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COMT Val158Met Genotype Alters the Effects of Methamphetamine Dependence on Dopamine and Dopamine-related Executive Function: Preliminary Findings

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Abstract

The Met allele of the *COMT* Val158Met polymorphism slows metabolism and increases bioavailability of dopamine (DA) in the prefrontal cortex compared to the Val allele. Healthy Met-carriers outperform Val-carriers on executive function (EF) tests, yet this 'advantage' disappears in methamphetamine (METH) dependence. Met-carriers may be disproportionately vulnerable to METH-related perturbations of DA, yet it is unknown whether *COMT* modulates METH effects on CSF DA biomarkers. Participants were 75 METH+ and 47 METH- men who underwent neurocognitive testing, *COMT* genotyping, and lumbar puncture. CSF was assayed for DA and its metabolite, homovanillic acid (HVA). Separate linear models regressed DA, HVA, and HVA/DA ratios on *COMT*, METH and their interaction. Pearson correlations examined associations between DA and EF. Significant interactions indicated that METH+ had lower DA and higher HVA/DA ratios among Met/Met, but not Val/Met or Val/Val. Met/Met exhibited the highest DA levels among METH-, whereas DA levels were comparable between Met/Met and Val-carriers among METH+. Higher DA correlated with better EF in METH- Met/Met, but did not predict EF

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Author Statement

R.S., M.C. and R.J.E. conceptualized and designed the study. R.S. conducted statistical analyses and wrote the manuscript draft. E.E.S. and C.W.W. assisted with drafting the manuscript. A.K. oversaw dopamine assays and J.E.I. and S.L.L. assisted with interpretation of biomarker data. All authors contributed to data interpretation, revised the manuscript for intellectual content, and approved the final manuscript.

Declaration of Competing Interest

None.

in the entire sample. DA was expectedly higher in METH- Met/Met, yet a discordant genotype-phenotype profile emerged in METH+ Met/Met, consistent with the notion that slow DA clearance exacerbates METH-associated DA dysregulation.

Keywords

dopamine; homovanillic acid; catechol-o-methyltransferase; methamphetamine; executive function; prefrontal cortex

1. Introduction

Repeated, heavy exposure to methamphetamine (METH) is associated with central nervous system (CNS) dysfunction across multiple neurotransmitter systems, including dopamine (DA), serotonin, GABA, and glutamate (Halpin et al., 2014). METH exerts particularly potent effects on the dopaminergic (DAergic) system by acting on the vesicular monoamine transporter (VMAT-2) and DA transporter (DAT) to stimulate release of DA from presynaptic vesicles and inhibit its reuptake, resulting in excessive levels of synaptic DA (Davidson et al., 2001). DA is highly active in frontostriatal pathways and DAergic excess disrupts frontal cortical circuitry that regulates motivation, self-control, decision-making and executive function, thereby perpetuating the cycle of addiction (Volkow et al., 2002). METH-dependence is linked to negative neurocognitive outcomes in domains supported by frontostriatal structures, including learning, memory, executive function, attention/working memory, and cognitive control (Salo et al., 2009; Scott et al., 2007). Cross-sectional brain imaging studies of METH exposure demonstrate lower gray matter volumes and greater white matter abnormalities in frontostriatal and limbic regions such as the striatum, amygdala, hippocampus, and the prefrontal cortex (PFC; Berman et al., 2008; Salo and Fassbender, 2011). Positron emission tomography (PET) studies, which have enabled *in vivo* and regionally-specific evaluation of DAergic activity, provide evidence of DAergic dysfunction in METH users across a number of molecular markers (e.g., DAT, D_2 receptor availability, and VMAT-2) in both the striatum and PFC (Ashok et al., 2017; Sekine et al., 2001; Volkow et al., 2001a). Notably, this DAergic dysregulation correlates with markers of neurobehavioral dysfunction, including psychomotor and memory impairment, impulsivity, and psychiatric distress (Lee et al., 2009; Sekine et al., 2001; Sekine et al., 2003; Volkow et al., 2001b).

While adverse neurocognitive findings are frequently observed in METH users, METH use is not always associated with neurocognitive impairment and the reasons for this heterogeneity are unknown (Dean et al., 2013). Therefore, a major area of research interest lies in determining what factors may attenuate or exacerbate risk for METH-related CNS dysfunction and associated neurocognitive deficits. Thus far, investigations of a dose-dependent relationship with greater METH exposure leading to more severe neurocognitive deficits have resulted in null findings (Dean et al., 2013). Self-reported duration of METH use, frequency of use, length of abstinence, and cumulative lifetime exposure do not predict neurocognitive performance (Cherner et al., 2010b; Johanson et al., 2006). While parameters of drug exposure show little predictive value, individual differences in genetic and

environmental factors may account for considerable variability in risk for METH-related neurocognitive deficits (Cherner et al., 2010a; Compton et al., 2005; Volkow, 2005). Identifying genetic variations that influence an individual's vulnerability to METH effects can inform personalized approaches to mitigate METH-related neurocognitive impairment.

The catechol-*O*-methyltransferase (COMT) enzyme is implicated in DA neurotransmission in the PFC, and specifically assists in regulating clearance of DA from the synapse via metabolic degradation (Li et al., 2004; Meyer-Lindenberg et al., 2006). Functional variation in the *COMT* gene occurs at a single nucleotide polymorphism (SNP) resulting in a valine (Val) to methionine (Met) amino acid substitution (Val158Met). Compared to the Val allele, the Met allele is associated with reduced thermostability and enzymatic activity, leading to slower degradation of DA at the synapse and higher DA concentration in the PFC (Egan et al., 2001; Palmatier et al., 1999). In contrast, the Val allele is associated with more efficient DA catabolism and lower levels of synaptic DA. In healthy adults, Met-carriers outperform Val-carriers on tests of PFC-dependent neurocognition, including executive function and working memory (Barnett et al., 2007; Starr et al., 2007; Wishart et al., 2011). It is hypothesized that higher DA bioavailability conferred by the Met allele underlies this Met-associated neurocognitive 'advantage' in healthy adults. However, we have previously demonstrated that in chronic METH users (both HIV-seropositive and HIV-seronegative), whose PFC is repeatedly exposed to excessive levels of DA, the Met/Met genotype is no longer associated with better executive function and may in fact confer risk for executive dysfunction (Bousman et al., 2010; Cherner et al., 2019).

Although these findings suggest that the Met/Met genotype confers disproportionate risk to METH-related neurocognitive dysfunction, it remains unclear whether *COMT* genotype similarly modulates the effects of METH on biomarkers that directly measure the DAergic system. Thus, the present study evaluated cerebrospinal fluid (CSF) levels of DA and its metabolite, homovanillic acid (HVA), among a cohort of adult men stratified by METH-dependence and *COMT* genotype. Additionally, relationships between CSF DA and executive function were assessed to examine the role of CSF DA as an intermediary linking the interactive effects of METH and *COMT* on neurocognitive function.

2. Methods

2.1. Participants

Participants were 75 METH-dependent (METH+) and 47 METH-non-using comparison (METH-) men enrolled in the University of California, San Diego's (UCSD) Translational Methamphetamine AIDS Research Center (TMARC), a NIDA-funded cohort study focusing on the CNS effects of HIV and METH. All participants gave written informed consent as approved by the UCSD Institutional Review Board. *COMT* genotyping in the parent study was restricted to male participants due to potential sexually-dimorphic effects of *COMT* (Tunbridge and Harrison, 2011) and inadequate numbers of female participants to support sex-stratified analyses. Exclusion criteria were: 1) DSM-IV diagnosis of other substance use dependence (except cannabis) within the last 5 years, or alcohol dependence within the last 12 months; 2) abuse of any substances (except alcohol and cannabis) other than METH within the last 12 months; 3) evidence of very recent METH use by positive urine toxicology

results; 4) history of psychotic or mood disorder with psychotic features, neurological, or medical condition that may confound neuropsychological test results.

2.2. Neuropsychiatric Assessment

Participants were evaluated for METH dependence, other substance use dependence, and Major Depressive Disorder (MDD) diagnoses using the Composite International Diagnostic Interview (CIDI; World Health Organization, 1998) or Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al., 1995), as study methodology was developed prior to the release of the DSM-5. Participants were classified as METH+ if they met DSM-IV diagnostic criteria for lifetime METH dependence and met criteria for METH dependence or abuse within the past 18 months. Lifetime METH use parameters were assessed using a timeline follow-back interview. Current depressive symptoms were measured using the Beck Depression Inventory version two (BDI-II; Beck et al., 1996).

2.3. COMT Genotyping

All participants were genotyped for *COMT* Val158Met by standard procedures. DNA for genotyping was isolated from stored whole blood or peripheral blood mononuclear cells (PBMCs) using the Qiagen QIAamp DNA Mini Kit (Qiagen, Valencia, CA). COMT Val158Met (rs4680) SNP was assayed using an array that included SNPs within catecholaminergic and other addiction-relevant genes (Hodgkinson et al., 2008).

COMT distribution across the 122 study participants was 27 (22.1%) Met/Met, 62 (50.8%) Val/Met, and 33 (27.1%) Val/Val, resulting in the following six groups: METH- Met/Met (n=12), METH- Val/Met (n=23), METH- Val/Val (n=12), METH+ Met/Met (n=15), METH + Val/Met (n=39), and METH+ Val/Val (n=21). *COMT* distribution was consistent with Hardy-Weinberg equilibrium in the full sample (χ^2=0.04, p=0.84) and within each METH group (METH-: χ^2 = 0.02, p = 0.88; METH+: χ^2 = 0.16, p = 0.69).

2.4. Dopamine Biomarker Assays

CSF DA biomarker assays were performed using high-performance liquid chromatography (HPLC), as described in detail by Kumar et al. (Kumar et al., 2009). HPLC is a reliable method for quantifying DA and HVA concentrations in CSF; Kumar et al. reported an intra-assay coefficient of variance (% CV) of 5.4% and 10.9% for DA and HVA, respectively, as well as an interassay % CV of 7.1% and 11.5% for DA and HVA, respectively (Kumar et al., 2009). DA levels were expressed as pg/ml and HVA levels were expressed as ng/ml. HVA/DA ratios were examined as a proxy for the rate of metabolism of DA into HVA, with higher ratios suggesting faster metabolism. DA, HVA, and HVA/DA ratios were log-transformed to reduce skewness and allow for parametric analysis.

2.5. Neurocognitive Assessment

Participants completed a comprehensive, validated neurocognitive battery covering ability domains commonly impacted by METH use and HIV (Rippeth et al., 2004). Raw test scores were converted to demographically-corrected standard T scores (mean of 50 and standard deviation of 10) that adjusted for the effects of age, education, sex and race/ethnicity, as appropriate (Heaton et al., 2004; Heaton et al., 2003; Norman et al., 2011). These

demographically-corrected individual test T scores were averaged within each neurocognitive ability domain to generate domain-specific T scores. Given the relevance of *COMT* to DAergic activity in the PFC (Meyer-Lindenberg et al., 2006) and our prior findings that *COMT* interacts with METH status to predict executive function, secondary analyses focused on the relationship between CSF DA and executive function T scores (Cherner et al., 2019). The executive function composite was composed of the Wisconsin Card Sorting Test 64-item-computerized version, Stroop Color-Word Test, and Trail Making Test Part B.

2.6. Neuromedical Assessment

All participants underwent a comprehensive neuromedical assessment, blood draw, and lumbar puncture. HIV disease was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Among HIV+ participants, HIV viral load in plasma was measured using reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN) and deemed undetectable at a lower limit of quantitation (LLQ) of 50 copies/ml. Hepatitis C virus (HCV) serostatus was diagnosed by standard clinical antibody detection.

2.7. Statistical Analysis

METH and *COMT* group differences on background characteristics (i.e., demographics, neuropsychiatric and medical characteristics) were examined using analysis of variance (ANOVA), Wilcoxon/Kruskal-Wallis tests, and Chi-square statistics as appropriate. First, univariable analyses were conducted to examine the main effects of METH status (METH+ vs. METH-) and *COMT* genotype (Met/Met vs. Val/Met vs. Val/Val) on CSF DA biomarkers (i.e., CSF DA, HVA, and the HVA/DA ratio). Next, separate multivariable linear regression analyses modelled CSF DA biomarkers as a function of *COMT*, METH status, and their interaction. *COMT* was dummy coded with the low enzymatic activity Met/Met genotype as the reference group. In order to probe models with significant interaction terms, we conducted follow-up analyses stratified by *COMT* genotype and separately, stratified by METH group. Cohen's *d* statistics are presented for estimates of effect size for pairwise comparisons. To determine if the interactive effects of *COMT* and METH on DA biomarkers were attenuated by covariates, backward model selection guided by Akaike information criteria was applied such that final models considered covariates that differed by *COMT* or METH status at p-value < 0.10 (i.e., race/ethnicity, BDI-II, HCV serostatus, and lifetime substance use disorders [alcohol, cannabis, and cocaine]). HIV serostatus, age, antidepressant use, and time of lumbar puncture were also considered as covariates given their potential to influence DA levels. Last, group-stratified Pearson's r correlations explored the relationship between CSF DA levels and executive function domain T scores. Given constraints in statistical power due to small METH × *COMT* cell size, analyses were not adjusted for multiple comparisons and are considered preliminary. All analyses were conducted using JMP Pro version 14.0.0 (JMP®, Version <12.0.1>. SAS Institute Inc., Cary, NC, 2018)

3. Results

3.1 Participant Characteristics

The full study sample was 66% non-Hispanic White with a mean age of 39.8 years (range: 19–57) and mean education of 13.0 years. Participant characteristics by METH group are presented in Table 1. METH+ participants reported higher BDI-II scores and were more likely to have lifetime non-METH substance use disorders (i.e., alcohol, cannabis, and cocaine) and HCV. Rates of HIV seropositivity did not differ between METH+ (n=30; 64%) and METH- (n=50; 67%) groups; however, HIV-seropositive METH+ individuals had higher rates of detectable virus in plasma than HIV-seropositive METH- individuals (63% vs. 37%). METH groups were comparable on all other HIV disease and treatment characteristics as well as demographic backgrounds. *COMT* groups were also comparable across demographic, neuropsychiatric, medical, and HIV characteristics, with the exception of race/ethnicity such that the prevalence of non-Hispanic White participants increased with each copy of the Met allele (χ^2=16.0, p<.001; Val/Val [45%] vs. Val/Met [66%] vs. Met/Met [92%]).

3.2 METH, COMT, and Dopamine Biomarkers

CSF DA ranged from 0.2 to 256.1 pg/mL (median 34.0, interquartile range [IQR] 9.3–65.5) and CSF HVA ranged from 0.7 to 158.1 ng/mL (median 10.3, IQR 4.3–22.7). Table 2 presents estimates for the multivariable linear regression modelling CSF DA, HVA, and HVA/DA ratios as a function of METH, *COMT*, and their interaction. Univariably, CSF DA levels did not significantly differ by METH (t=0.14, p=.885) or *COMT* (F=1.96, p=.145). However, results indicated a significant interaction such that the effect of METH on DA significantly differed between Met/Met and Val/Met groups (METH × Val/Met (vs. Met/Met): p=.022). Figure 1 displays the results of the follow-up analyses whereby DA levels were significantly lower in METH+ individuals compared to METH- individuals only within the Met/Met group (d=−0.77, p=.050). DA levels did not significantly differ between METH + and METH- individuals for the Val/Met and Val/Val groups (ps>.220). Among the METH- group, Met/Met individuals had significantly higher DA levels compared to Val/Val (d=0.82, p=.046) and trended toward higher DA levels compared to Val/Met individuals (d = 0.62, p = .082). Among the METH+ group, Val/Met individuals trended toward higher DA levels compared to Val/Val (d=0.53, p=.051).

Univariably, a trend-level omnibus effect of *COMT* on CSF HVA was detected (F=2.67, p=.073) such that Met/Met individuals had significantly higher HVA levels compared to Val/Val (d=0.59, p=.025) and trended toward higher HVA levels compared to Val/Met individuals (d=0.40, p=.083). HVA comparisons between Val/Met and Val/Val individuals as well as between METH groups did not reach statistical significance (ps>.390). Moreover, no significant interactive effects of *COMT* and METH were detected for HVA (ps>.290).

Univariably, CSF HVA/DA ratios did not significantly differ by METH (t=0.17, p=.868) or *COMT* (F=1.41, p=.249). However, results indicated significant interactions such that the effect of METH significantly differed in Met/Met individuals compared to both Val/Met (METH x Val/Met [vs. Met/Met]: p=.015) and Val/Val individuals (METH × Val/Val [vs.

Met/Met]: p=.026). Follow-up analyses indicated that within the Met/Met group, HVA/DA ratios were significantly higher in METH+ individuals compared to METH- individuals (d=0.88, p=.025; Figure 2). Conversely, HVA/DA ratios did not significantly differ between METH+ and METH- individuals in the Val/Met and Val/Val groups (ps>.299). Among the METH- group, a stair-step pattern emerged in which Val/Val displayed the highest HVA/DA ratios followed by Val/Met then Met/Met (d range −0.59 to −0.28); however, no individual pairwise comparisons reached statistical significance (ps>.151). Among the METH+ group, Met/Met individuals displayed significantly higher HVA/DA ratios compared to Val/Met individuals (d=0.85, p=.006) and trended toward higher HVA/DA ratios compared to Val/Val individuals (d=0.60, p=.077).

Additional models employing backward selection of covariates were conducted to determine whether the interactive effects of *COMT* and METH on DA and HVA/DA ratios were better explained by clinical and demographic factors (i.e., age, race/ethnicity, HIV, HCV, BDI-II, lifetime substance use disorders [alcohol, cannabis, and cocaine], and time of lumbar puncture). For both DA and HVA/DA ratios, time of lumbar puncture was the only covariate that improved overall model fit and was therefore retained in regression models. Later time of day of lumbar puncture was significantly associated with lower DA (b=−5.23, p=.006) and higher HVA/DA ratios (b=3.68, p =.046). However, the inclusion of time of lumbar puncture did not attenuate the interactive effects of *COMT* and METH as all statistically significant terms from Table 2 remained statistically significant in these adjusted models.

3.3 Dopamine and Executive Function

Exploratory Pearson's r correlations examined the relationship between CSF DA and executive function in the entire sample and within each METH × *COMT* group. DA was not significantly related to executive function in the entire study sample (r=.12, p=.20; Figure 3A), or within groups consisting of Val-allele carriers or METH+ individuals (rs<.24, ps>.26). However, among the METH- Met/Met group, higher DA levels were significantly correlated with higher (better) executive function (r=.70 [95% CI: .16 to .91], p=.026; Figure 3B).

4. Discussion

METH-dependence and *COMT* are known to alter DAergic pathways and PFC function. To our knowledge, the present study is among the first to examine how the interaction of these genetic and environmental factors impacts levels of DA and its metabolite, HVA, in the CNS. METH was associated with lower DA levels, accompanied by higher HVA/DA ratios, only among Met/Met individuals, suggesting that *COMT* genotype may underlie inter-individual differences in vulnerability to METH effects on DAergic tone. Among METH- individuals, Met/Met genotype exhibited significant (vs. Val/Val) or trend-level (vs. Val/Met) medium-to-large effects on higher DA levels and small-to-medium effects (statistically non-significant) on lower HVA/DA ratios (proxy for slower DA metabolism), consistent with the known functional effects of the COMT enzyme (Chen et al., 2004; Slifstein et al., 2008). However, this Met/Met-related DAergic 'advantage' disappeared in METH+ individuals, which parallels our prior findings demonstrating the absence of an executive function

'advantage' in METH+ Met/Met individuals (Bousman et al., 2010; Cherner et al., 2019). Notably, the strongest associations between DA and executive function occurred within METH- Met/Met individuals, who, on average, exhibited the highest levels of DA. Our findings highlight the conditional influence of *COMT* on neurobiological and behavioral markers of PFC function in METH use, particularly in the context of HIV, with potential relevance to other neuropsychiatric conditions characterized by DA and PFC dysfunction.

The discordant *COMT* genotype/DA endophenotype profile in METH+ individuals suggests that genetically-driven metabolism of synaptic DA can alter the extent to which chronic METH exposure disrupts DAergic activity. Preclinical data demonstrate that the repeated overstimulation of DA release into the synaptic cleft due to serial METH exposure results in the auto-oxidation of DA and subsequent production of reactive oxygen species that are toxic to monoaminergic terminals in the PFC, striatum, and hippocampus (McDonnell-Dowling and Kelly, 2017; Moszczynska and Callan, 2017). In an examination of DA biomarkers in post-mortem brain tissues, Kish et al. found 50–61% reductions in striatal DA levels in chronic METH users compared to age-matched controls, yet did not observe any group differences in brain concentrations of DA metabolites, including HVA (Kish et al., 2017). The preservation of DA metabolites in the context of low DA suggests that although complete DA neuronal death is unlikely in METH use, compared to the severe loss of DA neurons in Parkinson's disease, other mechanisms such as compromised storage of vesicular DA may explain why METH reduces DA but not HVA levels (Kish et al., 2017; Pifl et al., 2014). Although we did not observe a main effect of METH on DA biomarkers, these post-mortem results agree with our findings in METH+ Met/Met individuals, who exhibited substantially lower CSF DA and higher CSF HVA/DA ratios compared to METH- Met/Met individuals.

Our results extend our previous finding that the typically-observed positive effect of the Met allele on executive function is absent among METH users (Cherner et al., 2019). Specifically, *COMT* and METH use related to CSF DA levels, which in turn related to executive function. As such, this study helps to bridge the gap in the numerous neuropsychological studies that used *COMT* as a proxy for DA levels, which may be particularly complex in medical and neuropsychiatric conditions associated with DA dysregulation such as HIV. Interestingly, it was only in the group with the highest levels of DA, the METH- Met/Met group, that we observed a strong association between higher DA levels and better executive function. Associations between DA levels and cortical function are typically interpreted within the framework of the inverted-U hypothesis. DA levels at the peak of the curve (middle of curve) are optimal for PFC-dependent neurocognition, whereas DA levels that are supraoptimal (right side of curve) or suboptimal (left side of curve) lead to poorer performance on these tasks (Cai and Arnsten, 1997; Cools and D'Esposito, 2011; Mattay et al., 2003; Zahrt et al., 1997). Our findings are in line with previous findings in the general population that the Met/Met genotype and resulting higher levels of DA are optimal for PFC-dependent neurocognition and, even within this genotype group, higher DA levels are advantageous for PFC-dependent neurocognition. However, lower DA levels that result from the Val allele in METH- individuals and from stimulant-induced injury in METH+ individuals, may be too far left of the curve to detect neurocognitive benefits of higher DA. Taken together, this pattern of results may suggest a threshold effect whereby the

neurocognitive benefits of DA are only observed when DA levels reach a certain level and DA levels in METH users fall below this threshold.

It is important to consider our results and their interpretation in the context of our sample, which partially consisted of individuals with comorbid conditions that can impact the DAergic system (e.g., HIV disease). The majority of our sample was HIV+ (66%). HIV is known to cause DA dysregulation though the release of neurotoxic viral proteins on DA neurons (Bennett et al., 1995; Itoh et al., 2000), and this DA dysregulation is associated with neurocognitive deficits (Kumar et al., 2011). Thus, METH use can be particularly detrimental to brain and neurocognitive health in HIV+ individuals due to the compounding effects of METH and HIV on the DAergic system and the related mechanisms of oxidative stress, neuroinflammation, and blood brain barrier permeability (Kumar et al., 2011; Silverstein et al., 2011). Consistent with our own findings in METH- individuals without HIV disease (Cherner et al., 2019), previous studies reported a positive effect of the Met allele on PFC-dependent neurocognition in HIV+ individuals (Bousman et al., 2010; Saloner et al., 2019; Sundermann et al., 2015); however, this effect was absent in HIV+ men with METH dependence (Bousman et al., 2010).

Interestingly, our AIC regression analysis did not identify HIV serostatus or other comorbidities (e.g., depression, lifetime alcohol and non-METH substance use disorders) as relevant predictors of DA in this sample, suggesting that METH use and *COMT* genotype are more salient modulators of the DAergic system in our study sample. Nevertheless, it is possible that the background of DA dysfunction that occurs with HIV disease and other comorbid conditions in our sample can shift the inverted-U curve and, thereby, influence the effects of *COMT* and METH on neurocognitive function. For example, neuroinflammatory-mediated dampening of DAergic signaling in cortico-striatal circuitry is a putative pathogenic mechanism of depression (Felger, 2017; Felger and Miller, 2012), which may partially underlie the higher levels of depressive symptoms in the METH+ group. These DAergic driven depressive symptoms including apathy and anhedonia may also exhibit a reciprocal relationship with addictive behaviors (Leventhal et al., 2008), particularly in METH+ individuals with extensive histories of polysubstance use (Rawson, 2013). With respect to other factors, accounting for time of lumbar puncture significantly improved overall model fit but did not attenuate the effects of *COMT* and METH on DA and HVA/DA ratios. This is consistent with the literature examining diurnal fluctuations in CSF and plasma markers of catecholaminergic function and the influence of DAergic circuitry on clock gene expression (Janssens et al., 2019; Korshunov et al., 2017; Verwey et al., 2016). Given the potential for time of CSF sampling to influence catecholamine levels, it is important that studies aim to standardize the time of CSF collection across participants and/or adjust for time of collection in analyses.

We acknowledge several limitations to these data. Cell sizes were small for a gene by environment interaction analysis, which precluded correction for multiple comparisons. Accordingly, these data should be considered preliminary and require independent confirmation. Nevertheless, our sample size was sufficient to model each *COMT* allelic variant independently and the large magnitude of effects yielded statistically significant *COMT* by METH group differences in CSF DA. Our neurocognitive analyses also limited

multiple comparisons by conservatively focusing on the domain of executive function; importantly, our findings were consistent with prior studies that used the same well-validated tests of executive function. DA biomarkers in CSF provide a novel *in vivo* window into DA function in the CNS, yet they only represent a global measurement of DA and cannot formally test hypotheses about DA function in specific brain regions. Thus, future PET imaging studies are warranted to determine regional susceptibilities (e.g., PFC vs. striatum) to the impact of *COMT* on METH-related DAergic injury. Understanding genetic risk for prefrontal dysfunction is of clinical relevance for our study sample of predominantly HIV+ men, who are at risk for developing CNS complications and neuropsychiatric disorders. However, our results may not generalize to women given previously reported sexually dimorphic effects of *COMT* genotype on COMT enzymatic activity and risk of psychiatric disorders, as well as the reciprocal relationship between the regulation of COMT and estrogens (Tunbridge and Harrison, 2011). Thus, future studies should replicate our analyses in other clinical and non-clinical samples with adequate representation of women. Similarly, the absence of genetic ancestry markers is a limitation and studies that incorporate these markers in sufficiently sized samples to allow for stratified analyses within ethnic groups would increase confidence in these findings.

From a clinical perspective, our findings bear relevance for the treatment of METH-dependence. DA agonists have been considered as a means of stabilizing DA function and promoting abstinence from METH use (Verrico et al., 2013). In a clinical trial examining the incremental efficacy of modafinil in treating METH-dependence, on top of contingency management and cognitive behavioral therapy, relapse rates were lower in modafinil vs. placebo in Val/Val homozygotes, yet modafinil did not reduce relapse rates in Met-carriers (Heinzerling et al., 2012). Additionally, low baseline D2 receptor availability and blunted striatal DA release in response to methylphenidate predicts future relapse in METH users (Wang et al., 2012). Thus, the combination of chronic METH exposure and the Met allele may result in enough DAergic injury to render treatment-seeking METH users non-responsive to the pharmacological effects of DA agonists. Given the putative contribution of DAergic deficits to relapse even after the most effective psychosocial interventions (Venniro et al., 2017), approaches that target the endogenous production of DA (e.g., exercise (Robertson et al., 2016)) may confer neurobehavioral benefits and inform precision treatments for Met-carriers who are non-responsive to pharmacotherapy.

Taken together, the present study highlights the influence of genetically-driven differences in DA metabolism on the effects of chronic METH use on DA and DA-related executive function. Our observation of lower, albeit statistically non-significant, levels of CSF DA and significantly higher CSF HVA/DA ratios in METH+ Met/Met individuals compared to METH+ Val/Met individuals challenges the widely-held assumption that the Met-allele translates into higher levels of bioavailable DA. Such an assumption may be more appropriate in healthier samples, which is supported by the stair-step pattern of higher CSF DA with each additional Met allele in the METH- group; however, careful consideration should be given when forming hypotheses and interpreting data regarding the role of *COMT* in clinical populations that are characterized by DA dysfunction (e.g., METH use, schizophrenia, Parkinson's disease, attention-deficit/hyperactivity disorder). This conditional relationship between *COMT*, METH, and DAergic activity may help explain why some

studies have failed to find consistent independent effects of *COMT* and METH on neurobehavioral outcomes.

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Highlights

- Methamphetamine (METH) alters dopamine (DA) integrity and executive function (EF)
- METH-related EF deficits are greatest in Met/Met carriers of COMT Val158Met gene
- METH+ have lower CSF DA levels than METH- only in Met/Met, but not Val-carriers
- CSF DA is highest in METH- Met/Met and only correlates with better EF in this group
- Slow DA clearance conferred by Met/Met exacerbates METH-related DA injury

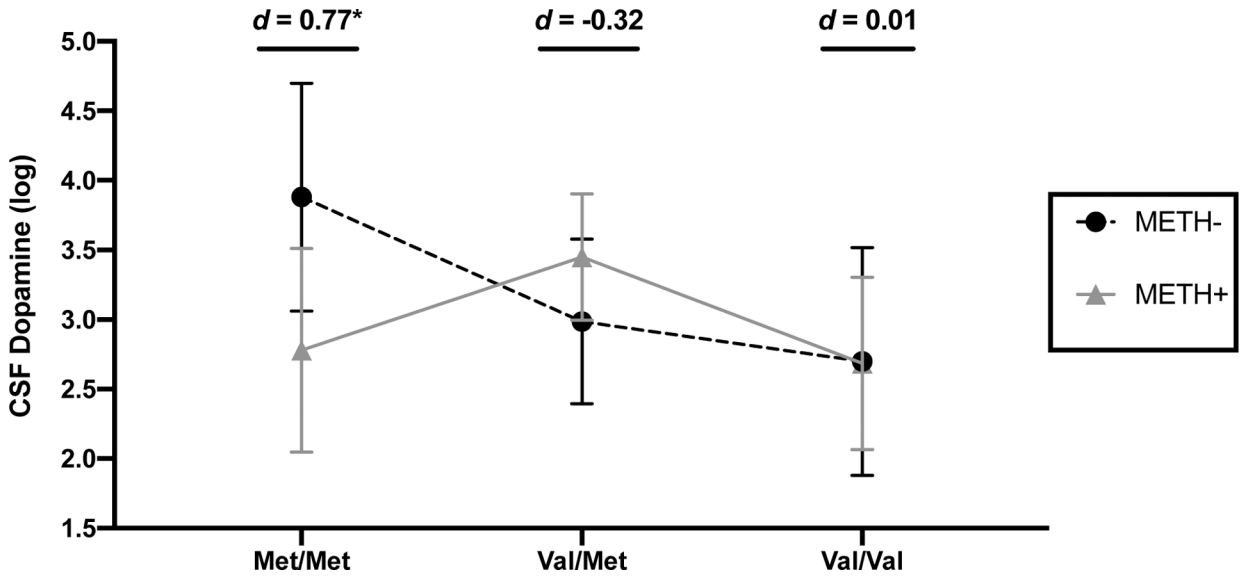

Figure 1. METH+ individuals have lower CSF dopamine levels than METH- individuals only among *COMT* Met/Met genotype carriers.

*p<.05. Error bars represent standard errors. Cohen's d estimates reflect METH+ vs.METH- group differences within each *COMT* genotype.

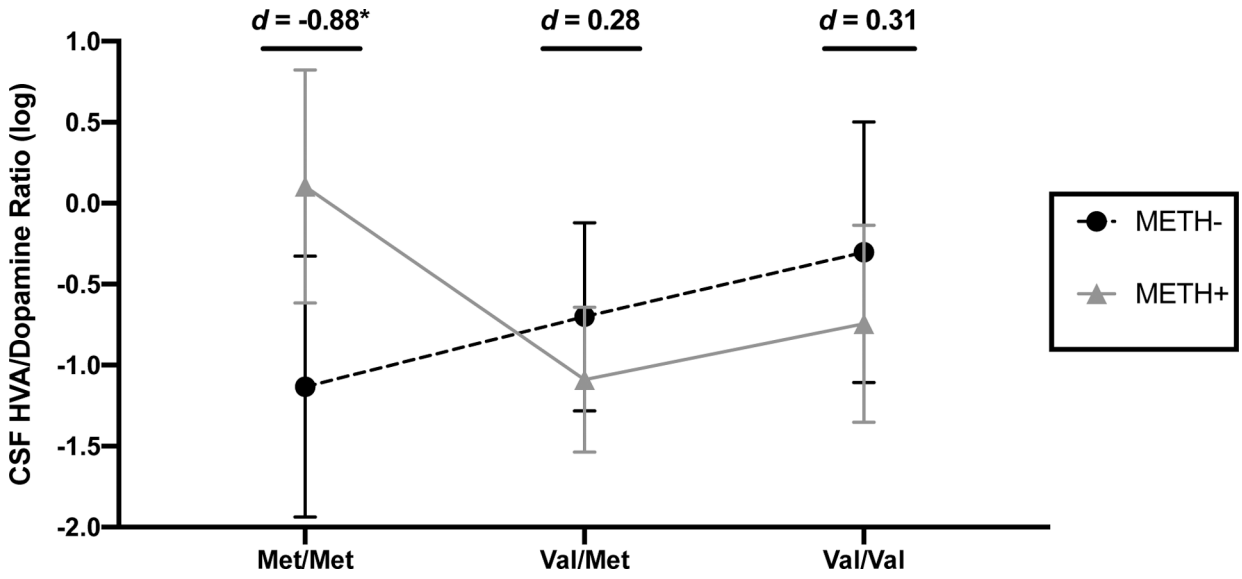

Figure 2. METH+ individuals have higher CSF homovanillic acid (HVA)/dopamine ratios than METH- individuals only among *COMT* Met/Met genotype carriers.

**p*<.05. Error bars represent standard errors. Cohen's *d* estimates reflect METH+ vs. METH- group differences within each *COMT* genotype.

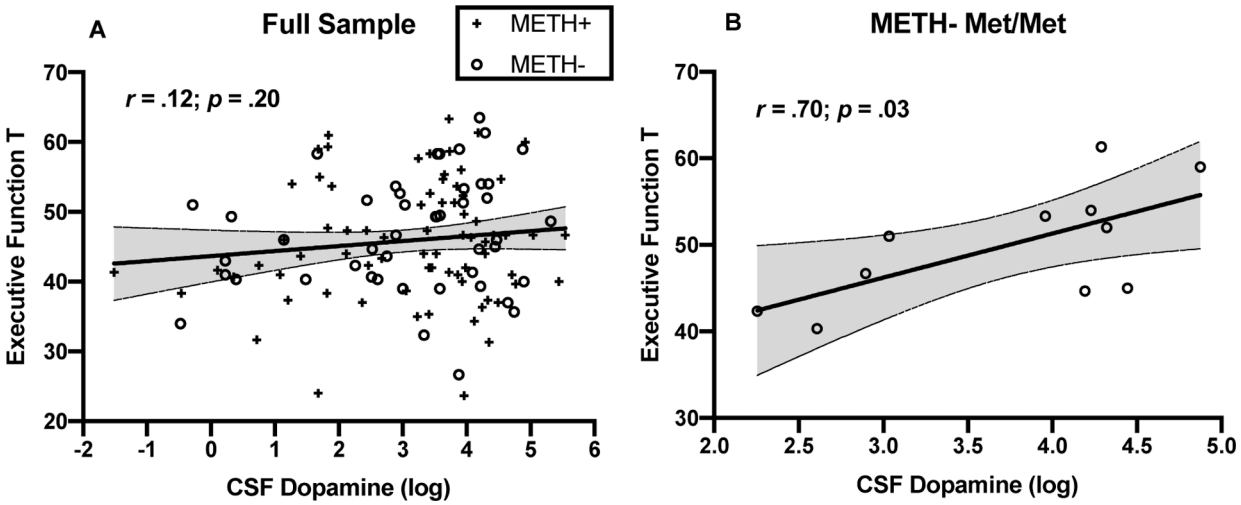

Figure 3. CSF dopamine correlates with executive function only in METH- Met/Met.

A) In the entire study sample, CSF dopamine levels do not significantly correlate with executive function T scores (r=.12, p=.20); B) Within the METH- Met/Met group, which had on average the highest levels of CSF dopamine, higher CSF dopamine significantly correlated with higher executive function T scores (r=.70, p=.03).

Table 1.

Demographic and clinical characteristics by methamphetamine (METH) group

Variable	METH− (n=47)	METH+ (n=75)	*P*
Demographics			
Age (years), mean (SD)	40.0 (10.04)	39.8 (7.44)	0.914
Education (years), mean (SD)	13.0 (1.92)	12.9 (2.16)	0.759
Estimated premorbid verbal IQ, mean (SD)	99.4 (12.00)	97.2 (12.52)	0.355
Race/Ethnicity Non-Hispanic White, n (%)	28 (59.6%)	52 (68.4%)	0.395
Hispanic, n (%)	8 (17.4%)	12 (16.0%)	
Black, n (%)	10 (21.7%)	8 (10.7%)	
Other, n (%)	1 (2.2%)	2 (2.7%)	
Neuropsychiatric Characteristics			
Lifetime Major Depressive Disorder, n (%)[a]	25 (54.4%)	36 (52.9%)	0.883
BDI-II score, median [IQR]	7 [2, 13]	15 [8, 21]	<0.001
Antidepressant use, n (%)	16 (34.0%)	28 (37.3%)	0.712
Lifetime alcohol use disorder, n (%)[a]	24 (52.2%)	52 (76.5%)	0.007
Current alcohol use disorder, n (%)[b]	2 (4.4%)	0 (0.0%)	0.158
Lifetime cannabis use disorder, n (%)[a]	14 (30.4%)	36 (52.9%)	0.017
Current cannabis use disorder, n (%)[b]	1 (2.2%)	1 (1.5%)	0.773
Lifetime cocaine use disorder, n (%)[a]	6 (13.0%)	27 (39.7%)	0.001
Medical Characteristics			
Hepatitis C virus seropositive, n (%)	5 (10.6%)	24 (32.0%)	0.031
HIV seropositive, n (%)	30 (63.8%)	50 (66.7%)	0.825
AIDS diagnosis, n (%)	17 (56.7%)	24 (48.0%)	0.452
Duration of HIV infection (years), median [IQR]	9.1 [1.5, 12.0]	6.9 [2.9, 12.7]	0.824
Current CD4 count (cells/mm^3), median [IQR]	470 [349, 653]	401 [297, 675]	0.228
Nadir CD4 count (cells/mm^3), median [IQR]	201 [56, 324]	218 [58, 381]	0.676
Detectable plasma viral load, n (%)	11 (36.7%)	30 (62.5%)	0.026
On ART, n (%)	21 (72.4%)	33 (66.0%)	0.552
Methamphetamine Use Parameters			
Lifetime days of use	-	1503 [669, 3611]	-
Lifetime grams consumed	-	1357 [408, 2825]	-
Lifetime average daily use (grams/day)	-	0.77 [0.38, 1.25]	-
Days since last use	-	61 [16, 122]	-
Age of first use	-	23.3 (7.62)	-

ART= antiretroviral therapy; BDI-II= Beck Depression Inventory- II;

[a] N = 117;

[b] N = 115

Table 2.

Results of multiple linear regressions examining the interaction of methamphetamine (METH) status and COMT genotype on dopamine (DA), homovanillic acid (HVA) and HVA/DA ratios

Outcome: CSF DA (log)	**beta (SE)**	**95% CI**	**p**
METH+ (vs. METH−)[a]	−1.10 (0.55)	−2.20, 0.00	0.050
Val/Met (vs. Met/Met)[b]	−0.89 (0.51)	−1.90, 0.12	0.082
Val/Val (vs. Met/Met)[b]	−1.18 (0.58)	−2.34, −0.02	0.046
METH+ x Val /Met	1.56 (0.67)	0.24, 2.89	0.021
METH+ x Val/ Val	1.09 (0.76)	−0.42, 2.59	0.154
Outcome: CSF HVA (log)	**beta (SE)**	**95% CI**	**p**
METH+ (vs. METH−)[a]	0.13 (0.47)	−0.81, 1.07	0.778
Val/Met (vs. Met/Met)[b]	−0.46 (0.44)	−1.33, 0.40	0.291
Val/Val (vs. Met/Met)[b]	−0.35 (0.50)	−1.34, 0.64	0.482
METH+ x Val /Met	−0.06 (0.57)	−1.19, 1.08	0.918
METH+ x Val/ Val	−0.59 (0.65)	−1.88, 0.70	0.366
Outcome: CSF HVA/DA (log)	**beta (SE)**	**95% CI**	**p**
METH+ (vs. METH−)[a]	1.24 (0.54)	0.16, 2.32	0.025
Val/Met (vs. Met/Met)[b]	0.43 (0.50)	−0.56, 1.42	0.391
Val/Val (vs. Met/Met)[b]	0.83 (0.57)	−0.31, 1.97	0.152
METH+ x Val /Met	−1.62 (0.66)	−2.93, −0.32	0.015
METH+ x Val/ Val	−1.68 (0.75)	−3.15, −0.20	0.026

[a]Represents effect of METH in Met/Met individuals only (reference group)

[b]Represents effect of *COMT* in METH- individuals only (reference group)