%, and Met/Met - 24.9%.

Of the 512 available DNA samples, genotyping was completed on 480. Participants whose samples were successfully genotyped vs. not genotyped did not differ in terms of gender, maternal prenatal smoking, or youth attentional or aggressive outcomes. Preliminary analyses of the Val108/158Met genotype and youth ethnicity revealed statistically significant differences in the distribution of alleles in Caucasians versus other ethnic groups \( (\chi^2(N=470)=7.21, p=0.03) \). All reported analyses were therefore restricted to the Caucasian youth in the sample \( (N=430) \). The allele frequencies remained consistent with HWE in the Caucasian only subsample (Val/Val – 22.8%, Val/Met – 50.9%, and Met/Met – 26.3%).

Offspring birthweight—Birthweight was recorded (in grams) by obstetrical staff at the Mater hospital, shortly after birth. In this sample, the children of mothers who smoked during pregnancy had lower birthweights \( (M=3379 \text{ grams}) \) than the children of mothers who did not \( (M=3379 \text{ grams}; t(1,428)=1.96, p=0.05) \). Gestational age at birth did not differ on the basis of maternal prenatal smoking \( (\text{smoking } M=39.28 \text{ weeks, nonsmoking } M=39.43 \text{ weeks}; t(1,428)=0.91, p=0.37.) \) Birthweight was statistically controlled in all analyses given its association with prenatal smoking and the previously reported \( \text{COMT} \times \) birthweight interaction predicting to antisocial behavior (Thapar et al, 2005).

Maternal depression—Maternal depressive diagnoses in the current study were based on the Structured Clinical Interview for \( \text{DSM-IV} \) (First et al., 1995) administered when the child was 15 and 20 years of age. The presence of lifetime and current diagnoses were ascertained...
blind to the woman’s previous scores on the DSSI. Ratings by independent judges yielded weighted Kappa values of 0.87 for current diagnoses of major depressive episode, dysthymic disorder, and subsyndromal depression and Kappa values of 0.84 for past depressive diagnoses or symptoms. In the current study maternal depression was operationalized as lifetime major depression or dysthymia reported on the SCID. A total of 211 women (45%) were classified as depressed at youth age 15 and 267 women (57%) were classified as depressed at youth age 20 according to these criteria. Because the current study was based on a high-risk subsample of the original birth cohort, maternal depression diagnoses were statistically controlled in all analyses.

Data Analysis Strategy

Structural equation modeling was used to test whether the interaction of maternal smoking during pregnancy and the Val108/158Met genotype (coded additively as 1=Met/Met, 2=Val/Met and 3=Val/Val) predicted to the dependent variables of offspring aggressive behavior and attention problems at ages 15 and 20. Gender, maternal depression and birthweight were included in all models as controls. Maternal smoking and Val108/158Met genotype variables were centered to reduce multicollinearity with the interaction term. In cases where hypothesized interaction terms were significant, estimated means of externalizing symptom counts were calculated across maternal smoking and allele groups, and plotted to interpret the exact nature of the interaction.

Structural equation modeling allows hypothesis testing at the construct level. Multiple measured variables derive the constructs, referred to as latent variables, minimizing the error associated with any one measurement by extracting the shared variance among the measured variables. Moreover, multiple reporting sources (e.g. assessment of aggressive behavior problems from the individual as well peer and parent informants) can comprise latent variables, hence minimizing the error associated with single reporter biases. The present study derived constructs from multiple reporters where possible.

The AMOS 17.0 program (Arbuckle, 2008) tested the structural equation models. Full information maximum likelihood estimation was used. We reported three fit statistics for each model: the $\chi^2$ index, the comparative-based fit index (CFI), and the root-mean-square error of approximation (RMSEA; Brown & Cudeck, 1993). The $\chi^2$ index compares how closely the path coefficients in the sample model compare with what would be expected in the population. Nonsignificant $\chi^2$ values are indicative of a good fitting model.

We also reported the CFI, an incremental index, and RMSEA (and 90 percent confidence intervals), a population-based fit index, because trivial discrepancies between the model-reproduced and sample covariance matrices may produce significant $\chi^2$ values. The CFI compares the sample model with the independence model yielding values ranging from 0 to 1. Values of 0.90 or greater indicate an acceptable model fit (Hu & Bentler, 1999). RMSEA tests the lack of fit between the sample model and the estimated population model covariance matrix (Kline, 2005). RMSEA values range from 0 to 1, with values less than .06 indicating an acceptable model fit (Hu & Bentler, 1999).

Results

Preliminary Analyses

Prior to testing the interaction models, we examined whether maternal smoking during pregnancy or Val108/158Met genotype predicted youth externalizing problems in the structural models when isolated. Results indicated that maternal smoking during pregnancy predicted aggressive behavior at ages 15 and 20 years ($\beta = .16, p < .01$ and $\beta = .11, p < .05$, respectively), whereas the Val108/158Met did not predict aggressive behavior at ages 15 or
20 (β = .07 and .04, respectively). Neither maternal smoking during pregnancy (age 15: β = .08; age 20: β = .03) nor the Val108/158Met (age 15: β = .05; age 20: β = .05) predicted attention problems in this sample. Maternal prenatal smoking was also unrelated to COMT allele variants in this sample (χ²(N=430)=.01, p=.99.

Maternal Prenatal Smoking and Val108/158Met Interactions

**Aggressive Behavior**—As predicted, maternal smoking during pregnancy and the Val108/158Met genotype interacted to predict increased aggressive behaviors at ages 15 and 20 (see Figures 1 and 2, respectively). The structural models predicting aggression at both ages 15 and 20 fit well (age 15: χ²(df = 25)=21.24, p=.68, CFI=1.00, RMSEA(90% CI)= .00(.00–.03); age 20: χ²(df =25)=18.86, p=.80, CFI=1.00, RMSEA= .00 (.00–.03)). Standardized beta weights are indicated on the paths in the diagrams. In addition to the G × E interaction (p<.05), both mother depression (p<.01), and gender (p<.05) significantly predicted aggressive behavior at age 15 in the structural model (Figure 1). In addition to the G × E interaction (p<.05), mother depression (p<.01) significantly predicted age 20 aggressive behavior (Figure 2).

In order to interpret the G × E interactions for aggressive behavior at ages 15 and 20, we plotted standardized aggression scores by maternal smoking and COMT genotypes (see Figure 3). Individuals with the Val/Val genotype and whose mothers smoked during pregnancy had the highest rates of aggressive behaviors.

**Attention Problems**—The interaction between the Val108/158Met genotype and maternal smoking during pregnancy was not predictive of attention problems at ages 15 or 20. The structural model for age 15 attention problems did not demonstrate adequate fit according to two of our three fit indices (χ²(df = 25)=39.35, p=.03, CFI=.88, RMSEA(90% CI)= .04(.01-.06). Poor model fit suggests that variables other than those included in our model are necessary for the adequate prediction of age 15 attention problems in this sample. In addition, whereas the three fit indices for the age 20 attention problems structural model indicated good fit (χ²(df =25)=21.64, p=.66, CFI=1.00, RMSEA=.00 (.00-.03)), the G × E interaction term was not a significant predictor in this model (p =.24). Instead, as can be seen in Figure 4, maternal depression (p<.01) and gender (p<.01) were the only significant predictors of age 20 attention problems in this sample.

**Discussion**

We found that individuals with the COMT Val/Val genotype whose mothers smoked during pregnancy were at an increased risk for aggressive behavior outcomes in adolescence and young adulthood. Because this is the first study to report these particular G × E associations, replication will be necessary before these findings may be informative for treatment or policy decisions.

In this sample, maternal smoking during pregnancy did not predict offspring attention problems, either on its own, or in interaction with the Val108/158Met polymorphism. Although there have been numerous studies linking maternal smoking during pregnancy to ADHD in children (e.g., Linnet, 2005; Milberger et al., 1996), a recent study found that maternal prenatal smoking was more strongly associated with hyperactive impulsive symptoms, than with inattention (Langley et al., 2007). Our behavioral measures did not allow us to tease apart these dimensions of ADHD, and therefore may be masking associations that would be apparent with a more specific focus on hyperactivity and impulsivity.
Our findings for aggressive behavior outcomes were significant when controlling for birthweight, and birthweight was not found to interact with the Val108/158Met polymorphism to predict externalizing behavior in this sample (data not shown). Although a previous study found that COMT variants interacted with birth weight to predict antisocial outcomes (Thapar et al., 2005), a second study failed to replicate this result (Sengupta et al., 2006). Our findings suggest that maternal smoking during pregnancy might be an alternative perinatal risk factor to assess in future externalizing behavior G × E studies focused on this gene. The authors’ previous study indicated that their data did not suggest evidence for an interaction between maternal smoking during pregnancy and COMT variants in the prediction of antisocial behavior (Thapar et al., 2005). However, they did not provide details concerning their maternal smoking measure and how it was assessed. Our study, like most in the field, relied upon maternal self-report of smoking. Future studies using biological confirmation may provide more accurate, quantitative data concerning the true levels of nicotine that the fetus was exposed to during pregnancy. Nevertheless, one notable strength of our data is that our maternal smoking measure was prospectively obtained during pregnancy, and was not a retrospective report obtained during later offspring development. Retrospective measures of maternal smoking during pregnancy and perinatal factors in general may be compromised by recall bias that is correlated with the level of behavior problems evident in the child at the time of the report.

Another strength of this study is that we used multi-informant reports for behavioral outcomes. Our measures of aggressive behavior and attention problems were obtained from multiple informants (mother, youth, and teacher at age 15; mother, youth, and peer at age 20) and our analyses capitalized on the strength of latent variable modeling to estimate a “true” score on these outcomes. Therefore, our study is not susceptible to problems of shared method variance that result from single informant designs.

Recent sibling control studies suggest that exposure to maternal prenatal smoking does not have direct environmental effects on externalizing behavior outcomes (D’Onofrio et al., 2010; Lindblad & Hjern, 2010). The results of the current study suggest that environmental effects of maternal smoking may impact aggressive outcomes for only those offspring with a particular genetic profile. In support of this interpretation, post-hoc analyses (data not shown) revealed that the interaction of maternal smoking prior to (but not during) pregnancy and the Val108/158Met polymorphism was not significant in predicting offspring aggressive outcomes. However, another possible interpretation of these findings is that familial background factors reflected by our measure of maternal prenatal smoking exposure (rather than the smoking exposure itself) interact with COMT genotypes to produce aggressive outcomes. Sibling discordant designs that incorporate the assessment of particular genotypes are necessary to test the direct environmental impact of maternal smoking in a G × E design.

Our study utilized a sample at high risk for maternal depression, and maternal depression significantly predicted all of the behavioral outcomes in this study. Our analyses controlled for maternal depression and our G × E findings were significant, after accounting for the potential influence of this factor. Nevertheless, until these findings are replicated, we cannot be sure that they will generalize to low risk populations of youth.

The COMT Val108/158Met polymorphism has been found to predict prefrontal cortex functioning, with the Met allele associated with more efficient processing, better working memory, and stronger behavioral inhibition (Diamond, 2007). Animal studies have also linked prenatal nicotine exposure to cognitive impairments and abnormal cell proliferation in the cortex (Ernst et al., 2001). Against the backdrop of these other research findings, our study suggests that the combination of neurological deficits from COMT risk alleles and
exposure to maternal smoking during pregnancy may be particularly potent in conferring risk for aggression in adolescence and young adulthood.

**Conclusion**

This study provides preliminary evidence that maternal prenatal smoking interacts with the Val/Val COMT risk allele to increase the risk of aggressive behaviors.

**Acknowledgments**

This study was supported by funds from the National Health and Medical Research Council in Australia, the Mater Misericordiae Mother’s Hospital in Queensland, Australia, and NIH grant R01 MH52239. The authors greatly appreciate the assistance of Robyne LeBrocque, Cheri Dalton Comber, and Sascha Hardwicke (project coordinators) and their staff, and Megan Campbell and Dixie Statham of the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research who coordinated genetic data collection and analysis. Thanks also to original MUSP Principal Investigators Margaret Andersen, Michael O’Callaghan and Gail Williams.

**References**


Diamond A. Consequences of variations in genes that affect dopamine in prefrontal cortex. Cerebral Cortex. 2007; 17(Suppl 1):i61–70. [PubMed: 17725999]


*Biol Psychol.* Author manuscript; available in PMC 2012 April 1.


Biol Psychol. Author manuscript; available in PMC 2012 April 1.


Slotkin TA, MacKillop EA, Rudder CL, Ryde IT, Tate CA, Seidler FJ. Permanent, sex-selective effects of prenatal or adolescent nicotine exposure, separately or sequentially, in rat brain regions: Indices of cholinergic and serotonergic synaptic function, cell signaling, and neural cell number and size at 6 months of age. Neuropsychopharmacology. 2007; 32:1082–1097. [PubMed: 17047666]


Figure 1.
Association between maternal smoking during pregnancy and age 15 aggressive behavior as a function of the Val108/158Met polymorphism.
Figure 2.
Association between maternal smoking during pregnancy and age 20 aggressive behavior as a function of the Val108/158Met polymorphism.
Figure 3.
COMT genotype, maternal prenatal smoking history and aggressive behavior outcomes.
Figure 4.
Structural Equation Model predicting age 20 attention problems.

Numbers on paths indicate standardized beta weights.
Table 1

Means and Standard Deviations for Youth Achenbach Measures

<table>
<thead>
<tr>
<th>Age and Reporter</th>
<th>Aggressive Behavior</th>
<th>Attention Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>(SD)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 15 Youth</td>
<td>8.69</td>
<td>(5.67)</td>
</tr>
<tr>
<td>Age 15 Mother</td>
<td>6.39</td>
<td>(6.44)</td>
</tr>
<tr>
<td>Age 15 Teacher</td>
<td>5.47</td>
<td>(8.61)</td>
</tr>
<tr>
<td>Age 20 Youth</td>
<td>3.02</td>
<td>(3.26)</td>
</tr>
<tr>
<td>Age 20 Mother</td>
<td>5.18</td>
<td>(5.86)</td>
</tr>
<tr>
<td>Age 20 Peer</td>
<td>6.31</td>
<td>(6.17)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 15 Youth</td>
<td>9.21</td>
<td>(5.33)</td>
</tr>
<tr>
<td>Age 15 Mother</td>
<td>5.30</td>
<td>(5.44)</td>
</tr>
<tr>
<td>Age 15 Teacher</td>
<td>3.47</td>
<td>(6.70)</td>
</tr>
<tr>
<td>Age 20 Youth</td>
<td>3.53</td>
<td>(3.37)</td>
</tr>
<tr>
<td>Age 20 Mother</td>
<td>4.97</td>
<td>(5.41)</td>
</tr>
<tr>
<td>Age 20 Peer</td>
<td>6.11</td>
<td>(5.47)</td>
</tr>
</tbody>
</table>