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Adverse Effect of Catechol-O-Methyltransferase (COMT) Val158Met Met/Met Genotype in Methamphetamine-related Executive Dysfunction

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Abstract

Introduction: The Val allele of the Val158Met single-nucleotide polymorphism of the catechol-o-methyltransferase gene (*COMT*) confers greater catabolism of dopamine (DA) in the prefrontal cortex (PFC) than the Met allele. Met/Met homozygotes typically outperform Val-carriers on tests of executive function (EF), perhaps resulting from increased DA bioavailability. Methamphetamine (METH) causes large releases of DA, which is associated with neurotoxicity and executive dysfunction in chronic METH users. We hypothesized that, contrary to its effect in non-METH-using populations, slower DA clearance conferred by Met/Met will relate to worse EF in METH users.

Methods: 149 non-Hispanic White men, stratified by METH dependence (METH+/−) and *COMT* (Val/Val, Val/Met, Met/Met), completed three tests of EF: Wisconsin Card Sorting Test (WCST), Stroop Color-Word Test (Stroop), and Trail Making Test Part B (Trails B). Demographically-adjusted test scores were averaged to create an EF composite T-score. We examined the interaction of METH and *COMT* on the EF composite and individual test T-scores, controlling for premorbid functioning and alcohol use.

Results: METH group differences in EF were evident only among Met/Met carriers (beta = −9.36, p <.001) but not among Val carriers: Val/Met (beta = −1.38, p=.44) and Val/Val (beta = −4.34, p= .10). These effects were most salient on the WCST.

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Conclusions: In the pre-frontal hyperdopaminergic state triggered by methamphetamine, greater DA inactivation conferred by the Val allele may protect against METH-related executive dysfunction, suggesting genetically-driven differences in vulnerability to METH.

Keywords

COMT Val158Met; methamphetamine; executive function; dopamine; cognition

1. Introduction

Heavy, chronic methamphetamine (METH) exposure is associated with central nervous system (CNS) injury (Davidson, Gow, Lee, & Ellinwood, 2001) and neurocognitive deficits (Scott et al., 2007). Human studies in abstinent users have described deficits in executive function, attention, learning and memory, information processing speed, and motor skills (Dean, Groman, Morales, & London, 2013; Scott et al., 2007). Functions localized to the prefrontal cortex (PFC) and frontostriatal connections may be especially vulnerable to METH effects (Chang et al., 2007; Bemacer et al 2013). The PFC plays a critical role in decision-making and inhibitory control (Sakagami, Pan, & Uttl, 2006), with DA as the major neurotransmitter implicated in the evaluation of rewards, maintenance of addictive behaviors, and differences cognitive function (Starr, Fox, Harris, Deary, & Whalley, 2007; Volkow, Fowler, Wang, & Goldstein, 2002).

Although METH-associated CNS injury is evident, METH exposure parameters (e.g., age at first use, total years of use, lifetime amount consumed, route of consumption, and post-acute length of abstinence) often do not inform the degree of impairment seen among people with a history of METH dependence (Cherner et al., 2010; McCann et al., 2008). This suggests individual differences invulnerability to the effects of METH, which may result from a combination of environmental and genetic factors. Examining genetic variability may offer insight as to how individual differences contribute to risk for cognitive dysfunction in chronic METH use.

Mechanisms of METH-related injury include alterations in dopamine (DA), serotonin, GABA and glutamate systems (Halpin, Collins, & Yamamoto, 2014; McCann et al., 2008). METH principally modulates DA neurotransmission and increases extracellular DA concentrations by a number of means, which include stimulating DA release and inhibiting reuptake via the DA transporter (Lin et al 2016). In addition to dopaminergic activity in the synapse, an important mechanism of DA-related METH neurotoxicity may occur at the receptor level; for example, a recent study shows that phasic METH-indueed DA release impacts D1 DA receptor availability which is negatively associated with cortical thickness (Okita et al., 2017). While DA is critical for cognitive function, overexposure to DA in the synapse caused by stimulant exposure likely plays a role in neural compromise, including damage to DA terminals, microvascular injury, and structural and functional abnormalities on neuroimaging (Nordahl, Salo, & Leamon, 2003; Schmidt, Ritter, Sonsalla, Hanson, & Gibb, 1985). Thus, regulatory mechanisms that assist in removing DA from the synapse, play an important role in DA homeostasis in the brain (Meyer-Lindenberg etal.,2006). Catechol-O-methyltransferase (COMT), COMT accounts for more than 60% of the

metabolic degradation of released DA in the PFC (Carboni & Silvagni, 2004; Li et al., 2004; Westerink & Spaan, 1982).

A single nucleotide polymorphism (SNP) of COMT involves a Val to Met amino acid substitution at codon 158 in the membrane-bound COMT (*COMT* Val158Met). Due to 40% higher enzymatic activity of the Val compared to Met allele (Chen et al., 2004), homozygote carriers of the Val allele (Val/Val genotype) metabolize PFC DA at a more efficient rate, resulting in lower levels of DA in the synapse, whereas those with Met/Met genotype have the lowest rate of DA clearance, resulting in higher level of DA in the synapse. As METH substantially augments the concentration of extracellular DA, we hypothesized that *COMT* genotype would be a relevant predictor of brain consequences of METH exposure.

COMT Val158Met has been examined in many contexts relevant to catecholamine function. With regard to cognition, it has been linked most consistently to differences in executive function (Bruder et al., 2005; Wishart, 2011), although some controversy remains about the replicability of findings (Barnett, Scoriels, & Munafo, 2008; Goldman, Weinberger, Malhotra, & Goldberg, 2009). In healthy adults, the Val allele has been linked to executive dysfunction (Barnett, Jones, Robbins, & Muller, 2007), whereas the Met allele is associated with enhanced executive function (Barnett et al., 2007; Egan et al., 2001). Some evidence suggests this effect may be specific to men (Egan et al., 2001; Solis-Grtiz, Perez-Luque, Morado-Crespo, & Gutierrez-Munoz, 2010). The Met-associated cognitive advantage is likely due to higher DA bioavailability in the PFC resulting from slower clearance coded by Met. Other findings point to an inverted U-shape relationship between DA activity in the PFC and cognitive performance (Mattay et al., 2003; Tunbridge, Harrison, & Weinberger, 2006) such that the relationship between *COMT* and PFC function is likely to be context dependent and more complex than a simple dichotomy in which a Val allele is harmful and a Met allele is protective. For example, under conditions of DA excess, such as after METH administration, the greater metabolic activity conferred by Val alleles may be more advantageous in restoring the brain to homeostasis. In an earlier study of *COMT* Val158Met and executive dysfunction in the context of HIV disease and METH dependence, we found that, regardless of HIV status, individuals with Met/Met genotype had better executive function compared (Wallace, Gudelsky, & Vorhees, 1999) to Val carriers, except if they were METH users, and this effect did not generalize to other cognitive domains (Bousman, Chemer, Glatt, et al., 2010). Although increased bioavailability of cortical DA associated with the Met/Met genotype is thought to enhance executive function under physiologically normal conditions, in the hyperdopaminergic state induced by METH, slow DA clearance can result in neurotoxicity, possibly via DA auto-oxidation (Moszezynska & Callan, 2017; Riddle, Fleckenstein, & Hanson, 2006; Wallace et al., 1999), thus attenuating any advantage, or posing a liability for executive function in METH-using Met/Met individuals.

Here, we aim to examine whether variability in *COMT* Val158Met contributes to individual differences in executive deficits reported after heavy chronic METH exposure, with the goal to potentially identify genotype groups that are at higher risk of METH-associated executive dysfunction. In this investigation, we are focusing on a more homogenous sample than in our prior work, reducing variability associated with sex and racial background, as well as HIV status, since HIV can also affect dopaminergic circuitry. Our analyses will examine the

main and interactive effects of *COMT* genotype and METH dependence on a three-test composite of executive function (Wisconsin Card Sorting Test, Stroop Color-Word Test, and Trail Making Test Part B). Follow-up analyses will examine the effects of *COMT* genotype and METH dependence on each test of executive function. We hypothesize that, contrary to its effect in the general population, among individuals with METH dependence, slower DA clearance in the PFC conferred by the Met/Met genotype, in conjunction with METH-induced dopaminergic excess, will be associated with worse executive function, while Val carriers will show comparatively better executive function.

2. Materials and Method

2.1 Participants

Participants were 85 METH dependent and 64 non-drug dependent comparison research volunteers evaluated at the University of California, San Diego All were HIV- non-Hispanic White men. We limited our sample to a demographically narrow group for the purpose of genetic analyses, as some sex and race differences in *COMT* effects and allele frequencies have been reported (e.g., Barnett et al., 2007; González-Castro et al., 2013), and we did not have sufficient numbers of women or non-White participants to conduct separate analyses.

Participants were excluded if: (l)they met DSM-IV criteria for lifetime dependence on any drugs other than METH or cannabis within the last 5 years, or alcohol dependence within the last 12 months; (2) they reported abuse of any substances other than METH within the last 12 months, with the exception of cannabis, alcohol and nicotine, given their high prevalence in this population; or (3) they had a history of neurologic, psychiatric, or developmental disorders of sufficient severity to confound neuropsychological test results. The Wide Range Achievement Test (WRAT) version 3 or 4 reading subtest was used as an estimate of preexisting cognitive ability. Participants who had WRAT reading scores below 80 were excluded to limit the confounding contribution of preexisting low intellectual functioning.

2.2. Procedure

Participants gave written informed consent prior to enrollment and collection of neuropsychological, neuropsychiatric, medical and genetic information. HIV status was determined using enzyme linked immunosorbent assays (ELISA) with a confirmatory test. Hepatitis C status was also determined and, while slightly more frequent in METH+, hepatitis C seropositivity did not differ significantly among the *COMT* genotypes. All procedures were approved by the Human Research Protection Program at UCSD.

2.2.1 Methamphetamine Status—Participants were evaluated for methamphetamine dependence and other substance use diagnoses using the Structured Clinical Interview for DSM-IV (SCID-IV) (Spitzer, Williams, Gibbon, & First, 1995) or the Composite International Diagnostic Interview (CIDI) (Robins etal., 1988), as the study was developed prior to the DSM-5. Lifetime exposure to METH and other commonly used substances was obtained with a timeline follow-back interview.

METH+ group status was based on: (1) a DSM-IV lifetime diagnosis of METH dependence; (2) METH dependence or abuse within the past 18 months; and (3) abstinence from METH for at least 10 days based on history and supported by urine toxicology screening conducted at the time of evaluation. Non drug-dependent (METH-) participants were allowed no more than 9 lifetime instances of METH use.

2.2.2 COMT Genotyping—DNA for genotyping was isolated from 0.2 ml whole blood stored at −70°C using the Qiagen QIAamp DNA Mini Kit (Qiagen, Valencia, CA) and QiaCube Robotic workstation for automated DNA purification. The *COMT* Val158Met (rs4680)SNP was assayed using an addiction-relevant gene array (Hodgkinson et al., 2008).

All participants were genotyped for *COMT* Val158Met by standard procedures. Genotyping involved hybridization of a locus-specific oligonucleotide and two allele-specific oligonucleotides to target genomic DNA, extension and ligation reactions, followed by PCR with common dye-labeled PCR primers (the dyes corresponding to the two allele-specific oligonucleotides, respectively). The PCR products were hybridized to the universal array, and imaged using a high-resolution scanner. Finally, the images were analyzed using software for automated genotype clustering and calling within BeadStudio software.

2.2.3 Executive Function—Participants completed three tests of executive function: Wisconsin Card Sorting Test 64-item-computerized version (WCST) (Kongs SK, 2000), Stroop Color-Word Test (Stroop), and Trail Making Test Part B (Trails B). The executive function (EF) composite consisted of (1) number of perseverative responses on the WCST, reflecting untimed ability to perceive complex pattern set-shifting; (2) score obtained in 45 seconds on the Stroop Color-Word interference condition, reflecting timed ability to selectively inhibit information and manage cognitive interference; and (3) time to complete Trails B, reflecting timed ability to switch and maintain attention between ongoing sequences. Raw scores from the component tests were converted to T-scores (M = 50, SD =10) adjusted for age, education, and gender according to published test norms, and then averaged across tests to form the EF composite T-score.

2.3 Statistical Analysts

To examine the conditional effects of METH dependence and *COMT* genotype on executive function, participants were classified into one of the following six groups: METH-Val/Val (n=19), METH- Val/Met (n=29), METH- Met/Met (n=16), METH+ Val/Val (n=16), METH + Val/Met (n=49), METH+ Met/Met (n=20). *COMT* genotype distribution was consistent with Hardy-Weinberg equilibrium in the full sample ($\chi^2 = 0.33$, $p = 0.57$) and within each METH group (METH−: $\chi^2 = 0.54$, $p = 0.46$; METH+: $\chi^2 = 2.06$, $p = 0.15$). To compare background characteristics across the six groups, univariable comparisons were performed using one-way analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Variables that differed significantly across the six groups were included as covariates in primary analyses. Groups differed significantly by years of education, reading level (WRAT), days since last alcohol use, and lifetime average drinks per day. Thus, these variables (except for years of education) were included as covariates in subsequent models for executive function. Years of education was not included as a

covariate given that the outcome variables of executive function are demo graphically-adjusted for years of education.

We used multivariable linear regression analyses to examine the effects of *COMT* genotype, METH dependence, and their interaction on the executive function composite, controlling for significant covariates. *COMT* genotype was coded with Val/Met as the reference group, given that it is the largest genotype group in our analyses and the most common in the general population, including White populations (Gonzalez-Castro et al., 2013). In order to probe significant *COMT**METH interactions and assess the differential influence of each predictor on executive function, we conducted follow-up analyses stratified by *COMT* genotype and separately, stratified by METH dependence. Similar analyses examined the same predictors in multivariable linear regression analyses with the individual tests of executive function (WCST, Stroop, Trails B) as outcomes. For these three individual tests, stratified analyses that followed-up on *COMT**METH interaction effects were interpreted using a Bonferroni-adjusted α-threshold of .0167 (i.e., .05/3).

3. Results

3.1 Participant Characteristics

Participants were all non-Hispanic White men, ranged in age from 18 to 66 years old (M=38.7, SD=10.9), and had an average of 12.6 years of formal education (SD=2.3). Table 1 provides sample demographic and lifetime substance use characteristics by METH status and *COMT* genotype (Val/Val, Val/Met, Met/Met) group. Across the six groups, METH+ participants had significantly fewer years of formal education, lower WRAT reading scores, more days since last alcohol use and higher average lifetime alcohol drinks per day compared to METH- participants. Importantly, within each METH group, *COMT* genotype groups had comparable background characteristics (age, years of education, WRAT reading scores), substance use histories, and proportion of hepatitis C seropositivity (Table 1).

3.2 Effects of METH and COMT genotype on Executive Function

Table 2 presents model estimates for the multiple regression analysis predicting the executive function composite. Controlling for WRAT reading score, days since last alcohol use, and lifetime average alcohol consumption per day of use, a significant Met/Met*METH interaction ($p = .01$) was detected such that the deleterious effect of METH on executive function was only significant in the Met/Met genotype group (beta = −9.36, $p < .001$) compared to the Val/Met (beta = −1.38,$p = .44$). There was no significant Val/Val*METH interaction ($p = .34$), indicating no significant effect of METH in Val/Val (beta = −4.34, $p = .10$), comparable to the lack of METH effect in Val/Met (Figure 1). Among METH- individuals, those with Met/Met genotype [M(SD) = 53.0 (8.0)] significantly outperformed the Val/Met group [M(SD) = 47.5 (6.2); $p = .03$] and non-significantly outperformed Val/Val group [M(SD) = 50.8 (10.4); $p = .08$]. Among METH+ individuals, Met/Met [M(SD) = 44.5(6.3)] displayed non-significantly poorer performance compared to those with Val/Met [M(SD) = 45.9(8.7), $p = .63$] and Val/Val genotypes [M(SD) = 47.1(5.3), $p = .19$]. Higher WRAT scores and greater lifetime alcohol use also significantly predicted higher executive function T-scores (ps<.01).

3.3 Effects of METH and COMT genotype across Executive Function Tests

Table 3 presents model estimates for each individual executive function test. Results demonstrated that the effect of METH on WCST performance differed significantly between Met/Met and Val/Val groups (Met/Met*METH interaction: $p = .02$). Follow-up analyses indicated that the deleterious effect of METH on WCST performance was only significant in the Met/Met genotype group (beta = −9.01, $p = .002$) compared to the effects of METH in Val/Met (beta = −2.47, $p = .45$) and Val/Val groups (beta = −4.14,$p = .40$). A similar interaction effect was detected for Trails B performance (Met/Met*METH interaction: p=.03) such that the deleterious effect of METH was significantly larger in the Met/Met group (beta = −10.23, $p = .008$) compared to Val/Met (beta = −0.77,$p = .75$). Although the effect of METH on Trails B performance did not significantly differ between Val/Met and Val/Val groups (ValVal*METH interaction: p= .053); the deleterious effect of METH also reached statistical significance in Val/Val (beta = −9.01, $p = .014$). For Stroop, no significant differences in executive function emerged by *COMT* genotype, METH status, nor their interaction (Met/Met*METH interaction: p = .54).

Figure 1 depicts these relationships by plotting least squares means estimates across the six groups for the executive function composite and individual test T-scores.

4. Discussion

Our results suggest genetically influenced differences in vulnerability to METH effects on executive dysfunction. Consistent with literature, healthy participants with Met/Met genotype had better executive function performance than Val carriers, while among METH dependent individuals, the reverse was true. Moreover, the performance of METH+ Val carriers was generally indistinguishable from that of METH− Val carriers. That is, the negative effect of methamphetamine on executive dysfunction was salient only in the Met/Met group, and Val carriers tended to perform similarly irrespective of METH dependence. Under ordinary conditions, Met/Met genotype is thought to be advantageous for cognition because it results in more optimal levels of brain DA. However, among METH users, whose prefrontal cortex is serially exposed to larger than normal concentrations of DA, the Met/Met genotype may confer risk for executive dysfunction as a result of less efficient DA clearance compared to Val carriers.

In our sample, the differential influence of COMT genotype between METH+ and METH− was most salient in the WCST. The WCST functions as an index of abstract reasoning, concept formation, and response to changes in context and may be the only executive function test of our composite that is complex enough to be affected by nuanced differences in dopamine bioavailability in the PFC. For example, WCST perseverative errors have strong associations with PFC volume (Eling, Derckx, & Maes, 2008; Yuan & Raz, 2014). Kim and colleagues reported a significant decrease in the grey matter density in the PFC of abstinent METH users compared to controls, which was correlated with poor performance on the WCST (Kim et al., 2006). Chung and colleagues observed decreases in frontal white matter integrity in chronic METH users compared to healthy comparison subjects using diffusion tensor imaging (DTI) (Chung et al., 2007). They noted that these structural changes were associated with greater perseveration on the WCST. A reduction of WCST errors has also

been correlated with recovery in DA transporter binding after METH abstinence (Chou et al., 2007). Beyond WCST and executive functioning deficits, a recent study found that adult METH users had deficits in attention and memory compared to controls, relative to the cognitive performance predicted by their childhood grade point averages; furthermore, these memory deficits were associated with lower whole-brain cortical thickness on structural magnetic resonance imaging (MRI) (Dean, Morales, Hellemann, & London, 2018).

Our findings confirm and extend previous work on the relationship between *COMT* Val158Met and executive abilities in METH-dependent individuals (Bousman, Cherner, Glatt, et al., 2010). In that sample of adult men, an interaction between *COMT* genotype, METH use, and HIV status indicated that Met/Met improved executive function among non-METH using individuals, but the effect was attenuated among those with history of METH dependence. We have also reported a complex association of the Met allele with increased sexual risk-taking behavior, seen among individuals with executive dysfunction (Bousman, Cherner, Atkinson, et al., 2010).

Mattay and colleagues were the first to report that *COMT* interacts with amphetamine acutely to produce harmful effects on cognitive performance among individuals with a Met allele (Mattay et al., 2003). More recently, *COMT* Val158Met was shown to modify the response of healthy participants to acute amphetamine administration, such that presence of the Val allele was associated with poorer baseline performance on measures of attention and processing speed, and greater improvement in performance post d-amphetamine exposure (Hamidovic, Dlugos, Palmer, & de Wit, 2010). The presence of the Val allele has also been associated with better response to modafinil, when the drug has been explored in the treatment of MA dependence (Heinzerling, McCracken, Swanson, Ray, & Shoptaw, 2012). While those studies highlight the relevance of *COMT* Val158Met in the acute response to stimulants, our studies in currently abstinent methamphetamine-dependent individuals inform our understanding of the role of this SNP in the long-term sequelae of chronic methamphetamine exposure.

Examination of covariates showed that greater lifetime alcohol use predicted better executive performance, independent of the interactive effects of *COMT* and METH. Although unexpected, our observations align with prior studies demonstrating that singly addicted stimulant abusers are at increased risk for executive dysfunction compared to individuals who simultaneously abuse stimulants and alcohol (Lawton-Craddock, Nixon, & Tivis, 2003; Robinson, Heaton, & O'Malley, 1999). From a neurophysiological perspective, alcohol's vasodilatory properties (Bau, Bau, Naujorks, & Rosito, 2005; Lee et al., 1990) may be beneficial in attenuating METH-related neurovascular dysfunction (i.e., vasoconstriction, brain thermotoxicity) (Kiyatkin & Sharma, 2009). Given the known adverse consequences of heavy alcohol use (Grant, 1987), such results should be interpreted with caution until they are confirmed by studies using experimental, rather than observational, design.

This study has several limitations. For a genotype-phenotype investigation, our sample was rather small and may impact the reliability of our effect size estimates. Analyses examined a single SNP in association to executive function, which while interesting and significant, is likely one of many pathways and downstream interactions, including pharmacokinetic and

pharmacodynamic mechanisms, as well as METH metabolic pathways (Cherner et al., 2010) that may impact cognition. Additionally, the results are limited to a demographically homogeneous group and many other environmental influences were not considered. Furthermore, racial/ethnic background was assessed via self-report and we did not access ancestry-informative genetic markers. Future research will need to determine whether the results are generalizable to diverse groups. Finally, examination of DA function markers via PET imaging has been helpful in documenting brain changes in METH-related injury (McCann et al., 2008; Volkow et al., 2001). Future studies might investigate the role of COMT genotype in the relationship between METH use, DA imaging markers, and executive dysfunction.

4.1 Conclusions

Our findings point to a context-dependent relationship between *COMT* Val158Met and executive function, such that Met/Met is advantageous for healthy individuals but a liability for long-term METH users. Results support the notion that in the context of supranormal exposure to dopamine associated with methamphetamine, greater dopamine clearance conferred by Val may be protective against neural injury. If this effect is replicated and generalizable, *COMT* Val158Met genotyping could inform personalized approaches to mitigate neurocognitive sequelae in chronic METH users and help to identify populations that may be especially vulnerable to METH effects on executive function.

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Highlights

- Executive dysfunction in methamphetamine users varies by COMT Val158Met genotype
- Methamphetamine effects on executive function are seen only in Met/Met carriers
- Val carriers have similar executive function irrespective of methamphetamine use
- Slower dopamine clearance conferred by Met is a liability in methamphetamine use
- COMT-controlled prefrontal dopamine bioavailability impacts methamphetamine injury

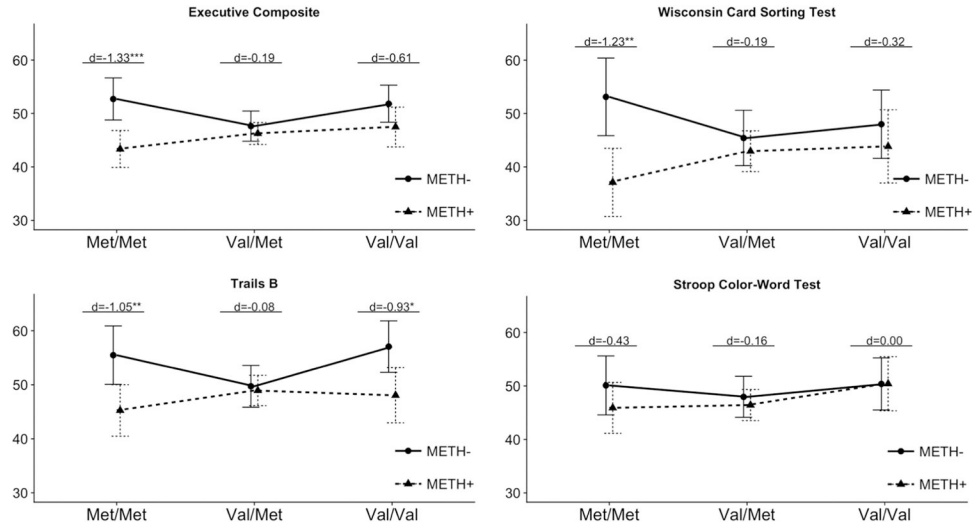

Figure 1. Adjusted means for executivefunctionT-scores by COMT x METH group.

Cohen's *d* estimates reflect the difference between METH+ and METH- participants within each *COMT* genotype. ***p<.001, **p<01, *p<.05.

Table 1:

Participant Characteristics by METH and *COMT* Status

Variable, *M(SD) or Median(IQR)*	METH− N=64 Val/Val n=19	Val/Met n=29	Met/Met n=16	METH+ N=85 Val/Val n=16	Val/Met n=49	Met/Met n=20	*p*[a]	METH− vs. METH+[b]
Age	31.8 (10.7)	39.6 (11.8)	39.9 (15.7)	38.6 (9.5)	40.4 (8.0)	38.9 (11.1)	.143	
Education	13.4 (2.4)	13.7 (1.9)	13.2 (1.8)	11.6 (1.9)	12.2 (2.4)	11.5 (2.5)	.012	METH− > METH+
Hepatitis C+, n (%)	0 (0%)	1 (3%)	1 (6%)	3 (19%)	9 (18%)	3 (15%)	.186	
WRAT Reading	106.3 (8.4)	104.3 (8.6)	108.1 (8.5)	95.5 (7.3)	99.6 (8.9)	99.5 (8.3)	<.001	METH− > METH+
Substance Use (lifetime use)								
Total Meth Exposure (lifetime grams)	–	–	–	3462 [977–11201]	3156 [1472–8406]	2840 [975–7632]	.937	
Meth Use (grams/day)	–	–	–	1.0 [0.3–1.5]	0.8 [0.6–1.7]	0.8 [0.4–1.7]	.912	
Meth Days Abstinent	–	–	–	75 [30–244]	91 [45–183]	114 [38–167]	.935	
Cannabis Use (grams/day)	0.2 [0.2–0.6]	0.2 [0.1–0.5]	0.2 [0.1–0.8]	0.5 [0.1–2]	0.4 [0.2–1]	0.4 [0.2–1.1]	.084	
Cannabis Days Abstinent	731 [35–2465]	1461 [3–4018]	548 [206–8309]	213 [82–731]	457 [114–2420]	97 [6–913]	.483	
Alcohol Use (drinks/day)	3.4 [2.3–5.6]	3.8 [2.4–5]	2.1 [1–5.3]	6.6 [4.6–8.3]	6.3 [3.3–8.8]	8.3 [4.9–16.6]	<.001	METH+ > METH−
Alcohol Days Abstinent	5 [2–93]	22 [5–639]	15 [2–221]	122 [61–548]	213 [49–875]	91 [8–183]	.003	METH+ > METH−
Tobacco Use (cig/day)	6.3 [4.9–15.8]	6.5 [5.3–16]	9.2 [4.8–16]	11.3 [5.4–18.4]	5.4 [4.8–16]	6.4 [5.3–12.5]	.665	
Tobacco Days Abstinent	22 [0–1674]	46 [0–2922]	365 [1–1826]	0 [0–7]	0 [0–7]	0 [0–0]	.262	

[a] Omnibus *p*-value for six-group comparison.

[b] Significant difference between METH− and METH+ across the entire sample.

Note. Within each METH group, there were no significant main effects of *COMT* genotype.

Table 2.

Full Multivariable Regression Model for Executive Function Composite

Variable	beta (SE)	95% CI	p
Met/Met[a]	5.08 (2.37)	[0.39, 9.77]	**0.034**
Val/Val[a]	4.19 (2.22)	[−0.19, 8.58]	0.061
METH+[b]	−1.38 (1.77)	[−4.88, 2.13]	0.439
Met/Met*METH+	−7.98 (3.13)	[−14.18, −1.78]	**0.012**
Val/Val *METH+	−2.96 (3.07)	[−9.04, 3.11]	0.336
WRAT[c]	0.27 (0.07)	[0.12, 0.41]	<**0.001**
Days Since Last Drink	0.00 (0.00)	[0.00, 0.00]	0.300
Alcohol Use[d]	0.36 (0.13)	[0.10, 0.62]	**0.007**

[a]Comparedto Val/Met

[b]Compared to METH−

[c]Wide-Range Achievement Test reading subtest

[d]Lifetime average drinks per day

Table 3.

Model Estimates for Individual Executive Function Test T-scores

	Wisconsin Card Sorting Test			Trails B			Stroop Color-Word Test		
Variable	**beta (SE)**	**95% CI**	**p**	**beta (SE)**	**95% CI**	**p**	**beta (SE)**	**95% CI**	**p**
Met/Met[a]	7.71 (4.37)	[−0.94, 16.36]	0.080	5.76 (3.26)	[−0.69, 12.21]	0.079	2.14 (3.3)	[−4.39, 8.68]	0.518
Val/Val[a]	2.58 (4.08)	[−5.5, 10.66]	0.529	7.35 (3.04)	[1.33, 13.37]	**0.017**	2.42 (3.08)	[−3.68, 8.52]	0.434
METH+[b]	−2.47 (3.29)	[−8.98, 4.03]	0.453	−0.77 (2.44)	[−5.59, 4.04]	0.751	−1.53 (2.44)	[−6.36, 3.31]	0.533
Met/Met*METH+	−13.53 (5.77)	[−24.96, −2.1]	**0.021**	−9.46 (4.30)	[−17.97, −0.94]	**0.030**	−2.67 (4.36)	[−11.3, 5.96]	0.542
Val/Val*METH+	−1.67 (5.66)	[−12.87, 9.52]	0.768	−8.24 (4.22)	[−16.58, 0.11]	0.053	1.56 (4.25)	[−6.85, 9.97]	0.714
WRAT[c]	0.19 (0.14)	[−0.08, 0.45]	0.174	0.24 (0.1)	[0.04, 0.44]	**0.018**	0.38 (0.1)	[0.18, 0.58]	**<0.001**
Days Since Last Drink	0.00 (0.00)	[0.00, 0.00]	0.868	0.00 (0.00)	[0.00, 0.00]	0.723	0.00 (0.00)	[0.00, 0.00]	0.111
Alcohol Use[d]	0.60 (0.24)	[0.11, 1.08]	**0.016**	0.41 (0.18)	[0.05, 0.77]	**0.027**	0.21 (0.19)	[−0.18, 0.59]	0.284

[a] Compared to Val/Met

[b] Compared to METH−

[c] Wide-Range Achievement Test reading subtest

[d] Lifetime average drinks per day