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Prefrontal white matter impairment in substance users depends upon the catechol-o-methyl transferase (COMT) val158met polymorphism

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ABSTRACT

Individuals addicted to most chemical substances present with hypoactive dopaminergic systems as well as altered prefrontal white matter structure. Prefrontal dopaminergic tone is under genetic control and is influenced by and modulates descending cortico-striatal glutamatergic pathways that in turn, regulate striatal dopamine release. The catechol-O-methyltransferase (COMT) gene contains an evolutionarily recent and common functional variant at codon 108/158 (rs4680) that plays an important role in modulating prefrontal dopaminergic tone. To determine if the COMT val158met genotype influences white matter integrity (i.e., fractional anisotropy (FA)) in substance users, 126 healthy controls and 146 substance users underwent genotyping and magnetic resonance imaging. A general linear model with two between-subjects factors (COMT genotype and addiction status) was performed using whole brain diffusion tensor imaging (DTI) to assess FA. A significant Genotype × Drug Use status interaction was found in the left prefrontal cortex. Post-hoc analysis showed reduced prefrontal FA only in Met/Met homozygotes who were also drug users. These data suggest that Met/Met homozygous individuals, in the context of addiction, have increased susceptibility to white matter structural alterations, which might contribute to previously identified structural and functional prefrontal cortical deficits in addiction.

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Introduction

Drug dependent individuals, regardless of their drug of choice, have marked decreases in striatal dopamine (DA) D2 receptors and attenuated striatal DA release (Volkow et al., 2001, 2005, 2007). This alteration in DA signaling, in addition to predicting relapse (Wang et al., 2012), is associated with reduced metabolism in several frontal cortical areas including the orbitofrontal, cingulate and dorsolateral prefrontal cortices (Volkow et al., 2009). These regions support behavioral and cognitive functions that are disrupted in addiction, including emotional regulation, self-control and executive function, respectively (Volkow et al., 2009). Dysregulated neuronal processing in these areas may thus contribute to compulsive, impulsive and impaired action regulation behaviors that characterize the addiction phenotype (Volkow et al., 2005, 2009).

In addition to these DA-associated prefrontal functional changes, structural changes in prefrontal cortex (PFC) have also been found in drug dependent individuals. For example, reduction in frontal gray matter volume is seen in cocaine dependent subjects (Matochik et al., 2003) that is inversely proportional to deficits in executive functioning (Fein et al., 2002; Franklin et al., 2002). Zhang et al. (2011) found reduced PFC gray matter density in smokers, with this reduction inversely related to the total lifetime cigarette use. They also reported a reduction in prefrontal white matter (WM) integrity that was negatively correlated with nicotine addiction severity as measured by the Fagerstrom index (FTND). Finally, Liu et al. (2008) reported reduced medial frontal FA that correlated with months of heroin use. That these WM structural alterations may have functional significance is suggested by a recent study showing that the P3 event-related potential during a go/no go task in alcoholics predicts FA in the bilateral cingulate bundle (Colrain et al., 2011).

Of course, both structural and functional alterations found in drug users may be either a consequence of or a cause for chronic drug use. Other factors not considered in the above studies, such as an individual's genetic background, may amplify or protect against the effects of chronic drug exposure on brain structure and function. One such potential genetic polymorphism is the relatively common COMT val158met gene, a major determinate of dopaminergic tone in the brain, particularly in the PFC where the DA transporter is particularly

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Table 1
Participant demographic data.

		Controls			Drug users		
		Met/Met	Met/Val	Val/Val	Met/Met	Met/Val	Val/Val
Allele		19	66	41	32	73	41
Gender		M: 11; F: 8	M: 28; F: 38	M: 24; F: 17	M: 17; F: 15	M: 51; F: 22	M: 30; F: 11
Age (mean ± SD)		31.4 ± 9.5	29.8 ± 8.5	30.6 ± 7.9	34.1 ± 10.1	34.3 ± 9.0	35.0 ± 10.3
Distribution of drug use across COMT gene	Nicotine	–	–	–	26	61	33
	Alcohol	–	–	–	19	48	30
	Cocaine	–	–	–	8	26	14
	Marijuana/THC	–	–	–	14	33	21
	Heroin/Opiates	–	–	–	4	9	2
FTND		–	–	–	6.08 ± 1.98	4.80 ± 2.24	4.50 ± 1.80
Initial smoking age		–	–	–	14.58 ± 4.95	15.50 ± 3.68	14.70 ± 4.32
AIM score (i.e., ethnic data) (mean ± SD)	Africa	0.38 ± 0.41	0.38 ± 0.41	0.35 ± 0.41	0.26 ± 0.38	0.41 ± 0.40	0.31 ± 0.38
	Europe	0.52 ± 0.43	0.39 ± 0.42	0.36 ± 0.42	0.56 ± 0.42	0.44 ± 0.43	0.49 ± 0.43
	Middle East	0.05 ± 0.07	0.07 ± 0.12	0.06 ± 0.10	0.06 ± 0.11	0.06 ± 0.11	0.07 ± 0.11
	Asia	0.03 ± 0.03	0.09 ± 0.19	0.12 ± 0.23	0.08 ± 0.16	0.05 ± 0.10	0.05 ± 0.08
	Far East Asia	0.00 ± 0.00	0.06 ± 0.21	0.09 ± 0.26	0.02 ± 0.09	0.02 ± 0.11	0.03 ± 0.15
	Oceania	0.01 ± 0.02	0.01 ± 0.01	0.01 ± 0.02	0.01 ± 0.01	0.01 ± 0.02	0.00 ± 0.00
	America	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.04	0.01 ± 0.02	0.01 ± 0.04	0.03 ± 0.10

sparse (Garris and Wightman, 1994). A valine (val) to methionine (met) substitution in a coding region of COMT is associated with a greater than two-fold decrease in COMT enzyme activity and DA catabolism (Chen et al., 2004; Lachman et al., 1996; Lotta et al., 1995) such that the Met allele confers a relative increase in local DA concentration (Tunbridge et al., 2004), especially in the PFC. Such elevated DA tone associated with the Met allele has been shown to confer an advantage for tasks involving sustained attention and memory and in contrast, a disadvantage for tasks involving cognitive flexibility (Bilder et al., 2004).

Dopamine also influences the structural development of the PFC (Bhide, 2009). Indeed, COMTVal158Met, as a surrogate measure of prefrontal DA levels, has been shown to affect prefrontal WM pathways (Thomason et al., 2010), such that the Val allele, conferring low prefrontal dopaminergic tone, is associated with significantly elevated FA values and attenuated cortical thinning in a longitudinal study of children and young adults, suggesting a role for DA in myelination development (Bongarzone et al., 1998; Karadottir and Attwell, 2007).

Fractional anisotropy (FA), an MRI based metric of WM pathway microstructure integrity measured using diffusion tensor imaging (DTI), is based on the degree to which water preferentially diffuses along WM tracts (Basser, 1995). Higher FA is generally associated with developmental advancement (Barnea-Goraly et al., 2005; Eluvathingal et al., 2007; Lebel et al., 2008; McGraw et al., 2002; Morriss et al., 1999; Sakuma et al., 1991; Schneider et al., 2004; Snook et al., 2005), in part due to enhanced myelination during development. Indeed, myelination is thought to be one factor contributing to WM tract coherence measures (Mori and Zhang, 2006). Critically, with respect to the current study, in vitro data suggests that high levels of DA can inhibit myelination (Bongarzone et al., 1998; Karadottir and Attwell, 2007). In humans, Val homozygotes, i.e. those with the lowest levels of prefrontal DA, also exhibit the highest FA (Thomason et al., 2010).

Since WM structural differences resulting from genetically determined neurotransmitter (and other) microenvironments are antecedent to any structural or functional alterations that might occur in the context of substance use environmental factors, we investigated the interaction between prefrontal DA (as inferred by the COMT Val158Met polymorphism) and substance abuse on WM structural integrity. Met allele carriers show higher levels of prefrontal DA than Val allele carriers (Tunbridge et al., 2004); chronic drug users show reduced D1 receptor availability (Narendran et al., 2005) and reduced striatal D2 availability (Fehr et al., 2008). We therefore hypothesized that previously observed effects of reduced prefrontal FA in substance users (Liu et al., 2008; Zhang et al., 2011) will be amplified in Met allele carriers whose elevated DA tone (Tunbridge et al., 2004) reduces WM integrity by impacting myelination (Bongarzone et al., 1998; Karadottir and Attwell, 2007). In addition, we hypothesized that WM integrity will be reduced in Val/Val homozygote drug users (vs. controls), though less so compared to the other two gene groups.

Methods and materials

Participants

Data were collected from 126 healthy controls and 146 drug users. The genotype distribution included 51 Met/Met homozygotes, 139 Met/Val heterozygotes, and 82 Val/Val homozygotes (see demographic details in Table 1 and Table S1 and S2 in Supplementary materials), which was consistent with Hardy–Weinberg Equilibrium ($X^2 = 0.34$, $p = 0.56$). The drug user group was assessed by the Structured Clinical Interview for DSM-IV (SCID), computerized self-report version, with follow-up clinical interview. Subjects in the drug user group met the DSM-IV abuse or dependence criteria for at least one of the following substances: nicotine (≥10 cigarettes per day or nicotine dependence), alcohol,[2] cocaine, marijuana, or heroin/opiates; the distribution of substance use did not differ across the COMT genotype (nicotine: $\chi^2 = 0.194$, $p = 0.907$; alcohol: $\chi^2 = 1.565$, $p = 0.457$; cocaine: $\chi^2 = 1.178$, $p = 0.555$; marijuana: $\chi^2 = 0.513$, $p = 0.774$; heroin/opiates: $\chi^2 = 1.801$, $p = 0.406$). Of the 146 drug users, 30 used nicotine only and 90 used both nicotine and at least one other drug. The remaining 26 were nonsmoking illicit drug users. Participants in the control group had no history of abuse or dependence on any substance ever in their lifetime and were not former smokers. Data for total years of exposure to drug of choice was available for 141 out of 146 drug users. FTND scores were available for 113 out of 120 cigarette smokers.

Participants were recruited through newspaper advertisements, flyers, and referrals. After complete description of the study to the subjects, written informed consent was obtained from NIDA-IRP Institutional Review Board approved protocols. Screening procedures included a history and physical exam and a comprehensive laboratory panel (CBC, blood chemistries, liver function tests, thyroid function screening, erythrocyte sedimentation rate, HIV antibody, syphilis screening, urinalysis, pregnancy (females) and a comprehensive urine drug screen). Participants were excluded if they had any major medical, psychiatric or neurological disorders, were left-handed or if their T1 weighted images revealed gross structural abnormalities.

[2] No subject met the DSM-IV criteria for alcohol dependence and no subject had only alcohol abuse as a substance use disorder diagnosis.