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Effect of *COMT* Val¹⁵⁸Met genotype on nicotine withdrawal-related cognitive dysfunction in smokers with and without schizophrenia

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Keywords

catechol-*O*-methyltransferase (*COMT*); schizophrenia; cognition; visuospatial working memory; cigarette smoking; nicotine

Dear Editor,

Cigarette smokers with schizophrenia exhibit more severe cognitive dysfunction during smoking abstinence than control smokers, and cognitive deficits are associated with higher rates of smoking cessation failure (Dolan et al., 2004; Wing et al., 2012). The pro-cognitive effects of nicotine may result from enhanced dopamine (DA) release in the prefrontal cortex (PFC). Catechol-*O*-methyltransferase (*COMT*) is the primary enzyme responsible for DA metabolism in cortical brain regions. Allelic variation at a single nucleotide polymorphism (SNP) in the *COMT* gene at position 158 in the membrane-bound form (rs4680 or

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Contributions: TPG designed the study and acted as Principal Investigator. KAS led the study and oversaw the neuropsychological testing. JFC led the genotyping component. VCW conducted the statistical analysis and prepared the first draft of the manuscript.

Conflicts of Interest: VCW, YLT and KAS have nothing to disclose. TPG reports receiving unrestricted grant support from Targacept, Inc., contract support from Pfizer, Inc., and compensation for service on a Data Monitoring Board for Novartis. JFC has received unrestricted grant support from Schering-Plough, contract support from Roche, Novartis and Bio-Marín, and consulted with Abbot Labs, all for projects unrelated to the current study.

val¹⁵⁸met) strongly influences the level of COMT activity. The valine-encoding Val allele leads to ~40% higher activity than the methionine-encoding Met allele, and is therefore associated with increased metabolism of DA and lower DA signaling (Chen et al., 2004).

COMT Val¹⁵⁸Met genotype has been associated with cognitive performance and tobacco dependence vulnerability and relapse. Presence of the Val-allele has been consistently associated with impaired performance and physiological efficiency in cognitive domains dependent on dorsolateral prefrontal cortex (DLPFC) activity such as executive function (as measured with the Wisconsin Card Sorting Task) and working memory (as measured by the N-back task), in both control and schizophrenia populations (Egan et al., 2001; Malhotra et al., 2002). Several studies have reported that Val-allele carriers are also less likely to quit smoking and more likely to relapse than Met/Met homozygotes (Munafo et al., 2008). These effects did not seem to be mediated by self-reported withdrawal or mood symptoms and therefore the authors propose that they may be related to the effect of COMT on cognitive function (Munafo et al., 2008). A recent study demonstrated that smokers with Val/Val COMT-genotype are more sensitive to cognitive dysfunction during tobacco abstinence compared to Met-allele carriers (Loughead et al., 2009). We examined the association of COMT Val¹⁵⁸Met genotype withdrawal-related cognitive dysfunction in smokers with schizophrenia in comparison to control non-psychiatric smokers.

Smokers with schizophrenia and control smokers were enrolled in a randomized, double-blind, within-subjects study to examine the effects of cigarette smoking and the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine hydrochloride on cognitive performance (Sacco et al., 2005). Neuropsychological assessments were performed after smoking as usual (baseline; day 2 AM), after overnight abstinence (day 3 AM) and after smoking reinstatement (day 3 PM). Here, we analyzed data from the placebo week of the trial to examine the effect of COMT on withdrawal-related cognitive dysfunction, specifically in the domain of visuospatial working memory, in a subsample of subjects (n=18 smokers with schizophrenia and n=17 control smokers) who were genotyped for the COMT Val¹⁵⁸Met polymorphism. We genotyped the Val-Met polymorphism in genomic DNA extracted from whole blood using PCR followed by restriction fragment length polymorphism analysis as described by Lachman and colleagues (Lachman et al., 1996).

The cognitive domain of interest was performance on a visuospatial working memory task, as performance on this measure was impaired by overnight abstinence from smoking; an effect which was specific to smokers with schizophrenia and not observed in controls (Sacco et al., 2005). The percent impairment in visuospatial working memory from baseline to overnight abstinence was calculated and the effect of diagnosis and COMT genotype examined in a two-way ANOVA (Figure 1). There was a main effect of diagnosis [$F(1,29)=5.94$, $p=0.001$] due to greater abstinence-induced visuospatial working memory deficits in the schizophrenia group compared to controls. While the effect of genotype [$F(2,29)=1.00$, $p=0.38$] and genotype by diagnosis [$F(2,29)=2.43$, $p=0.11$] did not reach statistical significance due to the small sample sizes, there was a trend for increased withdrawal-related visuospatial working memory impairment in Val-allele carriers (Val-Val: 73.3 ± 48.4 %; Val-Met 87.1 ± 47.3 %) compared to Met/Met homozygotes (25.3 ± 4.8 %).

in the schizophrenia group, while COMT genotype did not appear to modulate visuospatial working memory impairments in control smokers.

The sample size of this study was limited and therefore the results should be interpreted with caution. Nevertheless, these preliminary data support the existing literature that *COMT* Val¹⁵⁸Met genotype, specifically the Val-allele, is associated with greater nicotine-withdrawal related cognitive dysfunction (Loughead et al., 2009), and extend these findings to smokers with schizophrenia. We did not observe an effect of COMT genotype in control smokers which is likely due to the fact that overnight abstinence did not impair task performance in this group, unlike the previous study which used a different type of working memory task, the N-back, which may recruit different brain circuits (Loughead et al., 2009).

Understanding the genetic underpinnings of withdrawal-related cognitive dysfunction in schizophrenia could guide the development of smoking cessation medications and cognitive enhancers for this population of difficult to treat cigarette smokers and therefore the role of COMT genotype should therefore be explored in larger samples. Accordingly, COMT genotyping may help identify smokers at the greatest risk of cognitive impairment upon quitting and guide the developments of more effective treatments, such as specialized treatment involving neurocognitive-enhancement therapies.

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References

- Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet.* 2004; 75(5):807–821. [PubMed: 15457404]
- Dolan SL, Sacco KA, Termine A, Seyal AA, Dudas MM, Vessicchio JC, Wexler BE, George TP. Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. *Schizophrenia Research.* 2004; 70(2-3):263–275. [PubMed: 15329302]
- Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A.* 2001; 98(12):6917–6922. [PubMed: 11381111]
- Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics.* 1996; 6(3):243–250. [PubMed: 8807664]
- Loughead J, Wileyto EP, Valdez JN, Sanborn P, Tang K, Strasser AA, Ruparel K, Ray R, Gur RC, Lerman C. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. *Mol Psychiatry.* 2009; 14(8):820–826. [PubMed: 19065145]
- Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry.* 2002; 159(4):652–654. [PubMed: 11925305]

- Munafo MR, Johnstone EC, Guo B, Murphy MF, Aveyard P. Association of COMT Val108/158Met genotype with smoking cessation. *Pharmacogenet Genomics*. 2008; 18(2):121–128. [PubMed: 18192898]
- Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Archives of General Psychiatry*. 2005; 62(6):649–659. [PubMed: 15939842]
- Wing VC, Wass CE, Soh DW, George TP. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. *Annals of the New York Academy of Sciences*. 2012; 248(1):89–106.

Figure 1.

Percentage impairment in visuospatial working memory (measured as distance from target in mm) following overnight abstinence ($\text{Abstinence-Baseline}/\text{Baseline} \times 100$), as a function of diagnosis (schizophrenia vs. control) and COMT Val¹⁵⁸Met genotype (Val-Val, Val-Met, Met-Met). Error bars show Standard Error of the Mean.