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COMT and ALDH2 polymorphisms moderate associations of implicit drinking motives with alcohol use

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Abstract

Dual process models of addiction emphasize the importance of implicit (automatic) cognitive processes in the development and maintenance of substance use behavior. Although genetic influences are presumed to be relevant for dual process models, few studies have evaluated this possibility. The current study examined two polymorphisms with functional significance for alcohol use behavior (*COMT* Val158Met and *ALDH2**2) in relation to automatic alcohol cognitions and tested additive and interactive effects of genotype and implicit cognitions on drinking behavior. Participants were college students ($n = 69$) who completed Implicit Association Tasks (IATs) designed to assess two classes of automatic drinking motives (enhancement motives and coping motives). Genetic factors did not show direct associations with IAT measures, however, *COMT* and *ALDH2* moderated associations of implicit coping motives with drinking outcomes. Interaction effects indicated that associations of implicit motives with drinking outcomes were strongest in the context of genetic variants associated with relatively higher risk for alcohol use (*COMT* Met and *ALDH2**1). Associations of genotype with drinking behavior were observed for *ALDH2* but not *COMT*. These findings are consistent with the possibility that genetic risk or protective factors could potentiate or mitigate the influence of reflexive cognitive processes on drinking behavior, providing support for the evaluation of genetic influences in the context of dual process models of addiction.

Keywords

Alcohol; drinking motives; implicit cognitions; implicit association test; aldehyde dehydrogenase; catechol-O-methyltransferase

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Dual process models of addiction propose that drug use behavior is influenced by two distinct but interdependent cognitive-motivational systems (Bechara, 2005; Wiers et al., 2007). One is a controlled or *reflective* system, governed largely by explicit (i.e., conscious) processes; the other is an impulsive or *reflexive* system, guided primarily by implicit (i.e., automatic) processes that operate largely outside of conscious awareness (e.g., Bechara, 2005; Kalivas & Volkow, 2005; Wiers et al., 2007). Theoretically, the influence of implicit processes on behavior is partly contingent on the strength of countervailing explicit

influences. For example, conditioned drug cues could serve to engage reward-related associative networks, triggering appetitive responses (e.g., craving) through implicit mechanisms. Explicit processes (e.g., conscious deliberation to avoid drug use) can potentially curb these reflexive influences, assuming motivation and adequate self-regulatory resources for doing so (Wiers et al., 2007). Explicit and implicit systems are presumed to reflect largely distinct neural networks, with the former governed predominantly by prefrontal mechanisms and the latter by an incentive network reflecting limbic and ventral-striatal pathways (e.g., Bechara, 2005).

Dual process theories also propose that dispositional or situational factors can create “boundary conditions” that moderate the relative influence of implicit versus explicit cognitive processes on behavioral outcomes (Hofmann, Friese, & Strack, 2009). Among many possible moderating factors, executive cognitive functioning has been studied extensively (Barrett, Tugade, & Engle, 2004). Research in this area generally suggests that higher working memory capacity can mitigate the influence of impulsive cognitive processes on various appetitive behaviors, whereas reduced working memory renders impulsive processes more influential (Hofmann et al., 2009). This finding has been extended to alcohol use behavior, such that the association of implicit measures of alcohol motivation with reported consumption is stronger for individuals with relatively lower performance on measures of working memory and response inhibition (Grenard et al., 2008; Houben & Wiers, 2009; Thush et al., 2008).

Although genetic influences are theoretically relevant for dual process models of addiction, only one published study has examined genetic associations with implicit measures of alcohol cognitions (Wiers et al., 2009). Results of that study suggested that heavy-drinking males with the G allele of the *OPRM1* A118G polymorphism showed stronger automatic motivational tendencies toward alcohol cues than those without the variant (Wiers et al., 2009). This finding was consistent with prior evidence that individuals with the G allele show greater sensitivity to alcohol-induced stimulation and reward (Ray & Hutchison, 2004), suggesting that genetic differences in the endogenous opioid system (implicated in alcohol dependence; Herz, 1997) may be relevant for dual processes models of drinking behavior. The aim of the current study was to extend previous work by evaluating implicit alcohol cognitions in relation to genes with functional relevance for additional systems implicated in alcohol dependence; specifically, executive cognitive functioning and alcohol metabolism.

Variation in executive cognitive function is demonstrated to predict risk for alcohol use disorders (Finn et al., 2009) and to moderate associations of implicit alcohol cognitions and drinking behavior (Grenard et al., 2008; Houben & Wiers, 2009). Therefore, our first goal was to evaluate a gene with functional significance for executive cognitive ability. *COMT* encodes catechol-O-methyltransferase, an enzyme important for the degradation of central nervous system catecholamines and critical for degradation of dopamine in the prefrontal cortex (Bilder et al., 2004). A nonsynonymous G-to-A polymorphism at codon 158 (rs4680) results in an amino acid substitution (Val-to-Met) in exon 4, which is associated with 3- 4-fold variation in enzymatic activity (Bilder et al., 2004; Winterer & Weinberger, 2004). The high-activity variant (Val) is associated with reduced prefrontal dopamine due to more efficient dopamine clearance, whereas the low-activity variant (Met) is associated with increased tonic dopamine (Winterer & Weinberger, 2004). Notably, functional effects of Val158Met on cognition appear to involve a tradeoff between cognitive stability and flexibility. Presumably due to increased prefrontal dopamine, Met carriers appear to show better performance on working memory tasks requiring cognitive stability, but reduced cognitive flexibility on tasks requiring rapid cognitive shifting, disengagement and/or conflict processing/resolution (Neuhaus et al., 2009; Nolan et al., 2004; Tunbridge,

Harrison, & Weinberger, 2006). The Met variant is also predictive of increased limbic activity and reduced processing efficiency in response to emotionally evocative stimuli (Heinz & Smolka, 2006; Tunbridge et al., 2006) and has been linked to anxiety-related phenotypes (Enoch, 2006).

Though studied largely in the context of schizophrenia, *COMT* Val158Met has been implicated in the risk for alcohol use disorders (Bilder et al., 2004; Enoch, 2006; Foroud et al., 2007), such that the Met variant is associated with higher rates of alcohol dependence (Tiihonen et al., 1999; Wang et al., 2001) and social drinking (Kauhanen et al., 2000). Notably, Val158Met was recently linked to post-treatment relapse in alcohol-dependent individuals, such that Met carriers were about twice as likely to relapse in the year following treatment as those without the variant (Wojnar et al., 2009). Though mechanisms underlying increased risk for alcohol use in Met carriers have not been identified, it is proposed that the Met variant could confer increased risk by way of differential dopamine-modulated reinforcement from acute intoxication, diminished ability to cope with negative emotional states, and/or deficits in cognitive flexibility and task switching (Bilder et al., 2004; Enoch, 2006; Oroszi & Goldman, 2004). Of relevance to the current study, the ability to override impulsive processes and/or disengage from the influence of salient appetitive cues is presumed to be important for mitigating the influence of implicit alcohol cognitions on drinking (Grenard et al., 2008; Thush et al., 2008). Therefore, one possibility is that Met carriers would demonstrate stronger associations between implicit measures of alcohol motivation and drinking behavior, perhaps due to a relatively reduced capacity for cognitive flexibility and/or disengaging from emotionally evocative stimuli.

Our second goal was to evaluate implicit alcohol cognitions in relation to a variant with functional effects on alcohol metabolism. *ALDH2* encodes the mitochondrial aldehyde dehydrogenase (ALDH) enzyme, the principal catalyst for oxidation of acetaldehyde during alcohol metabolism. A single nucleotide substitution at exon 12 (rs671) results in a variant allele (*ALDH2*2*) that encodes a functionally inactive ALDH enzyme subunit, thereby limiting oxidation of acetaldehyde during alcohol metabolism. *ALDH2*2* is nearly exclusive to northeast Asian populations. Compared with the common *ALDH2*1* variant, *ALDH2*2* is associated with higher levels of post-drinking acetaldehyde, increased sensitivity to alcohol, and a significantly reduced risk for alcohol dependence (Wall, 2005). *ALDH2*2* has also been linked to explicit measures of alcohol cognitions, including lower drinking motives and higher self-efficacy for resisting alcohol (Hendershot et al., 2010). Based on these findings, one hypothesis is that individuals with *ALDH2*2* might show reduced automatic approach tendencies toward alcohol, and/or weaker associations between implicit measures of alcohol motivation and drinking behavior, compared to individuals without this variant.

Whereas most studies incorporating implicit measures of alcohol cognitions have examined general classes of automatic cognitions (e.g., implicit measures of positive or negative attitudes toward alcohol), the current study focused specifically on implicit measures of *drinking motives*. Drinking motives (Cooper et al., 1995) reflect individual differences in the perceived reinforcement value of alcohol and, when assessed with self-report measures, show strong associations with drinking outcomes (Kuntsche et al., 2005). Further, recent studies have linked explicit (self-report) measures of drinking motives to *ALDH2* (Hendershot et al., 2010) and *OPRM1* (Miranda et al., 2010). However, implicit measures of drinking motives have not been developed until recently (Lindgren et al., 2010).

The current study incorporated Implicit Association Tests (Greenwald, McGhee, & Schwartz, 1998) to evaluate associations among genetic factors (*COMT* and *ALDH2*), implicit alcohol cognitions, and drinking behavior. The hypotheses were as follows: a) *COMT* Met carriers (compared to Val/Val individuals) would show stronger implicit

drinking motives, b) those with the *ALDH2**1/*2 genotype (compared to *ALDH2**1/*1 individuals) would show weaker implicit drinking motives, and c) *COMT* and *ALDH2* genotypes would moderate associations of implicit motives and drinking behavior. Specifically, we predicted that associations of implicit motives with alcohol use would be stronger in the context of genetic variants associated with relatively higher risk (*COMT* Met and *ALDH2**1/*1).

Materials and Methods

Participants

This study included 69 undergraduates (55% female; mean age = 20.7 years [SD = 1.8] who were enrolled in a larger study of genetic and cognitive influences on drinking behavior at the University of Washington. Participants who enrolled in the parent study and reported lifetime alcohol use were invited to participate in a follow-up study to complete IAT measures. Because *ALDH2**2 is nearly exclusive to northeast Asian populations, inclusion criteria for the parent study included full Chinese, Korean or Japanese ethnicity (n = 48, 18 and 3, respectively, for the current analyses). Further details on recruitment procedures and baseline characteristics for the full sample can be found in Hendershot et al. (2009). Because participants' *ALDH2* status had been ascertained as part of the parent study, we used prospective genotyping to recruit roughly equal numbers of participants with the *ALDH2**1/*1 (n = 33) or *ALDH2**1/*2 (n = 36) genotypes for the current study. A third group, *ALDH2**2 homozygotes, was not targeted for this follow-up study due the low frequency of the *ALDH2**2/*2 genotype and very low alcohol consumption rates in this group. Genotyping for *COMT* occurred following the IAT study using participants' banked samples. For the current analyses *COMT* genotype was classified according to presence of the minor allele (A, coding for Met). This scheme resulted in two groups: Val/Val (n = 42) versus Val/Met or Met/Met (n = 26).

Measures

Alcohol use—Participants completed measures of recent drinking behavior during the laboratory session. Three primary outcomes were evaluated. Average number of drinks per week was assessed with the Daily Drinking Questionnaire (DDQ; Collins, Parks, & Marlatt, 1985). Recent heavy episodic drinking and peak lifetime consumption were assessed using items based on the National Institute on Alcohol Abuse and Alcoholism (NIAAA) question set (NIAAA, 2003). Specifically, participants reported the number heavy drinking episodes (defined as 4+ drinks for women or 5+ drinks for men) in the past 30 days and the lifetime maximum number of drinks consumed within a 24-hour period.

Implicit Association Tests—The IAT (Greenwald et al., 1998) is a computerized task that measures participants' reaction times when pairing two target concepts (e.g., "alcohol" and "water") with two attribute concepts (e.g., "cope" and "ignore"). Reaction time difference is presumed to be a proxy for the relative strength of the associations between mental constructs. The IATs used in the current study were designed to map onto theoretically relevant domains of drinking motivation that index positive reinforcement motives (Enhancement) and negative reinforcement motives (Coping). Enhancement and Coping motives are robust predictors of drinking behavior when assessed with explicit (self-report) measures (Kuntsche et al., 2005). Target stimuli were images of beer or water that were paired with attribute concepts. The Cope IAT attributes were words representing "cope" or "ignore." "Cope" words were soothe, calm, help, cope; and "Ignore" words were ignore, disregard, neglect, and dismiss. The Enhance IAT attributes were words representing "excite" and "diminish". The former were excite cheer, high, fun, amplify; and the latter were diminish, weaker, lower, lessen, decrease, and reduce.

Participants press the “d” and “k” keys on the computer keyboard to indicate whether they are placing the stimuli into the right or left category. Stimuli for each block were randomized, with the restriction that they alternate between targets (beverage pictures) and attributes (motivation words). Pairings were counterbalanced: half of the participants were exposed first to Pairing A (e.g., alcohol + cope & water + ignore); half of the participants were exposed first to Pairing B (e.g., alcohol + ignore & water + cope). IATs were composed of seven blocks: three of which are practice blocks and four of which are test blocks and are used to calculate the IAT score. For brevity, IAT blocks are not described in detail here; interested readers are referred to Lindgren et al., 2009 for a detailed description of IAT block sequence and procedures. IATs were created using Inquisit 3.0.3.1 software (2008) using Greenwald’s (2006) procedures. IATs scores were calculated using the *D* score algorithm (Greenwald, Nosek, & Banaji, 2003) by subtracting the average latencies of Pairing A from Pairing B and then dividing by the standard deviation of the latencies for both pairings for each participant. Positive *D* scores indicate a stronger/faster association between alcohol and the drinking motive; negative *D* scores indicate the opposite.

Genotyping

Blood samples were genotyped at the Alcohol Research Center at Indiana University. Genomic DNA was isolated with the “HotSHOT” method (Truett et al., 2000) using TaqMan probes for allelic discrimination (Applied Biosystems, Foster City, CA). For the *COMT* A → G substitution (rs 4680), the sequence is CCCAGCGGATGGTGGATTTCGCTGGC[A/G]TGAAGGACAAGGTGTGCATGCC TGA, which includes the ATG[Met] → GTG[Val] amino acid change. Two probes were designed according to the reference sequence (NM_000754) in a region that is 100% identical between three membrane-bound (MB-*COMT*) variants (NM_001135161, NM_001135162, and NM_000754) and a soluble form (S-*COMT*) variant (NM_007310). A was labeled with VIC and G was labeled with FAM. *ALDH2* genotyping was conducted using similar methods, in accordance with procedures reported previously (Hendershot et al., 2009). We also had available data for *DRD2/ANKK1* (rs1800497) and *OPRM1* (rs179971) for the present sample. Both of these markers were evaluated initially, however, preliminary analyses with these loci were not promising. Thus, subsequent analyses focused exclusively on *COMT* and *ALDH2* in order to reduce the overall number of statistical tests.

Analysis Plan

We employed multiple regression analyses to test additive and interactive associations of genetic factors and implicit drinking motives with drinking behavior. Main effects for genetic factor and IAT score were entered, as was the interaction between the two. All IAT scores were grand-mean centered, and interaction terms were created by multiplying participants’ grand-mean centered IAT scores by genotype score. Ethnicity and gender were entered as covariates. All predictors were entered in a single step. Significant main effects or interaction terms are denoted by a significant *t*-score, indicating that the variable predicted unique variance in a given drinking outcome. Analyses were conducted for each combination of IAT, genetic and drinking variable. We did not implement strict alpha correction for multiple testing given power considerations, including the small sample size, the small effect sizes typical for genetic associations with complex behaviors, and the relatively small number of statistical tests. Additionally, drinking variables were highly correlated, which reduces concerns that multiple statistical tests reflect independent hypothesis tests (e.g., Sankoh et al., 1997).

Results

Descriptive Statistics

Descriptive statistics were calculated for the drinking variables (typical drinks per week, heavy drinking episodes, and peak lifetime drinks) and cope and enhance IAT scores. Ten participants had missing data on alcohol use variables and the three participants who reported Japanese ethnicity were omitted given the small size of this group, resulting in a sample of 56. Correlations between genetic variables, IAT scores and drinking outcomes are presented in Table 1. Results indicated moderate to strong positive correlations among the drinking variables and a moderate positive correlation between the IAT scores. IAT scores had small to moderate positive correlations with the drinking variables and were not significantly correlated with *COMT* or *ALDH2*.

Multiple Regression Analyses

Multiple regression was used to investigate the unique effects of implicit cognitive processes and genetic factors as predictors of drinking. Predictor variables were entered in single step in the following order: gender, ethnicity, genetic factor, IAT score, and the genetic factor $\times$ IAT score interaction. Criterion variables were the three drinking outcomes. Analyses were conducted separately for each IAT (cope vs. enhance), genetic factor (*ALDH2* vs. *COMT*), and drinking variable (typical drinks per week, heavy drinking episodes, and peak lifetime drinks).

Implicit drinking motives and COMT—Models evaluating drinking variables as a function of implicit coping motives and *COMT* (Table 2) revealed that main effects of *COMT* and implicit coping motives were not significant predictors of drinking, with the exception of a non-significant trend of *COMT* predicting drinks per week ($p = .057$). Consistent with predictions, cope IAT scores showed stronger associations with drinking outcomes among *COMT* Met carriers compared to *COMT* Val/Val individuals, supporting our moderation hypothesis (see Figure 1). This pattern of results held for both drinks per week and heavy drinking episodes, and a non-significant trend in the same direction was found for peak life drinks ($p = .053$).

For the enhance IAT/*COMT* model, main effects of *COMT* and implicit enhancement were not significant predictors of drinking, with the exception of a non-significant trend of *COMT* predicting drinks per week, $p = .096$ (see Table 3). Moderation was supported for drinks per week only; the *COMT* $\times$ enhance IAT interaction was consistent with predictions ($p = .023$). Enhance IAT scores showed stronger associations with drinking among *COMT* Met carriers compared to *COMT* Val/Val individuals (see Figure 1).

Implicit drinking motives and ALDH2—A consistent pattern of results was observed in the regressions predicting drinking variables as a function of implicit coping and *ALDH2* (see Table 2). Main effects for *ALDH2* and the cope IAT were significant for all three drinking variables (all p 's $< .004$). In addition, there was a significant *ALDH2* $\times$ cope IAT interaction for all three drinking variables (all p 's $< .038$), supporting our moderation hypothesis. Consistent with predictions, associations of cope IAT scores were stronger among *ALDH2**1/*1 individuals and weaker in *ALDH2**1/*2 individuals (see Figure 1).

The results were less consistent for the enhance IAT and *ALDH2* (see Table 3). Main effects for *ALDH2* were observed for drinks per week ($p = .008$) and peak lifetime drinks ($p = .014$), and a main effect for the enhance IAT was observed for drinks per week ($p = .041$). No other main effects were found, and implicit enhancement motives were not found to moderate the relationship between *ALDH2* and drinking variables.

Discussion

This study evaluated additive and interactive associations of genetic factors (*COMT*, *ALDH2*) and implicit drinking motives with drinking behavior. The most notable findings concerned moderating effects of genotype on the association of automatic drinking motives with drinking outcomes. Specifically, associations of implicit coping motives with drinking behavior were strongest in the context of genetic variants associated with relatively higher risk for alcohol use (*COMT* Met and *ALDH2**1) and negligible in the context of variants associated with lower risk (*COMT* Val and *ALDH2**2). This pattern of results was less consistent for implicit enhancement motives, which interacted with *COMT* genotype in only one instance. Overall, the results offer preliminary evidence for the possibility that genetic risk or protective factors might potentiate or mitigate the influence of reflexive processes on drinking behavior, thereby representing possible “boundary conditions” (Hofmann et al., 2009) that might moderate the extent to which impulsive cognitive processes predict behavior.

Moderating effects of genotype were supported for polymorphisms implicated in two distinct mechanisms relevant for alcohol dependence; namely, executive cognitive functioning (*COMT*) and alcohol metabolism (*ALDH2*). The current findings for *COMT* Val158Met can potentially be interpreted in the context of existing knowledge about *COMT* and executive cognitive functioning (Bilder et al., 2004; Winterer & Weinberger, 2004). Specifically, Met carriers typically demonstrate higher performance on working memory tasks requiring cognitive stability, but diminished cognitive flexibility on tasks that require shifting cognitive demands, rapid alternation between response execution and inhibition, and/or disengagement of cortical states (e.g., Bilder et al., 2004; Neuhaus et al., 2009; Opgen-Rhein et al., 2008; Turnbridge et al., 2006). Therefore, one interpretation of the current findings is that relatively poorer cognitive flexibility among Met carriers renders these individuals less able to disengage from the influence of reflexive cognitive processes once initiated. While the current data cannot inform this prediction directly, this interpretation is consistent with findings concerning the joint influence of implicit alcohol cognitions and executive cognitive processes on drinking outcomes (Grenard et al., 2008; Houben & Wiers, 2009; Thush et al., 2008). In particular, these studies indicate a stronger association between implicit alcohol cognitions and drinking behavior in individuals with relatively weaker performance on cognitive tasks assessing working memory and response inhibition. Presumably, weaker executive abilities could diminish the capacity for executive control over reflexive cognitive processes, perhaps making it more likely that impulsive processes influence behavior (Houben & Wiers, 2009).

The moderating influence of *COMT* Val158Met in this study could also be interpreted in light of evidence that Met carriers display reduced processing efficiency and/or heightened neurobehavioral responses when presented with emotionally evocative stimuli (Enoch, 2006; Heinz & Smolka, 2006). For instance, fMRI studies indicate that Met carriers show heightened BOLD responses to emotionally evocative stimuli as well as decreased performance on tasks requiring emotional processing (Heinz & Smolka, 2006; Turnbridge et al., 2006). Accordingly, associations of the Met variant with alcohol use have been speculated to involve motivational pathways specific to the regulation of negative affect (Bilder et al., 2004; Enoch, 2006). If Met carriers show heightened neurobiological responses to cues signaling negative affect and/or diminished capacity to disengage from negative emotional states, these scenarios could potentially increase the likelihood of alcohol use in the context of negative affect. While speculative, this interpretation could be viewed as consistent with the current finding that Met carriers showed stronger associations between implicit coping motives and alcohol consumption. Importantly, additional explanations for *COMT* effects cannot be ruled out. Functional imaging studies suggest that

COMT Val158Met modulates neural processing of reward cues, such that Met carries evidence greater activation in prefrontal as well as ventral striatal regions during anticipation and/or receipt of reward-related information (Dreher et al., 2009; Schrack et al., 2008; Yacubian et al., 2007). Further, findings that *COMT* Val158Met modulates exploratory decision-making in conditions of uncertainty (Frank et al., 2009) and neural activity during response inhibition (Congdon et al., 2009) provide a basis for additional hypotheses as to possible mechanisms of *COMT* in the context of alcohol use. Finally, given our use of the IAT measure it should be noted that *COMT* is demonstrated to influence responding on cognitive tasks involving rapid responses and task switching. However, *COMT* showed no direct associations with IAT performance, which would argue against the possibility that *COMT* interactions can be attributed to genotype differences in cognitive processing abilities.

The current findings concerning *ALDH2* can be interpreted in the context of an extensive literature linking *ALDH2* to alcohol sensitivity and the risk for alcohol dependence. Due to elevated blood acetaldehyde during alcohol consumption, individuals with the *ALDH2**2 allele show heightened physiological responses to alcohol and lower rates of drinking (Peng & Yin, 2009; Wall, 2005). In the current study, a positive association between implicit drinking motives and alcohol use was found for individuals with the *ALDH2**1/*1 genotype, but not for individuals with the *ALDH2**2 variant. A parsimonious interpretation of this finding is that, due to the anticipation of aversive responses to alcohol, individuals with *ALDH2**2 are less likely to drink in response to reflexive cognitive processes and/or more likely to recruit controlled executive processes in the context of drinking opportunities. Consistent with these ideas, *ALDH2**2 has been related to weaker self-reported drinking motives and higher self-efficacy for abstaining from alcohol (Hendershot et al., 2010).

Consistent with previous work, *ALDH2**2 predicted lower rates of alcohol use in these analyses. In contrast, associations of *COMT* with drinking outcomes were limited to a non-significant trend for Met carriers to report more drinks per week. Additionally, neither *COMT* nor *ALDH2* showed direct associations with implicit drinking motives. These findings suggest that future studies should examine moderating as well as direct genetic associations in the context of implicit cognitions. The present findings also suggested significant (albeit inconsistent) associations of implicit motives with drinking outcomes, suggesting that implicit measures of two commonly studied drinking motives (i.e., coping and enhancement motives) could be useful for predicting drinking behavior. Although implicit measures of alcohol cognitions are sometimes found to predict alcohol use only among heavy drinkers (reviewed in Field, 2006; Wiers et al., 2007), the current results suggest that these measures could be sensitive to variation in drinking behavior in samples with relatively moderate drinking rates.

Several limitations to this study should be considered. First, the use of a relatively small sample reduces power for detecting genetic associations. As a possible consequence of low power, the significant interaction effects observed in the current study were modest. While the direction of interaction effects appeared consistent across models, the most consistent significant effects were limited to analyses that focused on coping motives. Also, associations of implicit motives with drinking outcomes were not entirely uniform across analyses. It should also be noted that interpretations of moderating effects for *COMT* and *ALDH2* are tentative in the absence of more detailed behavioral data. For instance, while we interpreted the moderating effects of *COMT* in the context of prior work showing genetic differences on measures of executive functioning, executive functioning measures were not included in this study. An additional limitation is the use of a cross-sectional design. Without experimental and/or prospective data, the possibility that drinking has a causal effect on implicit measures (rather than vice versa) cannot be ruled out. Finally, although

findings concerning *COMT* could potentially generalize to other populations, findings concerning *ALDH2* cannot be extended to most populations because *ALDH2*2* is exclusive to northeast Asian groups. Overall, it should be emphasized that the present findings are by definition preliminary given the small number of published studies evaluating genetic influences on alcohol-related cognitions and the availability of only one prior study examining genetic influences on implicit measures (Wiers et al., 2009). Thus, the current analyses are in some ways exploratory and replication of these findings will be important before drawing conclusions from the current results.

These limitations considered, the current findings are among the first to evaluate genetic associations with implicit alcohol cognitions. One avenue for future studies is to consider additional variants implicated in working memory, attentional processing and response inhibition (Bellgrove & Mattingley, 2008; Goldberg & Weinberger, 2004), as well those relevant for alcohol-related reward and/or sensitivity, in the context of dual process models. Notably, contemporary models of addiction propose that repeated drug use renders behavior increasingly responsive to reflexive processes and less amenable to the influence of inhibitory control networks (Baler & Volkow, 2006). Therefore, an interesting prospect for future work is to evaluate, prospectively, whether genetic variants moderate the development of drug-related reflexive cognitive processes as a function of repeated drug exposure. Finally, it is anticipated that the refinement of dual process models of addiction will be informative for interventions, which could potentially seek to alter the salience of reflexive drug-related cognitions or mitigate their impact by strengthening executive control processes (e.g., Houben et al., 2010; Volkow et al., 2010). Characterizing genetic influences in this context could aid in studying neurobiological processes that may be relevant for treatment development and response.

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References

- Baler RD, Volkow ND. Drug addiction: the neurobiology of disrupted self-control. *Trends Mol Med.* 2006; 12:559–566. [PubMed: 17070107]
- Barrett LF, Tugade MM, Engle RW. Individual differences in working memory capacity and dual-process theories of the mind. *Psychol Bull.* 2004; 130:553–573. [PubMed: 15250813]
- Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci.* 2005; 8:1458–1463. [PubMed: 16251988]
- Bellgrove MA, Mattingley JB. Molecular genetics of attention. *Ann N Y Acad Sci.* 2008; 1129:200–12. [PubMed: 18591481]
- Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology.* 2004; 29:1943–1961. [PubMed: 15305167]
- Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: The effects of social interaction and model status on the self-administration of alcohol. *Journal Consult Clin Psychol.* 1985; 53:189–200.
- Congdon E, Constable RT, Lesch KP, Canli T. Influence of *SLC6A3* and *COMT* variation on neural activation during response inhibition. *Biol Psychol.* 2009; 81:144–152. [PubMed: 19482231]
- Cooper ML, Frone MR, Russell M, Mudar P. Drinking to regulate positive and negative emotions: A motivational model of alcohol use. *J Pers Soc Psychol.* 1995; 69:990–1005. [PubMed: 7473043]

- Dreher J-C, Kohn P, Kolachana B, Weinberger D, Berman KF. Variation in dopamine genes influences responsivity of the human reward system. *Proc Natl Acad Sci USA*. 2009; 106:617–622. [PubMed: 19104049]
- Enoch MA. Genetic and environmental influences on the development of alcoholism: Resilience vs. risk. *Ann NY Acad Sci*. 2006; 1094:193–201. [PubMed: 17347351]
- Field, M. Attentional biases in drug abuse and addiction: Cognitive mechanisms, causes, consequences, and implications. In: Munafo, MR.; Albery, IP., editors. *Cognition and Addiction*. Oxford: Oxford University Press; 2006.
- Finn PR, Rickert ME, Miller MA, Lucas J, Bogg T, Bobova L, Cantrell H. Reduced cognitive ability in alcohol dependence: Examining the role of covarying externalizing psychopathology. *J Abnorm Psychol*. 2009; 118:100–116. [PubMed: 19222318]
- Foroud T, Wetherill LF, Dick DM, Hesselbrock V, Nurnberger JI, Kramer J, Tischfield J, Schuckit M, Bierut LJ, Xuei X, Edenberg HJ. Lack of association of alcohol dependence and habitual smoking with catechol-O-methyltransferase. *Alcohol Clin Exp Res*. 2007; 31:1773–1779. [PubMed: 17850222]
- Frank MJ, Doll BB, Oas-Terpstra J, Moreno F. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. *Nat Neurosci*. 2009; 12:1062–1068. [PubMed: 19620978]
- Goldberg TE, Weinberger DR. Genes and the parsing of cognitive processes. *Trends Cogn Sci*. 2004; 8:325–335. [PubMed: 15242692]
- Greenwald, AG. Generic IAT zipfile download. Implicit Association Test programming code, SPSS syntax for data analysis, and instructions. 2006. Retrieved from http://faculty.washington.edu/agg/iat_materials.htm
- Greenwald AG, McGhee DE, Schwartz JLK. Measuring individual differences in implicit cognition: The implicit association test. *J Pers Soc Psychol*. 1998; 74:1464–1480. [PubMed: 9654756]
- Greenwald AG, Nosek BA, Banaji MR. Understanding and using the Implicit Association Test: I. An improved scoring algorithm. *J Pers Soc Psychol*. 2003; 85:197–216. [PubMed: 12916565]
- Grenard JL, Ames SL, Wiers RW, Thush C, Sussman S, Stacy AW. Working memory capacity moderates the predictive effects of drug-related associations on substance use. *Psychol Addict Behav*. 2008; 22:426–432. [PubMed: 18778136]
- Heinz A, Smolka MN. The effects of catechol O-methyltransferase genotype on brain activation elicited by affective stimuli and cognitive tasks. *Rev Neurosci*. 2006; 17:359–367. [PubMed: 16878403]
- Hendershot CS, Collins SE, George WH, Wall TL, McCarthy DM, Liang TB, Larimer ME. Associations of *ALDH2* and *ADH1B* genotypes with alcohol-related phenotypes in Asian young adults. *Alcohol Clin Exp Res*. 2009; 33:839–847. [PubMed: 19298323]
- Hendershot CS, Witkiewitz K, George WH, Wall TL, Liang T, Larimer ME. Evaluating a cognitive model of *ALDH2* and drinking behavior. *Alcohol Clin Exp Res*. 2010 Epub ahead of print.
- Herz A. Endogenous opioid systems and alcohol addiction. *Psychopharmacology*. 1997; 129:99–111. [PubMed: 9040115]
- Hofmann W, Friese M, Strack F. Impulse and self-control from a dual-systems perspective. *Perspect Psychol Sci*. 2009; 4:162–176.
- Houben K, Havermans RC, Wiers RW. Learning to dislike alcohol: Conditioning negative implicit attitudes toward alcohol and its effect on drinking behavior. *Psychopharmacology*. 2010; 211:79–86. (Epub ahead of print). [PubMed: 20431994]
- Houben K, Wiers RW. Response inhibition moderates the relationship between implicit associations and drinking behavior. *Alcohol Clin Exp Res*. 2009; 33:626–633. [PubMed: 19183132]
- Kalivas PW, Volkow ND. The neural basis of addiction: A pathology of motivation and choice. *Am J Psychiatry*. 2005; 162:1403–1413. [PubMed: 16055761]
- Kauhanen J, Hallikainen T, Tuomainen TP, Koulu M, Karvonen MK, Salonen JT, Tiihonen J. Association between the functional polymorphism of catechol-O-methyltransferase gene and alcohol consumption among social drinkers. *Alcohol Clin Exp Res*. 2000; 24:135–139. [PubMed: 10698363]

- Kuntsche E, Knibbe R, Gmel G, Engels R. Why do young people drink? A review of drinking motives. *Clin Psychol Rev.* 2005; 25:841–861. [PubMed: 16095785]
- Lindgren, KP.; Hendershot, CS.; Neighbors, C.; Blaney, JA.; Otto, JM. Implicit alcohol motives predict unique variance in drinking among Asian-American college students. 2010. Manuscript under review
- Lindgren, KP.; Neighbors, C.; Ostafin, BD.; Mullins, PM.; George, WH. *J Stud Alcohol Drugs.* Vol. 70. 2009. Automatic alcohol associations: Gender differences and the malleability of alcohol associations following exposure to a dating scenario; p. 583-592.
- Miranda R, Ray L, Justus A, Meyerson LA, Knopik VS, McGeary J, Monti PM. Initial evidence of an association between OPRM1 and adolescent alcohol misuse. *Alcohol Clin Exp Res.* 2010; 34:112–122. [PubMed: 19860800]
- National Institute on Alcohol Abuse and Alcoholism. Task force on recommended questions of the National Council on Alcohol Abuse and Alcoholism: Recommended sets of alcohol consumption questions. 2003. Retrieved from <http://www.niaaa.nih.gov/Resources/ResearchResources/TaskForce.htm>
- Neuhaus AH, Opgen-Rhein C, Urbanek C, Hahn E, Ta TMT, Seidelsohn M, Strathmann S, Kley F, Wieseke N, Sander T, Dettling M. *COMT* Val(158)Met polymorphism is associated with cognitive flexibility in a signal discrimination task in schizophrenia. *Pharmacopsychiatry.* 2009; 42:141–144. [PubMed: 19585392]
- Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val(158)Met polymorphism in schizophrenia: Differential effects of Val and Met alleles on cognitive stability and flexibility. *American Journal of Psychiatry.* 2004; 161:359–361. [PubMed: 14754787]
- Opgen-Rhein C, Neuhaus AH, Urbanek C, Hahn E, Sander T, Dettling M. Executive attention in schizophrenic males and the impact of *COMT* Val(108/158)Met genotype on performance on the attention network test. *Schizophr Bull.* 2008; 34:1231–1239. [PubMed: 18199630]
- Oroszi G, Goldman D. Alcoholism: genes and mechanisms. *Pharmacogenomics.* 2004; 5:1037–1048. [PubMed: 15584875]
- Peng GS, Yin SJ. Effect of the allelic variants of aldehyde dehydrogenase *ALDH2*2* and alcohol dehydrogenase *ADH1B*2* on blood acetaldehyde concentrations. *Hum Genom.* 2009; 3:121–127.
- Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (*OPRM1*) and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res.* 2004; 28:1789–1795. [PubMed: 15608594]
- Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple endpoint adjustments methods in clinical trials. *Stat Med.* 1997; 16:2529–2542. [PubMed: 9403954]
- Schmack K, Schlagenhaut F, Sterzer P, Wrase J, Beck A, Dembler T, Kalus P, Puls I, Sander T, Heinz A, Gallinat J. Catechol-O-methyltransferase val¹⁵⁸met genotype influences neural processing of reward anticipation. *Neuroimage.* 2008; 42:1631–1638. [PubMed: 18634888]
- Thush C, Wiers RW, Ames SL, Grenard JL, Sussman S, Stacy AW. Interactions between implicit and explicit cognition and working memory capacity in the prediction of alcohol use in at-risk adolescents. *Drug Alcohol Depend.* 2008; 94:116–124. [PubMed: 18155856]
- Tiihonen J, Hallikainen T, Lachman H, Saito T, Volavka J, Kauhanen J, Salonen JT, Ryyanen OP, Koulou M, Karvonen MK, Pohjalainen T, Syvalahti E, Hietala J. Association between the functional variant of the catechol-O-methyltransferase (*COMT*) gene and type 1 alcoholism. *Mol Psychiatry.* 1999; 4:286–289. [PubMed: 10395222]
- Truett GE, Heeger P, Mynatt RL, Truett AA, Walker JA, Warman ML. Preparation of PCR-quality mouse genomic DNA with hot sodium hydroxide and tris (HotSHOT). *Biotechniques.* 2000; 29:52–54. [PubMed: 10907076]
- Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val(158)Met and beyond. *Biol Psychiatry.* 2006; 60:141–151. [PubMed: 16476412]
- Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage.* 2010; 43:2536–2543. [PubMed: 19913102]
- Wall TL. Genetic associations of alcohol and aldehyde dehydrogenase with alcohol dependence and their mechanisms of action. *Ther Drug Monit.* 2005; 27:700–703. [PubMed: 16404797]

- Wang T, Franke P, Neidt H, Cichon S, Knapp M, Lichtermann D, Maier W, Propping P, Nothen MM. Association study of the low-activity allele of catechol-O-methyltransferase and alcoholism using a family-based approach. *Mol Psychiatry*. 2001; 6:109–111. [PubMed: 11244495]
- Wiers RW, Bartholow BD, van den Wildenberg E, Thush C, Engels R, Sher KJ, Grenard J, Ames SL, Stacy AW. Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. *Pharmacol Biochem Behav*. 2007; 86:263–283. [PubMed: 17116324]
- Wiers RW, Rinck M, Dictus M, Van den Wildenberg E. Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele. *Genes Brain Behav*. 2009; 8:101–106. [PubMed: 19016889]
- Winterer G, Weinberger DR. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends in Neurosci*. 2004; 27:683–690.
- Wojnar M, Brower KJ, Strobbe S, Ilgen M, Matsumoto H, Nowosad I, Sliwerska E, Burmeister M. Association between Val66Met brain-derived neurotrophic factor (BDNF) gene polymorphism and post-treatment relapse in alcohol dependence. *Alcohol Clin Exp Res*. 2009; 33:693–702. [PubMed: 19170664]
- Yacubian J, Sommer T, Schroeder K, Gläscher J, Kalisch R, Leuenberger B, Braus DF, Büchel C. Gene-gene interaction associated with neural reward sensitivity. *Proc Natl Acad Sci USA*. 2007; 104:8125–8130. [PubMed: 17483451]

Figure 1. Interactions of genotype with IAT score predicting drinking behaviors. Plotted lines represent IAT scores one standard deviation above (high) or below (low) the mean as a function of genetic variant.

Table 1
Descriptive statistics and correlations of drinking variables, IAT scores, and genetic factors.

Measure	M	SD	1	2	3	4	5	6	7
1. Drinks per week	4.52	4.30	--	0.77***	0.78***	0.36**	0.28*	-0.44**	0.17
2. Heavy drinking episodes	1.34	1.97	--	--	0.63***	0.38**	0.28*	-0.43**	0.11
3. Peak lifetime drinks	8.29	4.92	--	--	--	0.35**	0.18	-0.44**	0.12
4. Cope IAT	-0.39	0.38	--	--	--	--	0.47***	-0.11	-0.11
5. Enhance IAT	0.08	0.43	--	--	--	--	--	-0.20	0.00
6. <i>ALDH2</i>	--	--	--	--	--	--	--	--	-0.13
7. <i>COMT</i>	--	--	--	--	--	--	--	--	--

Notes: Positive IAT scores indicate stronger alcohol-cope associations and stronger alcohol-enhance associations. Dummy-coded variables: *ALDH2* (0 = *ALDH2**1/*1, 1 = *ALDH2**1/*2), *COMT* (0 = Val/Val, 1 = Val/Met or Met/Met).

*
p < .05.
**
p < .01.
***
p < .001.

Table 2

Regressions examining drinking as a function of gender, ethnicity, genotype, and cope IAT.

Predictor	Drinks per Week				Heavy Drinking Episodes				Peak Lifetime Drinks			
	B	S.E.	t	p	B	S.E.	t	p	B	S.E.	t	p
<i>ALDH2</i>												
Gender	-0.56	0.99	-0.56	.578	0.47	0.47	1.00	.324	-0.77	1.10	-0.70	.486
Ethnicity	1.33	1.07	1.24	.221	-0.22	0.51	-0.44	.664	2.41*	1.18	2.04	.047
<i>ALDH2</i>	-3.15**	0.97	-3.24	.002	-1.68**	0.46	-3.65	.001	-3.42**	1.08	-3.18	.003
Cope IAT	6.46**	1.89	3.42	.001	3.30**	0.89	3.70	.001	7.24**	2.09	3.47	.001
<i>ALDH2</i> × Cope	-5.54*	2.59	-2.14	.037	-2.67*	1.22	-2.18	.034	-6.66*	2.86	-2.33	.024
<i>COMT</i>												
Gender	-1.45	0.99	-1.47	.148	0.06	0.50	0.12	.908	-1.64	1.15	-1.43	.159
Ethnicity	2.03 [†]	1.09	1.86	.069	0.32	0.55	0.58	.565	3.68**	1.27	2.90	.006
<i>COMT</i>	1.96 [†]	1.01	1.95	.057	0.74	0.51	1.46	.152	1.85	1.17	1.57	.122
Cope IAT	0.83	1.75	-0.47	.638	0.70	0.89	0.79	.423	1.14	2.03	0.56	.578
<i>COMT</i> × Cope	6.69*	2.54	2.64	.011	2.72*	1.29	2.11	.040	5.86 [†]	2.96	1.98	.053

Notes: Cope IAT scores were grand mean-centered. Dummy-coded variables: gender (0 = male, 1 = female), ethnicity (0 = Chinese, 1 = Korean), ALDH2 (0 = ALDH2*/1/*1, 1 = ALDH2*/1/*2), COMT (0 = Val/Val, 1 = Val/Met or Met/Met).

**
p < .01.

*
p < .05.

[†]
p < .10.

Table 3

Regressions examining drinking as a function of gender, ethnicity, genotype, and enhance IAT.

Predictor	Drinks per Week				Heavy Drinking Episodes				Peak Lifetime Drinks			
	B	S.E.	t	p	B	S.E.	t	p	B	S.E.	t	p
<i>ALDH2</i>												
Gender	−0.95	1.06	−0.90	.373	0.19	0.52	0.38	.709	−1.48	1.22	−1.22	.228
Ethnicity	2.03	1.13	1.80	.078	0.15	0.55	0.27	.788	3.31*	1.30	2.55	.014
<i>ALDH2</i>	−2.94**	1.07	−2.74	.008	−1.55	0.53	−2.94	.005	−3.16*	1.23	−2.56	.014
Enhance IAT	3.50*	1.67	2.10	.041	1.46	0.82	1.79	.080	2.19	1.92	1.14	.259
<i>ALDH2</i> × Enhance	−3.31	2.46	−1.35	.184	−1.18	1.20	−0.99	.329	−2.25	2.83	−0.80	.429
<i>COMT</i>												
Gender	−1.66	1.05	−1.58	.120	−0.07	0.54	−0.13	.896	−1.92	1.26	−1.53	.133
Ethnicity	2.29	1.15	2.00	.052	0.51	0.59	0.87	.391	4.16*	1.37	3.04	.004
<i>COMT</i>	1.82†	1.07	1.70	.096	0.62	0.56	1.12	.269	1.53	1.28	1.20	.237
Enhance IAT	0.14	1.58	0.09	.928	0.54	0.82	0.66	.515	0.50	1.88	0.27	.791
<i>COMT</i> × Enhance	5.16*	2.40	2.34	.023	1.67	1.24	1.35	.184	3.22	2.86	1.12	.267

Notes: Enhance IAT scores were grand mean-centered. Dummy-coded variables: gender (0 = male, 1 = female), ethnicity (0 = Chinese, 1 = Korean), ALDH2 (0 = ALDH2*/1/*1, 1 = ALDH2*/1/*2), COMT (0 = Val/Val, 1 = Val/Met or Met/Met).

**
p < .01.

*
p < .05.

†
p < .10.