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The Relationship between Risk-Taking Propensity and the COMT Val^{158}Met Polymorphism Among Early Adolescents as a Function of Sex

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Abstract

Although adolescents frequently engage in a variety of risky behaviors, much remains unknown about the specific etiologies of such tendencies. Candidate genetic variants, such as the *COMT* Val^{158}Met polymorphism, may be related to risk-taking propensity, particularly as this variant is linked to functional enzymatic differences influencing dopamine function in regions including the prefrontal cortex. The present study aimed to examine the *COMT* Val^{158}Met variant in relation to risk taking propensity in a community sample of youth. As part of a larger longitudinal study on adolescent risk behaviors, 223 youths (average age 11.3 years) from the metropolitan Washington D.C. area completed a measure of risk-taking propensity, the Balloon Analogue Risk Task-Youth Version (BART-Y), and provided saliva samples for DNA extraction and genotyping. Results indicate that females, but not males, who are carriers of the *COMT*^{158}Met allele had higher risk-taking propensity scores on the BART-Y compared to Val homozygotes. Analyses were also conducted in the 111 European American participants, and results were consistent with those of the full sample analyses. This study represents the first investigation of a genetic substrate of risk-taking propensity, measured by a behavioral task, in youth. Results should be taken as quite preliminary, given the small sample. Implications are discussed.

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Keywords

Risk taking; BART; *COMT* Val^{158}Met; Dopamine; Adolescents

Adolescence is marked by dramatic increases in risk-taking behaviors including substance use, unprotected sex, and delinquency (Eaton et al., 2010; Johnston, O'Malley, Bachman, & Schulenberg, 2011), which are of particular public health importance given their association with a variety of negative outcomes (McGue & Iacono, 2005; Resnick, Acierno, & Kilpatrick, 1997). Most examinations of risk-taking have used self-report measures, but recent work has begun to use laboratory-based behavioral measures such as the Balloon Analogue Risk Task (BART; Lejuez et al., 2002). Risk taking propensity as assessed by the BART has been shown to be a useful analogue, with risk-taking on the task consistently associated with self-reported real-life risk behaviors, such as alcohol and other substance use, sexual risk behavior, and delinquent behaviors (Lejuez et al., 2007; Lejuez et al., 2002; MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010a; MacPherson et al., 2010b). Although findings are mixed, modest correlations between BART performance and self-report measures of impulsivity and sensation-seeking have been reported (Lejuez et al., 2007; Lejuez et al., 2002) suggesting it captures a related but likely distinct appetitive trait.

Although these findings indicate promising practical applications of the BART, our theoretical models of the mechanisms underlying risk-taking on the task have been unstudied. As one promising direction, understanding risk-taking propensity on the BART as an intermediary phenotype (i.e., biological or psychological constructs that mediate the relationship between genetic underpinnings and expressed syndromes) may help clarify the mechanisms through which genetic and environmental influences confer risk for disorders characterized by high levels of risk-taking (e.g., substance use disorders, pathological gambling). Twin studies reveal self-reported risk-taking and sensation-seeking behaviors to be moderately heritable (Miles et al., 2001), although heritability estimates for the BART-Y have been found to differ by sex and possibly age. For example, a recent study of 12-year-old adolescent twins revealed performance on the BART to be genetically influenced (heritability estimates for males was .28 [95% CI .14-.42], and for females was .17 [95% CI .02-.34], with the same set of genes seemingly conferring risk in both sexes. In this same cohort, when the youth were 14 years-old, BART performance was only heritable among males (.55 95% CI .34-.70), suggesting that changes in biologic factors (e.g., hormonal changes related to the male/female divergence) or in non-shared environmental factors (e.g., non-shared social connections) may differ by sex at certain ages in early adolescence (Anokhin, Golosheykin, Grant, & Heath, 2009). This study extends the literature and suggests that genes may play a role in BART performance in a sex specific fashion; however, it should be noted that the sample size in Anokhin et al.'s study was modest, resulting in large confidence intervals.

Numerous candidates may be related to risk-taking propensity. For example, *COMT* codes for an enzyme that regulates dopamine (DA) levels (Karoum, Chrapusta, & Egan, 1994), a neurotransmitter associated with risk-taking (Kreek, Nielsen, RButelman, & LaForge, 2005). DA is also thought to be related to behavior and neurocognitive functions, such as working memory and decision making. Theory and data supports an inverted U-shape response curve for DA's effects in adults, with low or high levels being maladaptive (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007), implicating the need to investigate polymorphisms affecting DA. A commonly studied polymorphism affecting DA is referred to as the *COMT* Val^{158}Met (rs4680) polymorphism, which influences DA availability in the prefrontal cortex (Männistö & Kaakkola, 1999). The Val allele has higher activity (and therefore increased metabolism of DA) than the Met allele, and following,

research in adult populations supports that Met/Met carriers are at the apex of the hypothetical inverted U and Val carriers are at the lower end (Giakoumaki, Roussos, & Bitsios, 2008). Stein and colleagues (2006) have proposed that the Val allele can be thought of as related to "warrior" tendencies, whereas the Met allele is more closely related to "worrier" tendencies. Indeed, the Met allele has been broadly associated with anxiety-related phenotypes (e.g., Domschke et al., 2004; Enoch, Xu, Ferro, Harris, & Goldman, 2003; McGrath et al., 2004; Olsson et al., 2005; Olsson et al., 2007; Pooley, Fineberg, & Harrison, 2007; Woo et al., 2004), whereas the Val allele has been associated with greater flexibility in processing emotional stimuli compared to the Met allele (Drabant et al., 2006). With regard to substance use and abuse, an important category of risk-taking behaviors, both the low activity Met/Met genotype (e. g., Tiihonen et al., 1999; Wang et al., 2001), and the high activity Val/Val genotype (Enoch, Waheed, Harris, Albaugh, & Goldman, 2006; Vandenbergh, Rodriguez, Miller, Uhl, & Lachman, 1997) have been associated with addiction vulnerability.

Two important considerations should be made when interpreting the literature on *COMT* and risk behaviors as it pertains to youth. First, sex differences in motivation to engage in risk taking behaviors may be necessary in interpreting these seemingly discrepant findings, as females may engage in addictive or risk behaviors to escape negative emotional states more so than males (Blanco, Hasin, Petry, Sinson, & Grant, 2006). Specific to adolescence, emerging literature also suggests that negative affect pathways to risky behaviors, such as substance use, may be especially relevant for girls (e.g., Dakof, 2000; Measelle, Stice, & Springer, 2006; Schinke, Fan, & Cole, 2008). These discrepant findings might also relate to sex dimorphic properties of *COMT* (see Harrison & Tunbridge, 2008 for a review), as well as potential gene-by-age interaction effects (Dumontheil et al., 2011), suggesting that COMT effects may not be static, although more research is necessary to understand the relationship in youth. Second, developmental studies suggest that differential effects of *COMT* Val^{158}Met alleles may be found between youth and adults. Specifically, a recent study found that the Met allele effect for greater working memory was not found until youth reached 10 years of age (Dumontheil et al., 2011).

The current study sought to examine a possible association between *COMT* Val^{158}Met and risk-taking propensity. Based on the relationship between *COMT*, DA availability, and specific risk behaviors, it was expected that *COMT* variation would be related to BART performance measures with the Val allele associated with higher risk taking propensity. Based on past findings demonstrating differential relationships by sex, the current study included sex as a potential moderator, with the hypothesis that allelic variants associated with anxiety-related phenotypes (e.g., *COMT* Met) would be associated with risk-taking in girls as compared with boys.

Methods

Subjects

This study employed data from the first wave of data collection of a community sample of early adolescents (n = 277) ages 9 to 13 years at initial enrollment participating in a larger prospective study of behavioral, environmental, and genetic mechanisms of risk for HIV-related risk behaviors in youth. As part of this larger longitudinal study on adolescent risk behaviors, 223 children (44.4% female, mean age 11.3 years) and their parents/guardians attended laboratory sessions, during which they completed self-report measures, completed one session of the BART-Y (in which participants inflate 30 computerized balloons to earn prizes; see below for full description), and provided salivary samples. The 223 participants in this subsample of the larger study were chosen as they had complete data for all relevant variables in this study. The sample was racially and ethnically diverse by self-report: (50%

European American, 34.2% African-American, 2.7% Latino, and 13.1% other, including mixed ethnicity), as would be expected in the metropolitan Washington, D.C. area. However, as described below, we analyzed our data as self-reported European American non-Hispanic (EA, n=111) vs. non-EA (n=112), and follow-up analyses were conducted in the subsample of 111 EA participants. Permission to conduct research was obtained from the Institutional Review Boards of the participating institutions (University of Maryland for subject evaluations, Yale University for genetic analyses). At the start of the session, a detailed description of the study procedures was provided and the parent/guardian consented to his or her child's participation. Further, assent was obtained from the youth who participated in the study.

Measures

Demographics—The parents/guardians provided basic demographic information (age, gender, racial/ethnic status) about themselves and their child.

DNA Samples—Saliva samples were collected using the Oragene protocol. Samples were mailed to Yale University for DNA isolation and analyses. A fluorogenic 5' nuclease assay method ("TaqMan"), using the ABI PRISM 7900 Sequence Detection System (ABI, Foster City, CA, USA), was used to detect the *COMT* $Val^{158}Met$ SNP. All SNPs were assayed in duplicate and genotypes that were found to be discordant were discarded.

Balloon Analogue Risk Task - Youth Version (BART-Y)—The BART-Y is a reliable and valid indicator of risk-taking propensity among racially/ethnically diverse youth; see the following citations for a complete task description and relevant psychometric data (Lejuez et al., 2007; MacPherson et al., 2010a) that was developed from the original BART (Lejuez et al., 2002). During the BART-Y, participants inflate computerized balloon representations to earn prizes; the more a participant inflates a given balloon, the more points he or she is able to earn which determines the size of the final prize (small, medium, large, bonus). However, if the balloon explodes, the participant loses all earnings accrued for a particular balloon, mirroring the potential for loss that occurs in real-world situations when individuals engage in risky behaviors. The BART-Y measure correlating with a general propensity to engage in risk behaviors is the adjusted average pumps, calculated as the average number of times a given youth pumps the balloons that do not explode. This adjusted value is preferable to the unadjusted average because the number of pumps is necessarily constrained on balloons that explode, thereby limiting between-participant variability in the unadjusted averages (cf. Lejuez et al., 2002).

Statistical Analyses

First, descriptive statistics were conducted to examine the distributional properties of the adjusted average number of balloon pumps (i.e., BART performance). Second, *t*-tests were conducted to determine if the average number of pumps differed by sex (male vs. female) and by racial ethnic status (categorized by EA vs. non-EA). Next, descriptive statistics were conducted to examine genotype frequency in the full sample and in the EA vs. non-EA subsamples, as well as to examine the Hardy Weinberg Equilibrium assumption. The correlation between the number of adjusted average balloon pumps and the COMT $Val^{158}Met$ polymorphism (coded in an additive fashion as 0= Met/Met, 1=Val/Met, 2=Val/Val) was conducted. Adjusted average number of pumps was examined by genotype in girls and boys. Next, a linear regression was conducted to determine if the observed association between the polymorphism and BART performance remained significant after adjustment for covariates (age, EA vs. non-EA, sex), and as estrogen down-regulates *COMT*, the linear regression also tested for sex-moderation. Sex-stratified analyses were then conducted (i.e., two separate regression models, one for girls and one for boys, both adjusting for age [5

levels, ages 9-13], and EA vs. non-EA status). We also ran all regression analyses in the subset of European American (EA) youth (n=111).

Results

For the genetic analyses, racial/ethnic status was analyzed as EA vs. non-EA. The adjusted average number of balloon pumps was 30.46 (S.D.=13.09, range = 2-70) and this variable had acceptable skewness and kurtosis. The adjusted average number of pumps did not differ by sex ($t(221)=-.99$, $p=.32$); however, EA participants had a higher mean score compared to non-EA participants ($t(221)=-2.17$, $p<.05$; *M*s=32.35, 28.58, *S.D.*s=1.22, 1.24, respectively).

In the full sample, the genotype frequency was: 19.3% Met/Met, 46.2% Val/Met, and 34.5% Val/Val. Genotype frequency in EAs was: 27.0% Met/Met, 45.0% Val/Met, and 28.0% Val/Val; among non-EAs genotype frequency was: 11.6% Met/Met, 47.3% Val/Met, and 41.1% Val/Val. Genotype frequencies in the full sample, and by racial/ethnic status, were in Hardy-Weinberg equilibrium; however, genotype frequency did differ between EA and non-EAs ($\chi^2[2, n = 223] = 9.73$, $p<.01$) and therefore correction based on self-reported racial/ethnic status (EA versus non-EA) was used to ensure that population stratification did not result in false positive findings. Even so, considering the non-homogeneous nature of the non-EA sample, results from that part of the sample should be considered with caution.

The polymorphism (coded as 0= Met/Met, 1=Val/Met, 2= Val/Val) was significantly correlated with BART performance ($r=-.18$, $p<.01$), with the Met allele being associated with higher risk-taking propensity. Among Met/Met carriers the adjusted average number of balloon pumps was 40.6 (*S.D.*=12.62) for girls, and 32.79 (*S.D.*=14.23) for boys. Among Val/Met carriers the adjusted average number of balloon pumps was 28.85 (*S.D.*=11.59) for girls, and 30.55 (*S.D.*=14.00) for boys. Among Val/Val carriers the adjusted average number of balloon pumps was 26.09 (*S.D.*=11.27) for girls, and 31.17 (*S.D.*=12.49) for boys.

The linear regression model examining demographic factors (i.e., age, sex, EA vs. non-EA), the *COMT* Val^{158}Met polymorphism, and the interaction between sex and the *COMT* polymorphism was significant ($F(5, 217) = 4.89$, $p < .01$; $R^2=.09$; see Table 1). The Met allele was associated with higher risk-taking propensity, and this relationship was moderated by sex of the participant. When stratifying by sex, the relation between this polymorphism and risk-taking propensity holds for girls ($F(3, 95) = 8.58$, $p < .001$; $R^2=.21$), but not for boys ($F(3, 120)= .84$, $p = .47$; $R^2=.02$), suggesting the finding in the full sample is primarily driven by the girls. Results of sex-stratified analyses are presented in Table 2.

Given the non-homogeneous nature of the non-EA subsample, the regression analyses were conducted again in the subsample of EA participants (n=111). As shown in Table 3, the direction of the signal was the same as the full sample results, with the Met allele being significantly associated with higher risk-taking propensity; notably, the interaction did not meet statistical significance, perhaps due to limited power. The sex-stratified analyses, shown in Table 4, also are consistent with those found in the full sample in that the Met allele was statistically significantly associated with BART performance in girls, but not boys.

Discussion

Using a behavioral task, the BART-Y, to assess risk-taking propensity as a potential intermediary phenotype, the present study tested the association between risk-taking propensity and the *COMT* Val^{158}Met polymorphism in a community sample of children and young adolescents. Examination of the underlying correlates of risk-taking is needed in youth, as adolescence is a key period of increased engagement in risky behaviors (Eaton et

al., 2010; Johnston et al., 2011), and these behaviors have the potential for long-term impact on health (McGue, Iacono, Legrand, Malone, & Elkins, 2001). Results of the current study indicated that female carriers of the Met allele of *COMT* had higher risk-taking propensity compared to their Val-allele peers. This effect was not found for male participants. The results were highly consistent when selecting for the subsample of EA participants, again revealing an effect of the Met allele in females, but not males.

There are several plausible explanations, each requiring further empirical examination, which may shed light on the sex difference found in our study. Reports of sex-dependent findings relating to *COMT* polymorphisms are evident in the literature (Harrison et al., 2008), and numerous studies have reported sex specific findings with regard to the *COMT* polymorphism assayed in this study. In a recent study of adults by Chen and colleagues (2011) a sex-by-genotype interaction was reported for negative and positive affective personality traits, suggesting that in males the Val/Val genotype was associated with higher negative emotionality and lower positive emotionality, and the reverse was true for females (although non-significantly). Similarly, Lang et al., (2007) reported that variation in *COMT* was related to sensation seeking in adult females, but not in males.

Our findings could suggest that different processes are motivating risk-taking behavior in girls versus boys. The current findings may be understood within the context of the association between *COMT* allelic variants and affective and stress-related tendencies, and sex differences in these processes. The *COMT* Val^{158}Met polymorphisms have been associated with “warrior” (Val allele) and “worrier” (Met allele) tendencies based on findings that suggest that the Val allele may be protective with regard to stress and anxiety (Stein et al., 2006). For example, the Val allele, relative to the Met allele, has been associated with greater emotion-regulation capacity (Drabant et al., 2006) and the Met allele has been broadly associated with anxiety-related phenotypes (e. g., Domschke et al., 2004; Enoch et al., 2003; McGrath et al., 2004; Olsson et al., 2005; Olsson et al., 2007; Pooley et al., 2007; Woo et al., 2004). The Met allele has also been associated with lower perceived social acceptance and lower maintenance of positive emotions following stress in a sample of adolescent girls (Waugh, Dearing, Joormann, & Gotlib, 2009). Females as compared with males tend to experience affective disorders at greater rates and engage in risk-taking behaviors in order to escape from negative affective states. For example, depression is more closely related to problematic gambling behaviors in women than in men (Desai & Potenza, 2008) and women with pathological gambling are more likely to acknowledge gambling to escape from negative affective states than are men (Blanco et al., 2006). These tendencies may be expressed prior to adulthood, as a gambling-by-gender interaction was found indicating a four-fold stronger relationship between gambling and depression during adolescence in girls than in boys (Desai, Maciejewski, Pantalon, & Potenza, 2005). Emerging literature also suggests that negative affect pathways to substance use may be especially relevant for girls (Dakof, 2000; Measelle et al., 2006; Schinke et al., 2008). Specifically, in a 5-year prospective study of adolescent girls, elevated negative emotionality increased the risk for subsequent onset of substance abuse among adolescent girls (Measelle et al., 2006) and girls may be more vulnerable to negative affect and negative reinforcement processes maintaining risky behaviors including greater affect reduction expectancies about substances (Beck, Thombs, Mahoney, & Fingar, 1995; Wahl, Turner, Mermelstein, & R., 2005; Wiers, Hoogeveen, Sergeant, & Gunning, 1997). Taken together, it is plausible that different processes may motivate girls and boys to engage in risk-taking behaviors, with girls more likely than boys to be influenced by negative reinforcement processes against which the Val allele offers protection and for which the Met allele provides vulnerability. Additional investigation of this hypothesis is warranted, and such results may have implications for sex-specific prevention and intervention strategies for adolescents. Given the relationship between *COMT* Val^{158}Met polymorphisms and dopamine function

including within the prefrontal cortex, such interventions may include pharmacological or behavioral strategies in vulnerable individuals that influence dopamine function either directly or indirectly.

Although the findings in this study are novel and add to the literature on this polymorphism and behavioral phenotypes, there are several notable limitations of this study. First and foremost, this study was designed for original purposes other than genetic associations. Therefore, certain sample characteristics (e.g., sample size, racial/ethnic diversity) that were optimal for the original study purpose are limitations of a genetic investigation. Specifically, the sample size is very small for a human genetic study, and it is further limited by population admixture. The findings, although interesting, require replication in larger studies including a more homogenous population of youth. Although our findings may be interpreted within the context of factors motivating risk taking varying by girls versus boys, the literature on *COMT* is also nuanced by development (Hariri, 2011). Specifically, a recent report has suggested that there may be developmental effects of this polymorphism Dumontheil et al, 2011), with the relative benefit of the Met allele for working memory processes demonstrated in adults (Egan et al., 2001) not being expressed until after 10 years of age. Ideally samples should include large enough numbers of children of each age group to examine age-by-gene effects. Additionally, ancestral informative markers were not available in this study and therefore we had to rely on controlling for population stratification, based on self-reported racial/ethnic status, and by conducting the analyses in the full sample and in the subsample of EA participants. Additionally, only *COMT* was examined, and there are numerous candidate genes that should be examined. We also only focused on one candidate polymorphism. Future studies in larger samples should examine genetic regions of interest with fine mapping or other higher coverage techniques. Future, larger studies employing more complex analyses to tease apart the genetic and environmental interplay (e.g., possible interactions with traumatic or stressful life events) in the development and maintenance of risk-taking behavior in youth is warranted. Examination of this relation is an important question because the mechanisms underlying risk-taking propensity are not fully understood. As risk-taking behavior is intimately related to substance use disorders and other psychiatric phenotypes, elucidation of the mechanisms driving this intermediary phenotype, and gender variation in these factors, may help inform prevention and intervention efforts, as well as assist in our basic understanding of the etiology of risk-taking behaviors and its correlates.

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Table 1

Linear Regression Analysis of the Association between *COMT* genotype and BART Performance in the Full Sample (n=223)

	β	b	*t*	*p*
Age	.16	2.58	2.48	.01
Male Sex (vs. female)	-.20	-5.27	-1.60	.11
Caucasian Ethnicity (vs. non-Caucasian)	.12	3.17	1.84	.07
COMT Val^{158}Met (Met/Met, Val/Met, Val/Val)	-.30	-5.42	-2.97	.003
COMT Val^{158}Met × Sex interaction	.30	5.25	2.19	.03

Table 2

Linear Regression Analysis of the Association between *COMT* genotype and BART Performance by Sex in the Full Sample (n=223)

	Girls				Boys			
	β	**b**	***t***	***p***	**β**	**b**	***t***	***p***
Age	.28	4.24	3.02	<.01	.08	1.36	.89	.38
Caucasian Ethnicity (vs. non-Caucasian)	.08	1.89	.81	.42	.13	3.51	1.39	.17
COMT Val^{158}Met (Met/Met, Val/Met, Val/Val)	-3.26	-5.37	-3.27	<.01	-.01	-.17	-.01	.92

Table 3

Linear Regression Analysis of the Association between *COMT* genotype and BART Performance in EA Participants (n=111)

	β	b	*t*	*p*
Age	.00	.01	.01	.99
Male Sex (vs. female)	-.20	-5.08	-1.21	.23
COMT $Val^{158}Met$ (Met/Met, Val/Met, Val/Val)	-.33	-5.62	-2.30	.02
COMT $Val^{158}Met$ × Sex interaction	.31	5.52	1.67	.10

Table 4

Linear Regression Analysis of the Association between *COMT* genotype and BART Performance by Sex in EA Participants (n=111)

	Girls				Boys			
	β	**b**	***t***	***p***	**β**	**b**	***t***	***p***
Age	.15	2.33	1.08	.29	-.10	-1.79	-.79	.44
COMT Val^{158}Met (Met/Met, Val/Met, Val/Val)	-.34	-5.41	-2.49	.02	-.02	-.33	-.14	.89