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COMT Associations with Disordered Gambling and Drinking Measures

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Abstract

Disordered gambling and alcohol dependence are influenced by unique and shared genetic factors. Although the evidence is mixed, some research has linked COMT rs4680 (or COMT Val158Met) to the development of gambling or drinking problems; however, no molecular genetic study has jointly examined gambling and drinking problems. Furthermore, the majority of past studies examined gambling or drinking problems using a case-control design. The purpose of the current study was to examine associations of COMT rs4680 with dimensionally and categorically measured gambling and drinking problems in a nonclinical sample (139 Caucasian adults). The current study found that COMT rs4680 was related to both dimensionally and categorically measured gambling and drinking problems. It appears that the COMT Met/Met genotype may be a genetic risk factor that contributes to the development of both gambling and drinking problems.

Keywords

alcohol use; COMT gene; gambling; South Oaks Gambling Screen; Michigan Alcoholism Screening Test

Introduction

The lifetime prevalence of pathological gambling in adults is only about 1%; however, approximately twice as many adults (2%) have experienced problem gambling (i.e., subclinical pathological gambling), resulting in a lifetime prevalence of disordered gambling (i.e., problem or pathological gambling) of about 3% (Kessler et al. 2008). Similarly, the lifetime prevalence of alcohol dependence and alcohol abuse in adults is about 4% and 5%, respectively, resulting in a lifetime prevalence of alcohol use disorder of about 9% (Hasin et al. 2007). Gambling and drinking problems have been categorized even further according to level of problems, including at-risk gambling (Bonke and Borregaard 2009) and hazardous

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(or high-risk) drinking (Reid et al. 1999), which are less severe than disordered gambling and alcohol use disorder, respectively. In conjunction with this information, recent taxometric analyses have provided evidence supportive of the value of measuring gambling and drinking problems from both a categorical and dimensional perspective (Braverman et al. 2011; Green et al. 2011; Kincaid et al. 2013).

Importantly, twin studies have revealed that disordered gambling and alcohol dependence are moderately heritable and are modestly influenced by shared genetic factors (Agrawal et al. 2012; Lobo and Kennedy 2009). Given that disordered gambling and alcohol dependence are genetically influenced and related, it is important to identify specific genetic risk factors that may contribute to the development of both gambling and drinking problems. One single-nucleotide polymorphism (SNP) of interest in regard to gambling and drinking problems is COMT rs4680. Catechol-O-methyltransferase (COMT) is an enzyme responsible for the inactivation of dopamine (DA) and other catecholamines (Mannisto and Kaakkola 1999). COMT rs4680 is commonly known as COMT Val158Met because it involves a G → A (guanine-to-adenine) substitution at codon 158 of the COMT gene that causes an amino acid change of valine (Val) to methionine (Met) in COMT, resulting in reduced enzyme activity (Chen et al. 2004; Mannisto and Kaakkola 1999). Genotypic variation in COMT rs4680 has been shown to affect COMT activity in the brain, which presumably leads to variation in DA neurotransmission and may result in behavioral differences (Chen et al. 2004). Because DA is known to play a prominent role in reward and addiction (Berridge 2007; Wise 2004), it is reasonable to suspect that COMT rs4680 may be associated with both gambling and drinking problems.

Indeed, some studies have revealed a relationship between COMT rs4680 and pathological gambling (Comings et al. 2001) or alcohol dependence (Tiihonen 1999; Wang et al. 2001). Although recent genome-wide association studies have not linked COMT rs4680 to disordered gambling or alcohol dependence, individual SNPs rarely have reached genome-wide significance in relation to addictive behavior, and the contribution of any particular SNP to the development of addictive behavior is likely to be small (Bierut et al. 2010; Lind et al. 2013; Olfson and Bierut 2012). In addition, disordered gambling and alcohol dependence are not completely heritable (Agrawal et al. 2012), meaning that they tend to develop when genetically predisposed individuals are exposed to certain environmental influences. Thus, it is also important to see if COMT rs4680 and other SNPs are related to variability in gambling and drinking problems in non-disordered individuals. Notably, one study has associated the COMT Met/Met genotype with greater alcohol use in social drinkers (Kauhanen et al. 2000), although no such study has been conducted in relation to gambling.

Molecular genetic studies thus far have not jointly examined gambling and drinking problems. Furthermore, most of those studies have searched for genetic associations with disordered gambling or drinking using a case-control design. The purpose of the current study was to examine associations of COMT rs4680 with dimensionally and categorically measured gambling and drinking problems in a nonclinical sample.

Methods

Participants and Procedures

This study included 139 (77 male and 62 female) healthy Caucasian volunteers between the ages of 21 and 55 (*M* = 25.95; *SD* = 7.45) enrolled in a larger project examining the effects of alcohol on self-aggressive behavior. The project was approved by The University of Southern Mississippi Human Subjects Protection Review Committee. Written informed consent was obtained prior to participation.

Participants were recruited from the university and community through fliers, university-based e-mail announcements, and newspaper and online advertisements requesting volunteers for a paid study ($10 per hour) on “the effects of alcohol on motor skills.” Potential participants were screened by telephone interview and were excluded if they reported that they had previously participated in alcohol-related research, had not experienced alcohol intoxication during the past few years, were currently taking medication with which alcohol should not be consumed, had ever experienced a significant medical problem that was directly attributed to alcohol use, had been diagnosed with schizophrenia or bipolar disorder, had experienced a depressive or anxiety disorder in the past 6 months, were currently engaged in psychological treatment, or had a significant medical condition. During the phone screen, a cut-off score of 9 on the Alcohol Use Disorders Identification Test (AUDIT) was used to exclude probable problem drinkers (62% sensitivity; Kokotailo et al. 2004). In order to further limit the presence of problem drinking, non-excluded individuals scoring 7 or higher on the AUDIT (73% sensitivity; Kokotailo et al. 2004) were also administered the Short Michigan Alcoholism Screening Test (SMAST) and were excluded if they displayed an unweighted score of 3 or higher (94% sensitivity; Selzer et al. 1975). Because the larger project involved administering alcohol to participants based on weight, participants with a BMI greater than or equal to 35 were excluded for safety reasons. All gambling- and alcohol-related instruments were administered as online questionnaires on a lab computer.

Blood samples were obtained from each participant using an automatic fingerstick lancet device to puncture the index finger and 3MM chromatography paper (Whatman, Inc., Florham Park, NJ) to collect three small blots of blood. A total of 222 participants were genotype tested as part of the larger project. One participant was excluded from the larger project because of difficulty in genotyping across multiple polymorphisms, and two participants were excluded because of only having genotyping data. Other polymorphisms genotyped as part of the larger project included ADH1B rs1229984 (ADH1B*2), ADH1B rs2066702 (ADH1B*3), ADH1C rs698 (ADH1C*2), ALDH1A1 rs6151031 (ALDH1A1*2), ALDH1A1*3, ANKK1 rs1800497 (DRD2/ANKK1Taq 1A), GABRA2 rs279871, SNCA rs356195, and 5-HTTLPR. These other SNPs were genotyped primarily to examine associations with alcohol- and aggression-related measures (not with gambling-related measures). Although ANKK1 rs1800497 was another candidate for examining joint associations between gambling and drinking problems, there were less than 5 individuals with the rare variant of this polymorphism; therefore, we chose not to include ANKK1 rs1800497 in the current study. In order to limit the potentially confounding effects of

population stratification, only participants who self-identified as “Caucasian” were retained in the current study. Of the remaining 145 participants, 6 were excluded because of incomplete self-report data.

Measures

South Oaks Gambling Screen (SOGS)—The SOGS is a 20-item measure that was designed to screen for lifetime pathological gambling (Lesieur and Blume 1993). Higher SOGS scores are indicative of greater lifetime levels of gambling problems. A score of 5 or higher on the SOGS has been used to classify individuals as *probable pathological gamblers* (Lesieur and Blume 1993); scores of 3–4 have been used to classify individuals as *problem gamblers* (Lesieur and Blume 1993); and SOGS scores of 1–2 have been used to classify individuals as *at-risk gamblers* (Bonke and Borregaard 2009). In addition to analyzing dimensional SOGS scores, we analyzed SOGS scores that had been dichotomized in a manner that is most sensitive to the detection of gambling problems: The absence of any response suggestive of disordered gambling was coded as 0 (*non-DG-risk participants*), and the presence of any response suggestive of disordered gambling was coded as 1 (*at-least-at-risk gamblers*).

Michigan Alcoholism Screening Test (MAST)—The MAST is a 24-item measure that was developed to screen for alcohol abuse/dependence, or problem drinking (Selzer et al. 1975). Higher MAST scores are indicative of greater drinking problems. If specificity is valued over sensitivity, then a score of 7 or higher on the MAST (analogous to an unweighted score of 3 or higher on the SMAST) is recommended as being indicative of problem drinking (Selzer et al. 1975). Because during the phone screen we excluded some problem drinkers, we used a more sensitive cut-off score on the MAST to create a categorical problem-drinking variable: If sensitivity is valued over specificity, then a cut-off score of 5 on the MAST (analogous to an unweighted cut-off score of 2 on the SMAST) is recommended as being indicative of problem drinking (Selzer et al. 1975), which in the current study we used to classify participants as *mildly probable problem drinkers* and *probable non-problem drinkers*. A cut-off score of 5 on the MAST has yielded a sensitivity of 97% and a specificity of 75% for current or recent problem drinking (Selzer et al. 1975).

Genotyping

Dried blood samples were analyzed at the Indiana Alcohol Research Center. DNA was isolated using the HotSHOT method (Truett et al. 2000), in which TaqMan probes are used for allelic discrimination (Applied BioSystems, Inc., Foster City, CA). The allelic discrimination assay is a multiplexed, end-point assay. Each assay mix contains two different TaqMan probes labeled with VIC or FAM fluorescent reporter dye which bind preferentially to one of the alleles. The genotype of each sample is determined by the fluorescence levels of the reporter dyes and is clustered on a graph with other samples of the same genotype. Each reaction contains 5 ul of 2X TaqMan Universal PCR Mastermix, No AmpErase UNG, 3.75 ul of water, 0.25ul of 40X Assay Mix, and 1ul of DNA sample. Eight or eleven controls are included on each 96-well plate: 2 no template controls, 2 or 3 heterozygous samples, and 2 or 3 of each of the homozygous samples. Because genotyping is done by endpoint reading, thermocycling is carried out in MJ Research PTC-200

thermocyclers. The PCR products are then analyzed in an ABI PRISM® 7300 Sequence Detection System (SDS) instrument. SDS Software 1.3.1 converts the raw data to pure dye components and plots the results of the allelic discrimination on a scatter plot of Allele X versus Allele Y; each genotype appears on the graph as a cluster of points.

Data Analysis

Alpha was set at .05 for all analyses unless otherwise noted. For continuous variables, Levene's test was used to test for violations of homogeneity of variance. As recommended by Keppel (1991, p. 127) for a similar test of equality of variances (the Brown-Forsythe test), α for Levene's test was set at .25 in order to increase the power of the test. Because heteroscedasticity was found for both continuous variables, the Welch test was used to test for genotypic group differences in continuous outcomes, and the Games-Howell test was used for multiple comparisons. Two-tailed Fisher's exact tests were used in evaluating relationships between categorical variables and allelic groups (e.g., Met/Met and non-Met/Met groups). Hardy-Weinberg equilibrium was tested using the Hardy-Weinberg equilibrium calculator located at http://www.oege.org/software/hwe-mr-calc.shtml (Rodriguez et al. 2009).

Results

Correlations and Participant Classification

SOGS score was not significantly correlated with MAST score (r = .155, p = .068), and SOGS dichotomized score was not significantly correlated with MAST dichotomized score (r_ϕ = .151, p = .076). In regard to participant classification, 2.9%, 3.6%, and 25.9% of participants were classified as probable pathological gamblers, problem gamblers, and at-risk gamblers, respectively, for a total of 32.4% of participants classified as at-least-at-risk gamblers according to the SOGS (M = 1.96, SD = 1.46 vs. M = 0.00, SD = 0.00 for non-DG-risk participants). According to the MAST, 20.1% of participants were classified as mildly probable problem drinkers (M = 6.75, SD = 2.10 vs. M = 1.32, SD = 1.40 for probable non-problem drinkers).

Genotype Frequencies and Group Demographics

The COMT genotypic frequency distribution did not deviate significantly from expected Hardy-Weinberg equilibrium (χ^2= .83, p = .36). Genotypic groups did not differ significantly in respect to gender, age, years of education, or marital status (all ps > .05). Demographics for COMT genotypic groups are shown in Table 1.

Group Comparisons

SOGS—Differences in SOGS scores between COMT genotypic groups were significant, Welch statistic (2, 62.03) = 3.82, p = .027, η^2 = .075. The post hoc Games-Howell test revealed that Met/Met participants (M = 1.15, SD = 1.75) displayed significantly higher SOGS scores (p = .020, d = .60) than Val/Val participants (M = .28, SD = .74).

In regard to the relationship between COMT group membership and SOGS cut-off score category, a Fisher's exact test revealed a significant relationship between COMT allelic

group and at-least-at-risk gambling (p = .009, φ = .239, RR = 1.98), such that Met homozygotes were at greater risk of being at-least-at-risk gamblers in comparison to Val carriers. COMT genotypic group scores and categorical results are shown in Tables 2 and 3, respectively.

MAST—Differences in MAST scores between COMT genotypic groups were significant, Welch statistic (2, 67.80) = 4.75, p = .012, η^2 = .051. The post hoc Games-Howell test revealed that Met/Met participants (M = 3.18, SD = 2.72) displayed significantly higher MAST scores (p = .009, d = .73) than Val/Val participants (M = 1.36, SD = 2.02).

In regard to the relationship between COMT group membership and MAST cut-off score category, a Fisher's exact test revealed a significant relationship between COMT allelic group and mildly probable problem drinking (p = .034, φ = .196, RR = 2.15), such that Met homozygotes were at greater risk of being mildly probable problem drinkers in comparison to Val carriers.

Discussion

In the current study, COMT rs4680 was related to both dimensionally and categorically measured gambling and drinking problems. To the best of our knowledge, this is the first molecular genetic study to jointly examine gambling and drinking problems.

COMT Met homozygotes reported greater levels of gambling problems than Val homozygotes and were about twice as likely to be at-least-at-risk gamblers in comparison to Val carriers (small-to-medium effect sizes; Cohen 1988/2009). In contrast with current results, a recent genome-wide association study did not find an association between COMT rs4680 and disordered gambling (Lind et al., 2013); however, that study examined a quantitative factor score derived from four measures of gambling involvement and two measures of gambling problems (one of which was the SOGS), whereas the current study focused on gambling problems as measured by the SOGS, which may account for this discrepancy.

Although our results differ from a prior study, they may be explained by the tonic-phasic DA hypothesis (Bilder et al. 2004). According to this hypothesis, subcortical tonic (baseline) DA levels are modulated by and correspond with cortical DA concentrations, and subcortical phasic DA bursts (in response to behaviorally relevant stimuli) are downregulated by tonic stimulation of presynaptic DA autoreceptors. Previous research suggests that the COMT Met allele is associated with higher DA neurotransmission cortically, which according to the tonic-phasic DA hypothesis is expected to result in higher tonic DA levels and lower phasic DA release subcortically relative to the Val allele (Bilder et al. 2004). Consistent with current results interpreted in light of the tonic-phasic DA hypothesis, it appears that elevated tonic DA levels and tonic stimulation of DA receptors in subcortical regions of the brain (particularly in the striatum and mesolimbic pathway) heighten aspects of behavioral impulsivity and contribute to a greater preference for gambling-like rewards in rats and greater susceptibility to pathological gambling in chronically exposed humans (Johnson et al. 2012; Voon et al. 2010; Weintraub et al. 2010).

In addition, persistently elevated and reduced tonic DA levels in transgenic mice have been shown to increase and decrease motivation for rewards, respectively (Berridge 2007). These findings suggest that the Met/Met genotype may be associated with greater behavioral impulsivity and motivation for rewards compared to other groups. Although a few studies have associated the Val/Val genotype (Boettiger et al. 2007) or Val allele (Gianotti et al. 2012) with greater delay discounting, Met homozygotes have displayed worse Iowa Gambling Task (IGT) performance (suggestive of greater attentiveness to wins than losses) and greater reward-seeking behavior than Val homozygotes (Lancaster et al. 2012; van den Bos et al. 2009). In summary, the Met/Met genotype may be associated with higher tonic DA levels subcortically resulting in greater reward-seeking and impulsive behavior and heightened risk for the development of gambling problems relative to other groups.

One line of evidence that may seem contrary to our proposed explanation of current results is prior research indicating that there is an association between gambling problems and greater phasic DA release (Joutsa et al. 2012; Linnet et al. 2010; Steeves et al. 2009), which according to the tonic-phasic DA hypothesis is expected to be associated with the Val allele. However, such results possibly can be explained with the incentive sensitization theory of addiction (Robinson and Berridge 2008). According to this theory, the repeated intermittent use of certain drugs, such as amphetamine, by susceptible individuals causes the DA system to become increasingly responsive (sensitized) to those drugs and associated stimuli (drug cues), leading to the intensification of drug craving and ultimately to addiction. In support of the notion that chronic gambling has amphetamine-like effects on the brain, amphetamine has been shown to prime motivation to gamble in problem gamblers (Zack and Poulos 2004), and rats chronically exposed to gambling-like rewards have displayed sensitization to the locomotor effects of amphetamine (Singer et al. 2012). In short, non-disordered individuals who are vulnerable to the development of disordered gambling (e.g., Met homozygotes) may tend to display higher tonic DA levels and lower phasic DA release subcortically (consistent with the tonic-phasic DA hypothesis), whereas individuals who have developed disordered gambling (regardless of COMT genotype) may tend to display greater phasic DA release in response to gambling-related stimuli (consistent with the incentive sensitization theory of addiction). Therefore, studies showing a relationship between gambling problems and greater phasic DA activity may not be incompatible with our interpretation of current results, as those studies focused on individuals with more chronic exposure to gambling. Of course, more research is needed to provide support for this distinction. If this distinction is valid, however, then this may explain why greater phasic DA release has been associated with better IGT performance in healthy controls but with worse IGT performance in pathological gamblers (Linnet et al. 2011).

Similar to what was found with gambling problems, COMT Met homozygotes reported greater levels of drinking problems than Val homozygotes and were about twice as likely to be mildly probable problem drinkers in comparison to Val carriers (small-to-medium effect sizes; Cohen 1988/2009). Consistent with current results, some past studies have associated the COMT Met/Met genotype with greater alcohol use in social drinkers (Kauhanen et al. 2000) and with early-onset (Wang et al. 2001) and late-onset alcohol dependence (Tiihonen 1999). In addition, the Met/Met genotype has been associated with greater impulsive and reward-seeking behavior (Lancaster et al. 2012; van den Bos et al. 2009), and the

mesolimbic DA system, which is presumably modulated indirectly by COMT activity, appears to mediate motivation for reward (Berridge 2007). Although other past studies have reported conflicting results (Bierut et al. 2010; Foroud et al. 2007; Olfson and Bierut 2012; Schellekens et al. 2012), those studies attempted to relate COMT rs4680 to a diagnosis of alcohol dependence, whereas the current study used more sensitive categorical and dimensional measures of drinking problems. Thus, it is possible that the effect of the Met/Met genotype on drinking behavior is more easily detected in a nonclinical sample using more sensitive measures of alcohol abuse.

The tonic-phasic DA hypothesis may also be relevant to understanding the relationship between COMT rs4680 and drinking problems. Consistent with this hypothesis, greater alcohol-induced phasic DA release in social drinkers has been associated with a lower frequency of high-volume drinking episodes (Urban et al. 2010), and chronically elevated tonic DA levels in transgenic mice, which are accompanied by reduced phasic DA responses to electric stimulation, have been shown to increase motivation for rewards (Berridge 2007; Cagniard et al. 2006). In addition, abstinent alcohol-dependent individuals have displayed reduced baseline DA receptor binding and blunted psychostimulant-induced DA release in the striatum relative to control participants (Diana 2011), and an opposite set of findings in schizophrenia has been interpreted as evidence of greater phasic DA release (Abi-Dargham et al. 2000), which is apparently related to the increased attribution of salience to external and internal stimuli that culminates in psychosis (Kapur 2003). Perhaps individuals with lower subcortical phasic DA release (e.g., Met homozygotes) tend to attribute less salience to stimuli (particularly reward-related stimuli) and consequently tend to seek out more immediately rewarding stimuli such as drugs, which strongly activate and sensitize the DA system (Berridge 2007). However, the Met/Met genotype thus far has not been associated with the use of other substances (Bousman et al. 2010; Vandenbergh et al. 1997), although the Met allele has been associated with heaviness of smoking (Munafo et al. 2011).

Strengths of this study include the use of a nonclinical sample and the assessment of dimensionally and categorically measured gambling and drinking problems. However, this study also has limitations worth noting, one of which is the inclusion of only Caucasian individuals. Although this practice was employed in order to limit the potentially confounding effects of population stratification, it limits the ability to generalize results beyond that of Caucasians. Another limitation is that none of the instruments administered in the current study allowed us to diagnose pathological gambling or alcohol abuse/dependence, which in regard to a diagnosis of pathological gambling would have required a much larger sample given the low prevalence of the disorder. Finally, we cannot be certain that COMT associations with gambling and drinking problems are indicative of an influence of COMT on gambling and drinking problems. It is possible that COMT rs4680 was jointly associated with gambling and drinking problems by chance. However, this possibility is somewhat offset by the lack of significant correlations between gambling- and drinking-related variables.

In conclusion, it appears that the COMT Met/Met genotype may be a genetic risk factor that contributes to the development of both gambling and drinking problems. In addition to attempting to replicate current results, future studies should continue to search for

associations between COMT rs4680 and reward-seeking behavior, which may mediate the relationship between COMT rs4680 and gambling/drinking problems.

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Table 1

Demographics for COMT Genotypic Groups Expressed as a Ratio or as *M* (*SD*)

Variable	GG	AG	AA
Gender (Male/Female)	14/11	35/39	28/12
Age	25.08 (7.61)	25.97 (7.12)	26.46 (8.09)
Years of Education	16.68 (1.46)	16.44 (2.14)	16.74 (2.23)
Marital Status (Married/Unmarried)	5/20	12/60	6/32

Note: For marital status, 4 participants were missing data.

Table 2

COMT Genotypic Group Scores Expressed as *M (SD)*

Measure	GG (n = 25)	AG (n = 74)	AA (n = 40)
SOGS	.28 (.74)*	.47 (.93)	1.15 (1.75)*
MAST	1.36 (2.02)**	2.35 (2.77)	3.18 (2.72)**

SOGS—South Oaks Gambling Screen; MAST—Michigan Alcoholism Screening Test

* $p < .05$

** $p < .01$

Table 3

COMT Met/Met (AA) and Non-Met/Met (AG/GG) Groups by Gambling/Drinking Status Expressed as Frequency (Row Percentage)

Measure		
SOGS**		
	Non-DG-Risk	At-Least-At-Risk
Non-Met/Met	74 (74.7)	25 (25.3)
Met/Met	20 (50.0)	20 (50.0)
MAST*		
	PNPD	MPPD
Non-Met/Met	84 (84.8)	15 (15.2)
Met/Met	27 (67.5)	13 (32.5)

SOGS—South Oaks Gambling Screen; MAST—Michigan Alcoholism Screening Test; DG—Disordered Gambling; PNPD—Probable Non-Problem Drinker; MPPD—Mildly Probable Problem Drinker

* $p < .05$

** $p < .01$