HHS Public Access

Author manuscript

Pharmacogenomics J. Author manuscript; available in PMC 2014 June 01.

Published in final edited form as:

Pharmacogenomics J. 2013 December ; 13(6): 490–497. doi:10.1038/tpj.2013.1.

COMT Val158Met modulates subjective responses to intravenous nicotine and cognitive performance in abstinent smokers

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Abstract

The *COMT* Val158Met polymorphism may be a risk factor for nicotine addiction. This study examined the influence of the *COMT* Val158Met polymorphism on subjective, physiological, and cognitive effects of intravenous (IV) nicotine use in African American (AAs) (n=56) and European American (EAs) (n=68) smokers. Overnight abstinent smokers received saline followed by 0.5 and 1.0 mg/70 kg doses of nicotine, administered 30 minutes apart. Smokers with Val/Val genotype, compared to Met carriers, had greater negative subjective effects from IV nicotine and had more severe withdrawal severity following overnight abstinence from smoking. Women with Val/Val genotype reported greater difficulty concentrating and irritability than men with Val/Val or Met carrier genotypes. The Val/Val genotype was associated with better performance on the math task and in AA smokers it was associated with greater systolic blood pressure. These results support the rationale of pharmacologically inhibiting COMT to aid with smoking cessation among Val/Val genotype smokers.

Keywords

Nicotine; Genetics; Pharmacogenetic; Smoking; Cigarette; *COMT*

Introduction

Catechol-O-methyltransferase (COMT) is an enzyme that inactivates dopamine (DA), epinephrine, and norepinephrine as well as tightly regulating DA in the prefrontal cortical areas (1–3). The gene encoding COMT contains a well-studied single nucleotide polymorphism (SNP) that results in the presence of methionine (Met) or valine (Val) at codon 108 (in s-COMT) or codon 158 (in m-COMT) (4). The Val-coded allele is 3 to 4

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Disclosure/conflict of Interest

MS serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline.

times more active than the Met-coded allele, resulting in reduced DA levels in the synapse (5, 6). The *COMT* Val158Met variation has been widely researched for many phenotypes of psychiatric disorders including depression (7), psychosis (8), and drug addiction (9). Given the key role of DA in mediating drug reward, drug-seeking, and withdrawal states, studying the *COMT* Val158Met variation is especially important for addictive disorders, including nicotine addiction (10).

A recent meta-analysis concluded that the Val/Val genotype may be a risk factor for developing nicotine addiction (9). While some studies reported an association between the Val/Val genotype and poor response to smoking cessation treatments (11–13), other studies did not confirm these results, and some studies reported opposite findings (14, 15). Surprisingly, only a few studies have investigated the potential mechanism by which the *COMT* Val158Met polymorphism may modulate the risk for and treatment response to nicotine addiction. In a functional MRI study, abstinent smokers with the Val/Val genotype performed worse on the n-back test, which measures working memory (16). Furthermore, abstinent smokers with the Val/Val genotype had greater blood flow increases in brain areas associated with cigarette craving (17). These findings suggest that smoking cessation may be particularly difficult for smokers with the Val/Val genotype. However, systematic studies examining the *COMT* Val158Met polymorphism on withdrawal severity and nicotine responses are lacking. Such studies may provide better insight into the mechanisms of the observed *COMT* Val158Met effects on nicotine dependence.

The goal of this study was to determine the influence of the *COMT* Val158Met polymorphism on nicotine responses in smokers. The outcomes examined were those predicted to be likely modulated by the COMT enzyme, including measures of cognitive performance, withdrawal severity, subjective drug effects, and cardiovascular responses to nicotine (18–21). To assess the outcomes of interest, we used an IV nicotine administration procedure. In contrast to other slower nicotine delivery systems, IV nicotine administration produces rewarding effects in male and female smokers (22). Based on the known biological effects of the *COMT* Val158Met variant, we hypothesized that smokers who carry two copies of the Val allele would experience less rewarding effects from nicotine, perform worse on selected cognitive tasks, and experience more severe withdrawal symptoms compared with those who carry the Met allele.

Materials and methods

Subjects

We recruited 124 non-treatment-seeking cigarette smokers in and around New Haven, Connecticut through newspaper advertisements and flyers. All participants were between 18 and 50 years old and smoked between 10 and 25 cigarettes per day during the past year. The study sample included 100 smokers that were described in a previous study (23) as well as 24 additional smokers. The demographics are shown in Table 1.

The participants were medically healthy and did not have current active medical problems (including hypertension) and were not on any current prescription medications. Potential participants were excluded if they were dependent on alcohol or any drugs other than

nicotine, as determined by the Structured Clinical Interview for DSM-IV (24) and verified by urine drug screening. Written informed consent was obtained from each participant prior to study participation. The IV nicotine experimental sessions were conducted in the Biostudies Unit located at the West Haven campus of the VA Connecticut Healthcare System. The participants were compensated for their participation. This research protocol was approved by the Yale and VA Connecticut Healthcare System Human Subjects Subcommittees.

Procedure

Following an overnight abstinence from smoking, the participants arrived at the outpatient clinic at approximately 8 AM for the experimental session, which lasted about 3 hours. Abstinence from smoking was confirmed by measuring expired carbon monoxide (CO; <10 parts-per-million). The participants were instructed to continue their usual caffeine intake (to prevent caffeine withdrawal) and were asked to fast after midnight to minimize the nicotine-induced nausea that can be enhanced with food. Prior to the experimental sessions, a urine drug screen was conducted to rule out recent drug use and ensure that the inclusion criteria were met. An indwelling catheter was set in an antecubital vein, and the baseline measures were collected. The study used a single-blind design. Smokers received IV saline, followed by two increasing doses of IV nicotine, (0.5 and 1.0 mg/70 kg). An escalating dose schedule was selected to increase study safety. Subjects were first exposed to saline, followed by a low dose of nicotine, and finally a high dose of nicotine. This administration schedule was also used to avoid residual effects from the preceding nicotine dose to saline.

Nicotine Administration

Nicotine bitartrate was acquired from Interchem Corporation (Manchester, Connecticut). A research pharmacist at the VA CT Healthcare System prepared the nicotine samples. A total volume of 5 ml, containing either 0.5 mg or 1 mg/70 kg of nicotine, was injected intravenously over a 30-second interval via a catheter located in a forearm vein. The nicotine doses administered were within the range of nicotine delivered by smoking one cigarette. Our prior research demonstrated that these doses produced robust physiological and subjective responses in male and female smokers (22). The injections were given 30 minutes apart, which allowed subjective and cardiovascular responses to return to baseline levels (25–27). The genotyping was conducted after the experimental sessions were completed using a blinded method.

Dependent Measures

Outcome measures assessed biochemical, physiological, subjective, and cognitive domains. Biochemical measures included CO, plasma nicotine, cotinine, and 3-hydroxycotinine (3HC). The plasma nicotine concentrations and expired CO were used to confirm the overnight abstinence from smoking. Plasma cotinine concentrations were used as a measure of prior nicotine exposure (28). Expired CO, plasma nicotine, 3HC, and cotinine measurements were taken before the experimental session. Physiological measures included blood pressure (systolic and diastolic) and heart rate. These measures were taken during the medication treatment and in the experimental sessions at −5, 1, 2, 3, 5, 8, 10, and 15 min intervals following the saline or nicotine deliveries. Plasma cortisol measurements were

taken at baseline, before each of the three injections, and at the end of the session. Plasma cortisol has been shown to be sensitive to nicotine administration and abstinence from nicotine (29–32). Studies also suggest that the COMT Val158Met polymorphism may influence cortisol release in response to stress or drugs of abuse (33, 34).

The subjective measures included the Drug Effects Questionnaire (DEQ), the Brief Questionnaire on Smoking Urges (BQSU), the Minnesota Nicotine Withdrawal Scale (MNWS) and the Positive and Negative Affect Schedule (PANAS). The DEQ was used to measure acute effects from IV nicotine and consisted of 10 items: drug strength, high, feel stimulated, good effects, bad effects, anxious, sedated, feel down, want more drug and like drug. Smokers rated each item on a visual analog (Likert) scale, from “not at all” to “extremely.” The DEQ was given at 1, 3, 5, 8, 10, and 15 minutes after the saline and nicotine administration. The BQSU is a 10-item scale originally developed by Tiffany and Drobes (35, 36). Smokers were asked how strongly they agreed or disagreed with items on a 7-point Likert scale. This scale has been found to be highly reliable in reflecting nicotine deprivation levels (37, 38). The MNWS measures withdrawal symptoms from tobacco and includes items to assess cigarette craving, irritability/anger, anxiety, difficulty concentrating, restlessness, increased appetite, depressed or sad mood, and insomnia (39, 40). The PANAS is a 20-item scale, which assesses both negative and positive affective states (41). The BQSU, MNWS and PANAS were administered before and after the session.

Cognitive testing was measured using the Mathematical Processing (MP) task, the Running Memory Continuous Performance Test (CPT) and the Stroop Test within the Automated Neuropsychological Assessment Metrics (ANAM) computer package, a computer-administered cognitive battery of performance tests developed by the Department of Defense (42). As the main cognitive outcome measure, we used the throughput score, which combines response speed, accuracy and consistency, and reflects cognitive efficiency (42). The MP, CPT, and Stroop assessments were chosen for their sensitivity to acute nicotinic administration (43–45).

The MP assessed basic computational skills. This task displays arithmetic problems involving three single-digit numbers and two operators (e.g., "5 − 2 + 3 ="). The participant presses buttons to indicate whether the answer to the problem is less than five or greater than five.

The CPT measured attention, concentration, and working memory. This task involves single characters shown on a computer monitor in rapid sequence. The participant presses designated buttons to indicate if the displayed character matches or does not match the preceding character.

The Stroop test assessed attention/concentration, shifting perceptual sets, and the suppression of a habitual response in favor of an atypical one (46). This task instructs the participant to say the color of the word displayed on a monitor, which may or may not differ from the actual word text. For example, a participant would push the designated blue button when observing the word written in blue that could spell red, blue or green. Cognitive assessments were conducted at the beginning and end of the session, about 2 hours apart.

Assays—Nicotine, cotinine and trans-3'-hydroxycotinine (3HC)/cotinine ratios were determined by tandem mass spectrometry (LC/MS/MS) employing stable isotope (deuterated) labeled internal standards as we have previously reported (47) and similar to that reported by others (48). Nicotine and cotinine were determined to compare baseline nicotine exposure between the three genotypes, and 3HC/cotinine ratios were determined to control for possible differences in the rate of nicotine clearance (48).

Genotyping

DNA was extracted from peripheral blood using a commercial kit (PureGene™; Gentra, Minneapolis, MN). We genotyped rs4680 using the TaqMan method and primers (supplied as pre-validated SNP Assays on Demand, Applied Biosystems). The rs4680 genotyping was performed using ABI PRISM 7900 Sequence Detection System (Applied Biosystems). All samples were genotyped in duplicate. An ancestry informative marker (AIM) panel of 90 SNPs chosen by our group for their ability to differentiate between major continental populations was genotyped using the Illumina BeadXpress Reader with VeraCode assays and the manufacturer's protocol (Illumina, Inc., San Diego, CA). Genotypes were called using BeadStudio software (Illumina, Inc., San Diego, CA).

Data Analysis

Study outcomes were analyzed with a repeated-measures model using the Statistical Analysis System (SAS), version 9.2 (SAS Institute Inc., 2007). Because of the small number of smokers (n=22) with Met/Met genotype, we combined Met/Met group with Met/Val and compared this combined group with the Val/Val group, similar to previous studies on *COMT* and cigarette smoking (16, 49). For blood pressure, heart rate and the DEQ, multiple assessments were collected for each saline and nicotine dose. For these outcomes, the model included the *COMT* rs4680 genotype (Val/Val vs. Val/Met or Met/Met), nicotine dose (saline, 0.5 and 1mg/70 kg), sex (male vs. female), race (African-American vs. Caucasian), nicotine metabolite ratio, BMI, and interaction terms including genotype × dose, genotype × race, and genotype × sex. In previous studies, race, sex, BMI, and NMR have been shown to modulate nicotine's pharmacological effects (23, 50). For the NWSC, BQSU, PANAS, and cognitive measures, the assessments were completed at the beginning and end of the session. For these outcomes, the model included time of measurement (pre- vs. post-session), rather than the dose. Significant main effects were followed by post hoc testing. Genotypes for AA and EA groups were consistent with Hardy Weinberg Equilibrium expectations [EA: χ^2 (1) = 0.56, p = ns, AA: χ^2 (1) = 0.70, p = ns]. Values of $p \leq 0.05$ in two-tailed tests were considered statistically significant unless otherwise specified.

Subjects were classified as genetically AA or EA on the basis of the AIMs panel, using the program STRUCTURE v 2.3.2.1 (51), as described previously (52). Among the subjects included in the current study, 2 subjects reporting to be of AA descent clustered in the EA group, and 2 subjects reporting to be EA clustered in the AA group. Adjusting for the degree of admixture did not significantly change our results on the influence of *COMT* Val158Met variation on the study outcomes.

Results

Physiological

The systolic blood pressure, diastolic blood pressure, and heart rate responses were dose-dependent such that responses to 1.0 mg nicotine>0.5 mg nicotine> saline (all p values<0.0001) (Figure 1). Significant findings for heart rate, and systolic and diastolic blood pressure are summarized in Table 1 and Figure 1. The BMI was not significant for heart rate or blood pressure. The NMR values were positively correlated with the nicotine-induced heart rate and systolic blood pressure ($p<0.01$).

Subjective—For all the DEQ assessments, the rating for the 1.0 mg nicotine or 0.5 mg nicotine does were > than for saline (all p values<0.05). For the rating of "Stimulated," "High," "Feel Drug Strength," the ratings for the 1.0 mg nicotine> 0.5 mg nicotine ($p<0.05$). The NMR values were positively correlated with the ratings of "Stimulated" "High," and "Feel Anxious" ($p<0.05$). The results for the DEQ items are summarized in Table 1 and Figure 2.

The results for withdrawal severity, as measured by MNWS and BQSU, are summarized in Table 2 and Figure 3. The NMR values were positively correlated with the MNSW and BQSU factor 1 scores ($p<0.05$). For the PANAS, neither a main effect of genotype nor a genotype × session interaction was found to influence positive and negative affect states ($p>0.05$).

Cognitive

As expected, the MP, CPT and Stroop Test performances at the end of the session were better than they were at baseline ($p<0.0001$). The results of the cognitive assessments are summarized in Table 3.

Cortisol

Plasma cortisol measurements did not show significant main effects for genotype or genotype × time interactions ($p<0.05$).

Discussion

We found that smokers with the Val/Val genotype, compared to the Met carriers, had greater negative subjective effects from IV nicotine and more severe withdrawal severity following overnight abstinence from smoking. Women with the Val/Val genotype reported greater difficulty concentrating and irritability than men with the Val/Val or Met allele containing genotypes. The Val/Val genotype was associated with better performance on the math task and in AA smokers, it was associated with greater systolic blood pressure readings. These findings are consistent with most of our hypotheses regarding *COMT* Val158Met polymorphism effects on nicotine responses.

In our study, smokers with the Val/Val genotype, compared with Met carriers, reported higher ratings of mostly negative drug effects, including "Feel Anxious," "Feel Bad Effects," "Feel Sedated," "Feel Down" and "Feel the Drug Strength." In contrast, no

genotype effects were observed for the ratings of items that reflect nicotine's reinforcing properties including "Good Drug Effects," "Like the Drug Effects" or "Want More Drug." This genotype effect was primarily observed in response to nicotine, and not to saline, administration, suggesting a pharmacogenetic effect of the Val/Val genotype. *COMT* effects were observed for both 0.5 and 1.0mg/70 kg of nicotine dose. Previous studies have shown that *COMT* Val158Met variation moderates responses to non-drug rewards or aversive stimuli (19, 20); however, the influence of the *COMT* Val158Met polymorphisms on the rewarding or aversive drug effects has not been reported. For example, healthy controls with the Val/Val genotype report a decreased ability to experience reward in the routine of daily life and report less happiness compared with those with the Met/Met genotype (20). In a recent functional fMRI study healthy controls with the Val/Val genotype had greater activation of amygdala in response to fearful/angry facial stimuli (53). Our findings extend these studies further by demonstrating that *COMT* Val158Met variation may also moderate subjective drug responses to nicotine.

Consistent with the DEQ findings, we found that smokers Val/Val genotype had greater withdrawal severity following an overnight abstinence, as measured by the MNWS and the BQSU. Further analysis of the individual MNWS items showed that smokers with the Val/Val genotype had greater craving, more difficulty concentrating and more irritability than Met carriers. To our knowledge, these findings are the first to demonstrate that the *COMT* Val158Met variation moderates withdrawal severity in smokers. In a previous study, smokers with the Val/Val genotype had greater blood flow to prefrontal cortical regions that are associated with cigarette craving upon abstinence from smoking (17). More severe withdrawal in smokers with the Val/Val genotype may have important treatment implications (see below).

The Val/Val genotype was associated with faster reaction time in the math test but did not influence the performance on the CPT and Stroop tasks. In contrast to our findings, a functional MRI study revealed that abstinent smokers with the Val/Val genotype performed worse on the n-back test, a test of working memory (16). The reason for these conflicting findings regarding the influence of Val/Val genotype on cognitive performance is not clear. In previous studies, the Val/Val genotype was associated with better or worse performance across many cognitive tasks. It has been argued that while individuals with the Val/Val genotype perform worse on tasks that require cognitive flexibility, they may perform better on tasks that require cognitive stability (54). The N-back is a relatively difficult task that requires sustained attention and working memory function, while the mathematical processing task is an easier task that assesses single-digit calculations (54). We did not observe a genotype effect on the Stroop or CPT tasks.

Understanding the underlying mechanisms that mediate the moderating effects of *COMT* Val158Met on subjective drug effects, withdrawal severity, and cognitive performance are an important topic for further research. The high COMT enzyme activity associated with Val allele may reduce tonic DA and increase phasic DA release in subcortical areas as well as reduce DA levels in prefrontal cortical areas (55). This reduced tonic DA release in smokers with the Val allele, may be further accentuated by smoking abstinence, which also reduces DA transmission in subcortical regions (56). As a result, the Val/Val genotype may

be associated with more severe withdrawal symptoms. In contrast, the enhanced phasic DA release associated with the Val/Val genotype may contribute to greater responses to some of nicotine's subjective effects. It is unclear why the *COMT* Val158Met variation was related to particularly the negative or aversive responses to nicotine. Both the aversive and rewarding effects of nicotine are likely be mediated by DA release in the nucleus accumbens, although the exact mechanisms remain to be determined.

We observed that AA, but not EA, cigarette smokers with the Val/Val genotype had significantly higher systolic and diastolic blood pressure readings throughout the session. In previous studies, the Val/Val genotype has been associated with higher blood pressure in mainly EA populations (57, 58). To our knowledge, the influence of the *COMT* Val158Met polymorphism on blood pressure regulation in cigarette smokers has not been examined. The underlying mechanism for the association of the Val/Val genotype with higher blood pressure in AA smokers is unclear. Previous studies have shown that AAs excrete less sodium and are more salt-sensitive than EAs (59–61). DA plays an important role in blood pressure regulation, primarily by influencing sodium excretion from the kidneys. Other mechanisms, such as the noradrenergic system, may also contribute to our findings, although the role of *COMT* Val158Met polymorphism on NE function has not been well described. Higher systolic and diastolic blood pressure in AA cigarette smokers with the Val/Val genotype may have noteworthy health and treatment implications, especially given the cardiovascular risks associated with smoking (62).

Our results also indicated a significant sex-by-*COMT* interaction for withdrawal severity. Women with the Val/Val genotype reported greater difficulty concentrating and irritability than men who were with Val/Val or Met carriers. These findings are consistent with the sexually dimorphic activity of the *COMT* enzyme that may be mediated by multiple mechanisms including the estrogen response element in *COMT* promoter, reduced *COMT* mRNA expression by estradiol as well as breakdown of catechol estrogens by the *COMT* enzyme (63). Similar to our findings, other studies have shown that the Val/Val genotype may have greater influence in women for endophenotypes related to negative affect (53, 64). The association of greater irritability, and difficulty concentrating with the Val/Val genotype in women may contribute to greater difficulty of women quitting smoking than men. As mentioned before, the Val/Val genotype may be a risk factor for developing nicotine addiction (9) and poor treatment response to smoking cessation treatments (11–13). Whether *COMT* variation contributes to the greater difficulty of women to quit smoking remain to be examined.

Our study also had several limitations. First, due to the small number of smokers with the Met/Met genotype, this group was combined with the Met/Val group. As a result, we could not test for the differences between the Met/Met and Met/Val groups. Similarly, due to small sample sizes of the race and sex subgroups, we could not conduct detailed analysis to explain race and sex interactions with the *COMT* Val158Met polymorphism. Second, the smokers were tested once following overnight abstinence from smoking. For optimum assessment of withdrawal or cognitive performance, multiple days of abstinence from smoking may be needed. Third, the IV nicotine responses may not be generalizable to cigarette smoking, given that tobacco addiction includes both nicotinic and non-nicotinic

components (65). Fourth, we did not assess smokers during a smoking as usual condition, which would have allowed further delineation of the influence of *COMT* Val158Met polymorphism on the study outcomes. Lastly, we did not correct for multiple testing due to exploratory and hypothesis-generating nature of the study. Thus, the results should be interpreted cautiously, although we fell they warrant replication in larger studies.

With these caveats in mind, our results have several treatment implications. As suggested by previous studies, the association of the Val/Val genotype with greater withdrawal severity, worse cognitive performance and greater negative subjective effects suggests that smokers with this genotype, especially female smokers, may experience greater difficulty with smoking cessation. If greater activity of the COMT enzyme is associated with a poor treatment response for smoking cessation, then COMT inhibitors such as tolcapone and entacapone may improve outcomes for smoking cessation in smokers with the Val/Val genotype. Pharmacological COMT inhibition via increased synaptic DA levels improved working memory function and reduced marijuana craving (66–68). This treatment may be especially helpful for female smokers if it is provided immediately after the quit date, when the withdrawal severity is high and smokers are most likely to relapse.

Acknowledgements

Ann Marie Lacobelle, Greg Kay, Christa Robinson, Michelle Cucinelli, Catherine Aldi, Ellen Mitchell, Lance Barnes, and Stacy Minnix provided excellent technical assistance. This research was supported by the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC) and NIH grants R03 DA027474, K12 DA00167 (AH); and R01 DA12690 and R01 DA12849.

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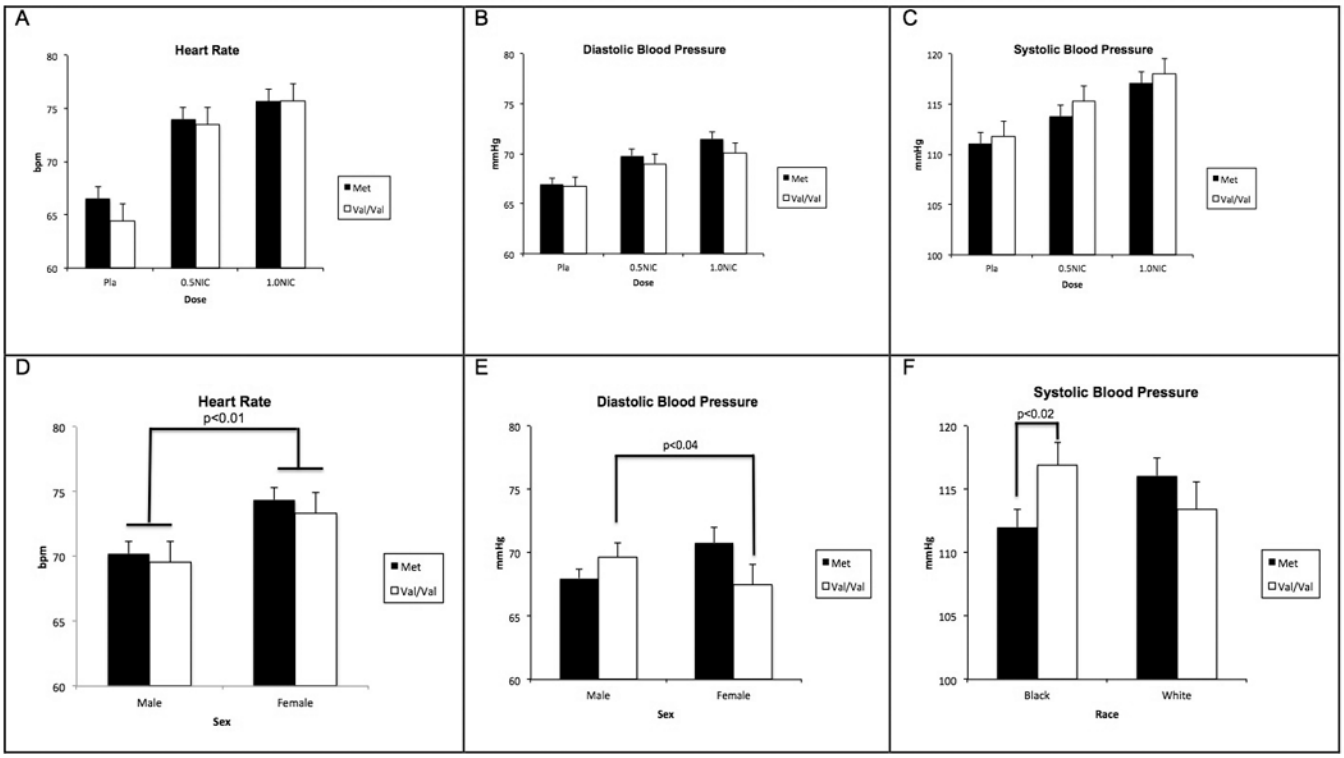

Figure 1.

Mean±SEM of A) heart rate B) systolic and C) diastolic blood pressure as functions of *COMT* genotype and nicotine dose. Mean±SEM of D) heart rate E) diastolic blood pressure as functions of *COMT* genotype and sex and F) systolic blood pressure as functions of *COMT* genotype and race.

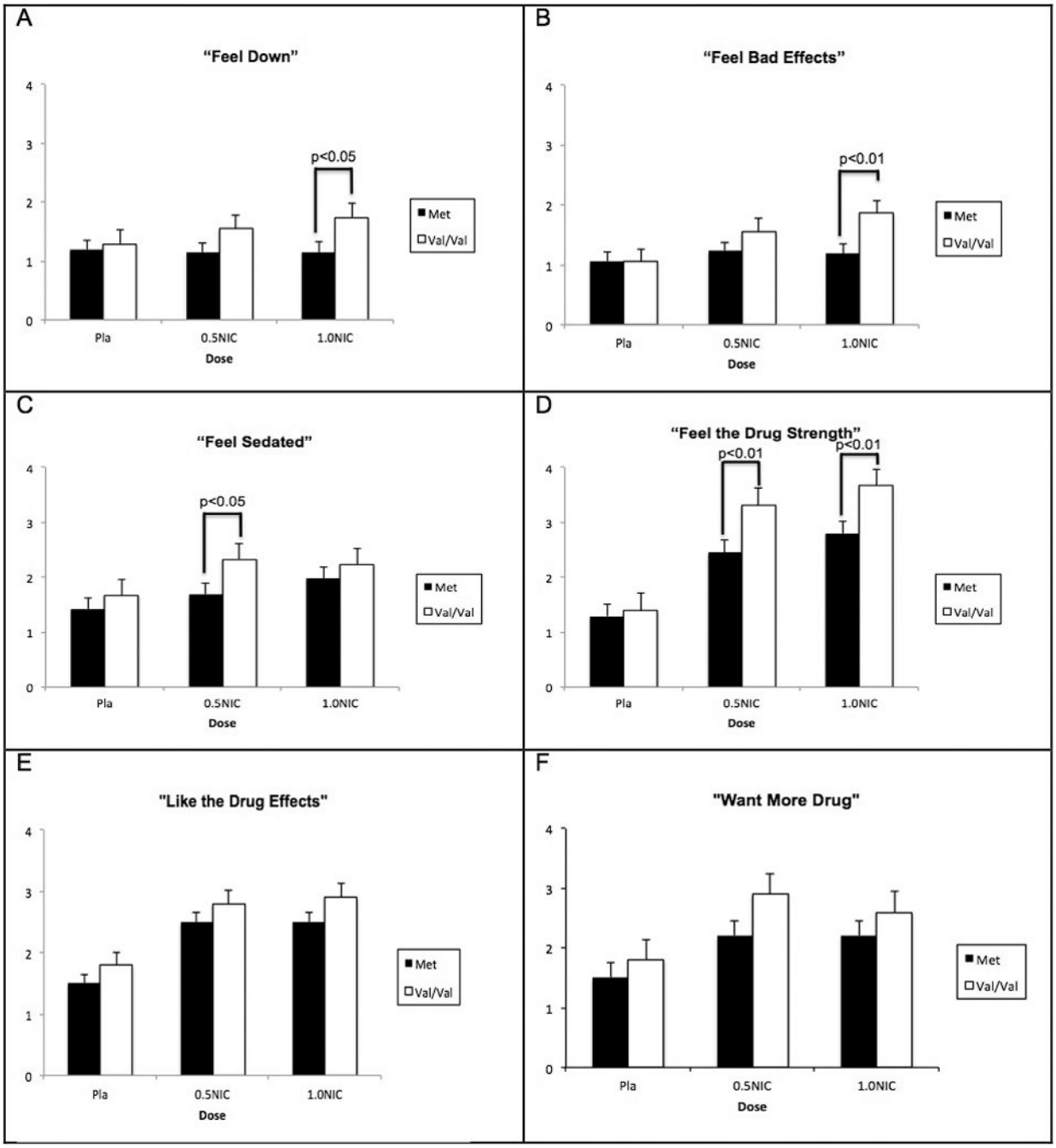

Figure 2.

Mean±SEM of selected DEQ domains A) Feel Down B) Feel Bad C) Sedated D) Drug Strength E) Like the Drug, and F) Want More as functions of *COMT* genotype and nicotine dose.

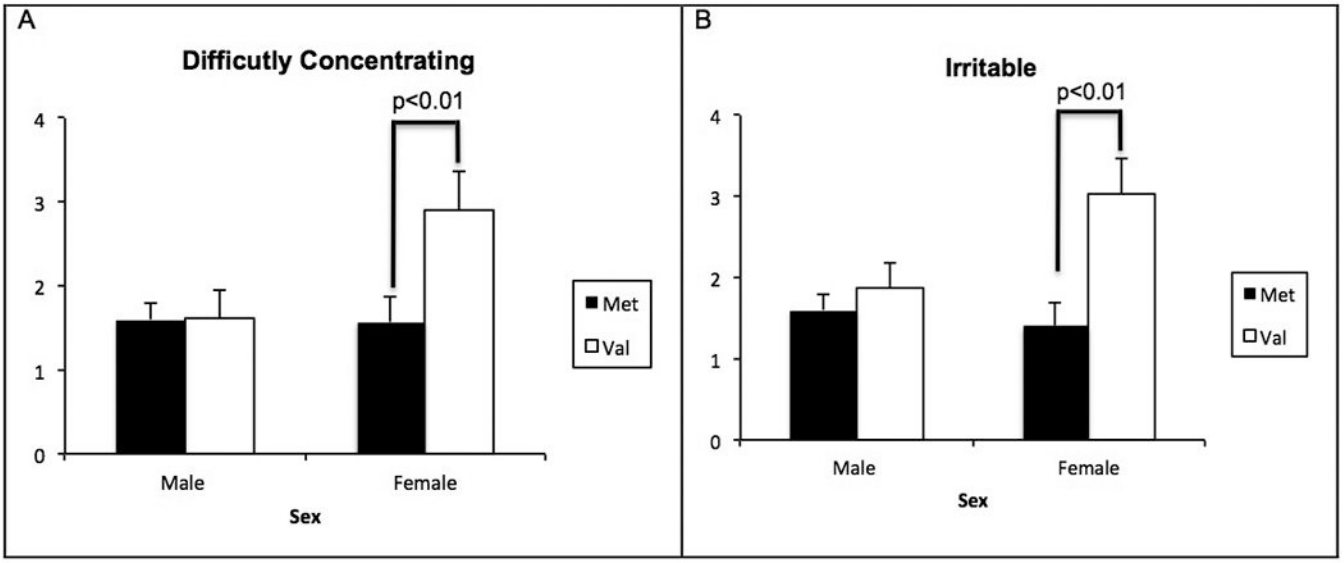

Figure 3.

Mean±SEM of MNWS domains A) Difficulty Concentrating B) Irritable as functions of *COMT* genotype and sex.

Table 1

Baseline measures for the study sample

***COMT* genotype (rs4680)**	**Overall**	**Met (n=80)**	**Val/Val (n=44)**	***p****
Sex (male/female)	90/34	59/21	31/13	NS
Age, years	37.4(8.5)	37(8.7)	39(8.1)	NS
Race (AA/EA)	56/68	31/49	25/19	0.05
Body Mass Index	28.9(5.5)	28.3(5.3)	30.1(5.8)	NS
FTND	5.5(2.1)	5.2(2.2)	6.1(2.0)	0.02
Cigarettes per day	18.7(12.2)	18.5(14.2)	19.1(7.4)	NS
Years of smoking	16.7(4.5)	16.6(4.5)	16.9(4.5)	NS
3HC/Cotinine	0.38(0.03)	0.41(0.03)	0.33(0.04)	NS
Nicotine (ng/ml)	3.1(3.3)	3.3(0.37)	2.77(0.50)	NS
Heart rate	67.5(10.4)	68.0(10.9)	66.5(9.4)	NS
Systolic blood pressure	116.4(12.4)	115(12.2)	119(12.7)	NS
Diastolic Blood Pressure	68.2(7.0)	67.3(70)	69.9(7.1)	0.05

Table 2

Vital and Drug Effects Questionnaire (DEQ) results as a function of *COMT* genotype and higher order interactions

Measure	*COMT*	*COMT*X**Sex**	*COMT*X**Race**	*COMT*X**Dose**	**Sex**	**Race**
Heart rate	X	X	X	X	F=4.37, p=0.04 F>M	X
Systolic BP	X	X	F=5.27, p=0.02 AA Val>AA Met	X	X	X
Diastolic BP	X	F=4.41, p=0.04 F Val>M Val	F=6.92, p=0.01 AA Val>EA Val	X	X	X
Anxious	F=4.82, p=0.03 Val>Met	X	X	X	X	X
Feel Bad	X	X	X	F=10.58, p<0.0001 Val>Met 1.0NIC	X	X
Feel Down	X	X	X	F=7.29, p=0.0007 Val>Met 1.0NIC	X	X
Sedated	X	X	X	F=3.43, p=0.03 Val>Met 0.5NIC	X	F=4.64, p=0.03 B>W
Drug Strength	X	X	X	F=7.76, p=0.0004 Val>Met 0.5NIC Val>Met 1.0NIC	X	X

X No significant effect (p<0.05).

Table 3

Subjective and cognitive results as a function of *COMT* genotype and higher order interactions

Measure	Factor	*COMT*	*COMT*XSex	*COMT*XRace	*COMT*XTime	Sex	Race
MNWS							
	Total score	F=3.77, p=0.05 Val>Met	X	X	X	X	X
	Crave cigarette	F=7.49,p=0.0072 Val>Met	X	X	X	X	X
	Difficulty Concentrating	F=3.89,p=0.05 Val>Met	F=3.87,p=0.05 F Val>M Val F Val>M Met	X	X	X	X
	Irritable	F=8.41,p=0.0045 Val>Met	F=4.46,p=0.04 F Val>M Val F Val>M Met	X	X	X	X
BQSU							
	Factor 1	F=4.44,p=0.04 Val>Met	X	X	X	X	X
	Factor 2	F=6.12,p=0.01 Val>Met	X	X	X	X	X
Cognitive							
	Math Throughput Score	F=5.03,p=0.03 Val>Met	X	X	X	X	X
	CPT	**X**	**X**	**X**	**X**	**X**	**X**
	Stroop	**X**	**X**	**X**	**X**	**X**	**X**

X No significant effect (p<0.05).