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COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia

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Abstract

Preliminary evidence suggests that a single nucleotide polymorphism (SNP), the val108/158met SNP, within the gene that codes for catechol-*O*-methyltransferase (COMT), a key enzyme involved in regulating dopamine (DA) transmission within the prefrontal cortex (PFC), is related to cognitive function in schizophrenia and cognitive improvement with atypical antipsychotic drugs (APDs). Specifically, several studies have identified an association between working memory and executive functions, and COMT val108/158met genotype in schizophrenia; although there have been several negative findings that are likely related to small sample sizes and, possibly, medication status of patients at the time of testing. The association between COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine was investigated in a relatively large prospective sample of patients with schizophrenia, most of whom were unmedicated at baseline. Patients were genotyped for the COMT val108/158met SNP after completing a cognitive battery consisting of tests of attention, working memory, verbal learning and memory, executive function, and verbal fluency at baseline and after 6 weeks and 6 months of treatment with clozapine. Consistent with several previous studies, an association between COMT genotype and tests of executive function and working memory was identified at baseline. In addition, a novel interaction between genotype and improvement on tests of attention and verbal fluency was identified. Specifically, met homozygous and val/met heterozygous patients demonstrated significantly greater improvement than val homozygous patients following 6 months of treatment with clozapine. The results are discussed in relation to previous cross-sectional studies and prospective investigations of the associations between COMT genotype, cognition, and cognitive improvement with atypical APDs in schizophrenia.

Keywords: Schizophrenia; Neuropsychology; Catechol-*O*-methyltransferase; Pharmacogenetics; Clozapine

1. Introduction

Dopamine (DA) projections to the prefrontal cortex (PFC) comprising the mesocortical DA system are essential for normal cognition (Aalto et al., 2005; Brozoski et al., 1979). Reductions in mesocortical DA function, either by chemical ablation or disease, result in cognitive impairment, particularly in executive functions and working memory (Phillips et al., 2004; Brozoski et al., 1979; Roberts et al., 1994; Owen, 2004). Similarly, exogenous manipulation of DA under normal conditions enhances working memory and executive functions in primates and rodents. However, this effect is biphasic as either too little or too much DA impairs cognition (Mattay et al., 2000; Granon et al.,

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2000) suggesting that DA function in the PFC follows an inverted U-curve whereby increases or decreases from an optimal level result in cognitive impairment (Goldman-Rakic et al., 2000).

It has been hypothesized that the cognitive deficits observed in schizophrenia, especially those related to executive functions and working memory, arise to some extent from reduced DAergic transmission in the PFC (Doran et al., 1987; Davis et al., 1991; Weinberger et al., 1988). Post-mortem and in vivo imaging investigations have directly linked PFC DA function to cognitive impairment (Abi-Dargham et al., 2002; Weinberger et al., 1988), and pharmacological studies indicate that direct and indirect DA agonists improve PFC cognitive functions and cerebral neurophysiology in patients (Barch and Carter, 2005; Goldberg et al., 1991; Dolan et al., 1995). Recently, evidence that genetic polymorphisms related to DA function and susceptibility for schizophrenia influence cognitive functions related to PFC function has provided further evidence that mesocortical DA dysfunction is related to cognitive impairment in schizophrenia (for review see Weinberger et al., 2001). A single nucleotide polymorphism (SNP) in the gene that codes for catechol-*O*-methyltransferase (COMT), an enzyme that contributes to the removal of DA from the synapse, has attracted considerable attention due to the importance of COMT in regulating prefrontal DA flux (Axelrod and Tomchick, 1958). The substitution of met for val at codon 108/158 results in the transcription of a theromolabile variant of the COMT enzyme with approximately 40% less enzymatic activity in humans (Chen et al., 2004). The reduced activity associated with the met variant of the COMT gene presumably results in greater availability of DA in the PFC and, thus, may be linked to some aspects of cognition in humans, hypotheses supported by findings from a gene knockout investigation in mice (Gogos et al., 1998) and an imaging study in humans (Meyer-Lindenberg et al., 2005).

Numerous studies have identified associations between COMT genotype and cognition in humans. The first study to examine the link between COMT val108/158met genotype and cognition found that, as anticipated, schizophrenia patients and normal controls homozygous for the less effective met allele made fewer perseverative errors on the Wisconsin Card Sorting Test (WCST) than subjects homozygous for the val allele (Egan et al., 2001). Subsequent studies confirmed the association between COMT genotype and WCST, and identified novel associations between COMT genotype and other tests sensitive to PFC DA function including the N-back and letter–number span tests of working memory (Goldberg et al., 2003; Bruder et al., 2005; Joober et al., 2002; Malhotra et al., 2002). However, there have also been several negative findings in both patients and controls using the WCST and variants of the N-back test (Ho et al., 2005; Bilder et al., 2002b; Tsai et al., 2003; Stefanis et al., 2004). In some cases the failure to replicate the association between COMT genotype and performance on the WCST and other tests of executive functions and/or working memory is likely related to small sample sizes within genotype groups (Bilder et al., 2002b; Tsai et al., 2003), medication status of the patients at the time of testing, or differences in the sensitivity of the selected tests to PFC DA function (Goldberg et al., 2003; Stefanis et al., 2004). However, in other cases the reason for the discrepancy is not obvious. Moreover, there is a paucity of data on the specificity of the association between COMT genotype and cognition since most studies only included one or a few measures of cognition.

In addition to the cross-sectional studies supporting associations between COMT genotype and cognition, there is emerging evidence from longitudinal studies that COMT genotype might also interact with cognitive improvement with antipsychotic drugs (APDs), particularly atypical APDs, in schizophrenia. Atypical APDs including clozapine, olanzapine, risperidone, quetiapine, and, to a lesser extent, ziprasidone and amisulpride improve cognitive function in schizophrenia (Woodward et al., 2005; Wagner et al., 2005; Harvey et al., 2004). The improvements may be due to the unique ability of atypical APDs to increase DA and acetylcholine release in the PFC; although the exact mechanism(s) remains to be determined (Meltzer, 2002; Meltzer and Sumiyoshi, 2003). Preclinical and clinical data suggests that variation in COMT activity may influence the degree of cognitive improvement and cerebral physiological changes observed with atypical APDs, including clozapine (Tunbridge et al., 2004; Bertolino et al., 2004; Weickert et al., 2004). The results from two studies indicate that met homozygous schizophrenia patients demonstrate greater improvement in working memory, as measured using the N-back task, than val homozygous subjects after several weeks of treatment with a variety of atypical APDs (Weickert et al., 2004) or just olanzapine (Bertolino et al., 2004). Remarkably, in one case the improvement also corresponded with enhanced function of the dorsolateral PFC during performance of the N-back task suggesting that met homozygous patients may benefit more from enhanced cortical DA transmission as a result of treatment with atypical APDs than val homozygous subjects (Bertolino et al., 2004). An additional implication of the finding that COMT genotype interacts with cognitive improvement with atypical APDs is that the results from previous cross-sectional studies in patients might have

been influenced by the medication status of patients at the time of neuropsychological testing and that this might explain some of the discrepant findings (e.g. Rosa et al., 2004; Ho et al., 2005).

Unfortunately the conclusions reached regarding the potential interactions between atypical APDs and COMT genotype must be considered preliminary until studies with larger sample sizes and more comprehensive neuropsychological batteries are carried out. The two prior investigations of interactions between COMT genotype and atypical APD related cognitive improvement included 30 patients or less, including 5 or less met homozygous subjects and employed relatively circumscribed neuropsychological test batteries (Bertolino et al., 2004; Weickert et al., 2004). It is plausible that interactions between COMT genotype and cognitive improvement are not limited to the N-back task given the relatively broad impact that atypical antipsychotics may exert on cognitive function. Similarly, it remains to be determined if the interactions are observed with the atypical APD clozapine specifically.

In order to address several questions relating to the relationship between COMT genotype, cognition, cognitive improvement with clozapine in schizophrenia, and methodological shortcomings of earlier studies, the associations between COMT genotype, cognitive function at baseline, and cognitive improvement with atypical APDs was examined in a relatively large sample of patients with schizophrenia who underwent neuropsychological evaluation at baseline when they were largely unmedicated and after 6 weeks and 6 months of treatment with clozapine. It was anticipated that the current study would 1) clarify the specificity of the association between COMT genotype and cognitive function at baseline in a largely unmedicated sample of patients; and 2) identify the interactions between COMT genotype and cognitive improvement with clozapine, a drug previously shown to increase cortical DA release in rodents and primates (Youngren et al., 1999; Kuroki et al., 1999).

2. Methods

2.1. Subjects

86 schizophrenia patients with preserved blood samples available for genetic analysis were included in this study. The subjects included in this study represent the sub-set of patients with DNA available for genotyping included in a larger cohort of approximately 280 followed at the Case Western Reserve University. All subjects underwent at least one neuropsychological evaluation at baseline and after 6 weeks and 6 months of treatment with clozapine. The majority of patients (82%) were unmedicated at baseline. The rest were receiving typical APDs. The methods surrounding the recruitment and screening of subjects are described in detail in several prior reports (Kenny and Meltzer, 1991; Lee et al., 1999; Hwang et al., 2005). Briefly, diagnoses were based on a structured interview from which DSM-III-R or DSM-IV criteria were extracted and reviewed by a research psychiatrist (H. Y. Meltzer). Exclusion criteria included history of learning disabilities, drug/alcohol abuse, head trauma, stroke, or neurological illness. Subjects were genotyped by the Vanderbilt University Human Genetics Core Laboratory for the COMT val108/158met SNP using previously described methods (Bilder et al., 2002b). The demographics and baseline neuropsychological test results for the 86 subjects included in this study are presented in Table 1. The genotype groups were in Hardy–Weinberg equilibrium ($\chi^2(3)=2.70, p<.449$). The only variable the genotype groups differed on was ethnicity ($\chi^2(2)=14.47, p<.002$). A significantly greater proportion of the val homozygous group was composed of African Americans than the met homozygous ($\chi^2(1)=12.49, p<.001$) and val/met heterozygous groups ($\chi^2(1)=6.04, p<.015$).

2.2. Neuropsychological testing

Patients were administered a neuropsychological battery to determine neurocognitive functioning at baseline and after six weeks and six months of treatment with clozapine. The battery consisted of frequently used neuropsychological tests sensitive to cognitive impairment in schizophrenia (Kenny and Meltzer, 1991). The battery included tests of working memory (Auditory Consonant Trigram Test (ACTT): Peterson and Peterson, 1959), executive function (WCST: Heaton, 1980; Wechsler Intelligence Scale for Children—Revised (WISC-R) Mazes Subtest: Wechsler, 1974), verbal learning and memory (Buschke Selective Reminding Test (BSRT); Buschke and Fuld, 1974), verbal fluency (Category Instance Generation Test (CIGT): Newcombe, 1969; Controlled Oral Word Association Test (COWAT): Benton, 1968), and processing speed (Digit Symbol Subtest (DSST) from WAIS-R: Wechsler, 1981). All tests were administered manually according to published guidelines by trained psychology assistants.

2.3. Statistical analysis

The set of nine neuropsychological variables derived from the seven tests was reduced to three domain scores based on a principal components analysis carried out on the entire cohort of approximately 280 patients and a

Table 1
Sample demographics and baseline neuropsychological functioning

Variable	Genotype			Total sample	Test statistic
	met/met	val/met	val/val		
n	21	35	29	86	$\chi^2=2.70$, $p<.448$
Age	29.0 (8.1)	31.2 (8.1)	31.8 (8.1)	30.8 (8.1)	$F(2,85)=0.80$, $p<.455$
Education [a]	11.5 (1.7)	12.1 (2.0)	11.6 (1.7)	11.8 (1.8)	$F(2.74)=0.65$, $p<.527$
Sex (men/women)	13/8	26/9	24/6	63/23	$\chi^2=2.10$, $p<.352$
Ethnicity (White/AA)	19/1	26/8	14/16	59/25	$\chi^2=14.47$, $p<.002$
Age at onset [b]	19.2 (7.2)	21.1 (5.3)	22.0 (5.6)	20.9 (5.9)	$F(2,84)=1.31$, $p<.277$
Illness duration [b]	9.7 (5.8)	10.1 (7.2)	9.9 (7.7)	10.0 (7.0)	$F(2,84)=0.22$, $p<.980$
Previous hospitalizations [b]	6.1 (7.5)	5.2 (4.6)	6.1 (6.3)	5.7 (6.0)	$F(2,84)=0.24$, $p<.787$
Medicated at baseline (No/Yes) [c]	16/5	28/5	23/5	67/15	$\chi^2=0.65$, $p<.724$
Cognitive domain Z-scores					
Global cognitive score	−1.28 (0.78)	−1.52 (1.03)	−1.71 (0.85)	−1.52 (0.92)	$F(2,80)=1.30$, $p<.279$
Memory	−1.33 (0.97)	−1.50 (1.31)	−1.94 (1.15)	−1.60 (1.19)	$F(2,81)=1.84$, $p<.166$
Attention and verbal fluency	−1.40 (0.76)	−1.51 (0.90)	−1.51 (0.79)	−1.48 (0.82)	$F(2,82)=0.13$, $p<.876$
Executive function	−1.13 (1.48)	−1.60 (1.57)	−1.67 (1.30)	−1.51 (1.46)	$F(2,85)=0.95$, $p<.391$
Neuropsychological test raw scores					
ACTT	30.0 (6.9)	30.0 (9.1)	23.6 (8.7)	27.7 (8.9)	$F(2,84)=5.61$, $p<.006$
BSRT immediate recall	7.6 (1.7)	6.8 (2.9)	6.7 (2.7)	7.0 (2.6)	$F(2,84)=0.87$, $p<.426$
BSRT delayed recall	6.7 (2.5)	5.8 (3.5)	5.7 (3.3)	6.0 (3.2)	$F(2,84)=0.68$, $p<.509$
COWAT	29.8 (11.6)	30.5 (14.3)	29.9 (13.9)	30.1 (13.4)	$F(2,83)=0.22$, $p<.979$
CIGT	41.0 (11.5)	37.9 (16.6)	41.6 (11.9)	39.9 (14.0)	$F(2,83)=0.62$, $p<.544$
WAIS-R DSST	6.4 (2.2)	6.3 (2.2)	5.6 (2.2)	6.1 (2.2)	$F(2,84)=1.10$, $p<.339$
WCST categories	3.1 (2.5)	2.5 (2.3)	2.5 (2.2)	2.7 (2.3)	$F(2,85)=0.47$, $p<.626$
WCST perseverative errors	16.9 (9.2)	20.3 (10.1)	24.1 (9.0)	20.9 (9.8)	$F(2,77)=3.30$, $p<.043$
WISC-R mazes subtest	8.4 (5.7)	8.8 (4.0)	7.5 (5.2)	8.3 (4.8)	$F(2,82)=0.54$, $p<.585$

Mean and (SD)
[a] Unavailable for 11 subjects.
[b] Unavailable for 1 subject.
[c] Unavailable for 4 subjects.

sample of 26 healthy controls that completed the same battery of tests in order to reduce the number of dependent variables included in the statistical analyses. Based on the observed scree plot and Eigen values, along with the proportion of variance explained by the model, a reliable three factor model was selected. The three factors explained 69% of the total variance and the minimum loading of any test on its respective factor was .58. The three domain scores, and individual tests within each, were: 1) memory function (BSRT immediate and delayed recall, ACTT, WISC-R Mazes subtest); 2) attention and verbal fluency (COWAT, CIGT, DSST); and 3) executive function (WCST categories and percent perseverative errors scores). The factor scores are reported as *Z*-scores which were created by standardizing each neurocognitive variable to the control sample and averaging the standardized scores included in each factor. In addition, a global cognitive score was created by averaging the mean *Z*-scores of the nine neurocognitive variables.

Group differences on each of the three cognitive factors and the global cognitive score at baseline were examined using one-way ANOVAs. Except for preplanned contrasts carried out on the ACTT and WCST percent perseverative errors scores based on a-priori hypotheses, group differences on specific neuropsychological test variables at baseline were not the focus of this analysis. Given the previous findings of a significant association between COMT genotype, WCST and working memory, it was anticipated that met homozygous subjects would demonstrate fewer perseverative errors on the WCST and higher scores on the ACTT than val homozygous subjects at baseline. As such, one-tailed contrasts between the met/met and val/val groups on the WCST percent perseverative errors score and the ACTT were performed on the baseline data. The effect of genotype on the WCST percent perseverative errors score and ACTT was also examined after covarying for global cognitive scores and ethnicity, and within the subset of patients that were unmedicated at baseline.

Longitudinal changes in cognitive function and interactions between COMT genotype and cognitive change with clozapine were examined using linear mixed model analyses due to the fact that not all subjects completed every assessment. Linear mixed models provide a more powerful alternative to traditional repeated measures models in datasets where some subjects have incomplete data (Maxwell and Delaney, 2004). The covariance matrix was modeled as compound symmetric in the mixed models analyses and baseline score was entered as a covariate. As with the cross-sectional analysis of baseline data, the analyses were restricted to the global cognitive and domain scores, with the exception of the WCST percent perseverative and ACTT measures, which were examined separately due to previous reports suggesting that COMT genotype may interact with working memory changes related to antipsychotic treatment.

3. Results

3.1. Group differences at baseline neuropsychological evaluation

Group means at baseline for the global cognitive measure, three domain scores, and each neuropsychological test are presented in Table 1. No genotype effects were observed on the global cognitive score or any of the domain variables at baseline (all F statistics <1.27, p-values $<.820$). The results remained unchanged when the analysis was limited to unmedicated patients.

A main effect of genotype was observed on the ACTT at baseline ($F(2,82)=5.61$, $p<.006$). The pre-planned contrast between met and val homozygous patients indicated that met homozygous patients performed better on the ACTT than val homozygous patients ($t(82)=2.67$, one-tailed $p<.005$). In addition, val/met heterozygous patients also performed better on the ACTT than val homozygous patients ($t(82)=3.04$, two-tailed $p<.004$). The results remained unchanged when global cognitive score was entered as a covariate. Similarly, the main effect of genotype observed on the ACTT remained significant when the analysis was restricted to patients who were unmedicated at baseline ($F(2,63)=3.30$, $p<.044$; as did the pre-planned contrast between met and val homozygous groups ($t(63)=1.76$, one-tailed $p<.045$) and the post-hoc contrast between val/met and val homozygous groups ($t(63)=2.48$, two-tailed $p<.017$). As can been seen in Fig. 1A, the means for medicated and unmedicated patients were similar within each genotype group. The main effect of genotype remained significant ($F(3,79)=4.02$, $p<.022$), as did the met/met vs. val/val and val/met vs. val/val contrasts, after covarying for ethnicity. Moreover, ACTT scores did not differ between Caucasians and African Americans within the val/val genotype group ($t(28)=0.04$, $p<.966$) indicating that the different ethnic composition of the val homozygous group did not account for the results.

Inspection of the distribution of WCST percent perseverative errors scores at baseline prior to comparing scores between genotypes revealed that the distribution was highly skewed (skewness = 1.24; SE = 0.26) due to the presence of eight outlier scores. The distribution of scores improved substantially after removing these subjects from the analysis (skewness = 0.24; SE = 0.27). Of the eight

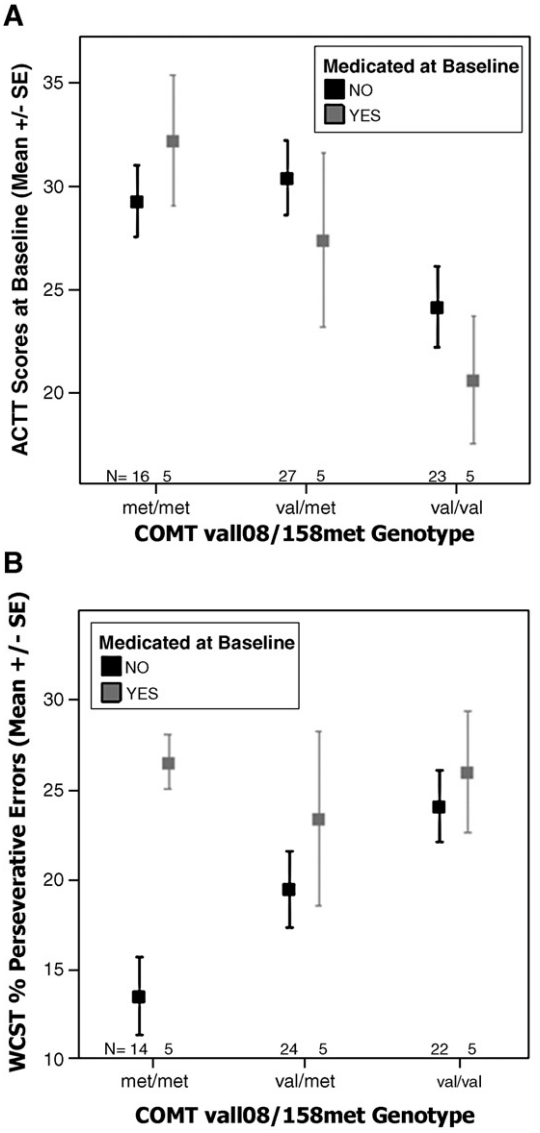

Fig. 1. Association between COMT val108/158met genotype and (A) working memory and (B) perseverative errors on the WCST in unmedicated patients and patients receiving typical APDs at baseline.

patients excluded from the WCST analysis at baseline, two, four, and two were from the met/met, val/met, and val/val groups, respectively. As anticipated, a main effect of genotype was observed for WCST percent perseverative errors scores at baseline ($F(2,75)=3.30$, $p<.043$) due to the fact that met homozygous subjects made fewer perseverative errors than val homozygous subjects ($t(75)=2.54$, one-tailed $p<.007$). No difference was observed between the val/met and val/val groups ($t(75)=1.52$, two-tailed $p<.133$). The met/met vs. val/val contrast remained significant after covarying for global cognitive scores. Similarly, the results remained significant when the analysis was restricted to unmedicated patients ($F(2,57)=5.29$, $p<.009$; met/met vs. val/val contrast $t(57)=3.24$, one-tailed $p<.001$). The means for WCST percent perseverative errors scores for medicated and unmedicated patients within each genotype group are presented in Fig. 1B. The met/met vs. val/val contrast only reached significance at the trend level after covarying for ethnicity (one-tailed p-value$<.095$); however, there was no difference in WCST perseverative error scores between African Americans and Caucasians within the val homozygous group ($t(26)=0.81$, two-tailed $p<.427$).

3.2. Interactions between COMT genotype and cognitive improvement with clozapine

The global cognitive score, domain Z-scores, and raw neuropsychological test scores following 6 weeks and 6 months of clozapine treatment are listed in Table 2. Linear mixed model analyses identified a main effect of time on the global cognitive score ($F(2,95)=3.43$, $p<.037$) and the attention and verbal fluency domain ($F(2,96)=26.44$, $p<.001$); both in the direction of improved performance over time, and a significant interaction between COMT genotype and improvement on the attention and verbal fluency domain score ($F(4,96)=2.78$, $p<.032$). Follow-up contrasts revealed that the global cognitive score improved significantly from baseline to 6 months ($t(95)=2.62$, $p<.011$). Follow-up contrasts within the attention and verbal fluency domain indicated that both the met/met and val/met groups demonstrated superior performance at the 6 month assessment compared to the val/val group ($t(96)=2.48$, $p<.016$; and $t(96)=3.84$, $p<.001$, respectively), after controlling for baseline performance. As depicted in Fig. 2, the differences observed between groups at 6 months were due to the fact that met homozygous and val/met heterozygous groups, but not the val homozygous group, demonstrated significant improvement from baseline to 6 months. The interaction observed on the attention and verbal fluency domain remained significant when the analysis was restricted to patients that were unmedicated at baseline ($F(4,71)=4.06$, $p<.006$). Again, the interaction was due to the fact that both met homozygous and val/met heterozygous patients demonstrated superior performance at 6 months compared to val homozygous patients ($t(71)=2.21$, $p<.031$; and $t(71)=4.55$, $p<.001$).

Each neuropsychological measure within the attention and verbal fluency domain (COWAT, CIGT, DSST) was

Table 2
COMT val108/158met genotype and cognitive change with clozapine

	Genotype											
	met/met				val/met				val/val			
	6 weeks		6 months		6 weeks		6 months		6 weeks		6 months	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Cognitive domain												
Global cognitive score	11	−1.2 (0.9)	13	−1.0 (1.0)	25	−1.5 (0.9)	24	−1.2 (1.0)	16	−1.6 (0.8)	15	−1.8 (0.8)
Memory	12	−1.5 (1.0)	14	−1.5 (1.4)	25	−1.7 (1.1)	24	−1.3 (1.3)	17	−2.0 (1.1)	15	−1.5 (1.3)
Attentional and verbal fluency	12	−0.9 (0.9)	13	−0.7 (0.8)	25	−1.2 (0.9)	24	−0.9 (0.7)	16	−1.1 (1.0)	15	−1.3 (0.7)
Executive function	13	−0.9 (1.3)	14	−0.8 (1.1)	25	−1.6 (1.7)	24	−1.7 (1.4)	17	−1.9 (1.5)	15	−1.9 (1.4)
Neuropsychological test scores												
ACTT	13	23.7 (7.4)	14	23.2 (10.0)	25	25.6 (6.4)	24	26.6 (9.1)	17	21.1 (6.2)	15	20.6 (9.0)
BSRT immediate recall	13	8.0 (1.9)	14	8.5 (2.3)	25	7.4 (2.5)	24	8.3 (2.5)	17	7.4 (2.3)	15	7.4 (2.8)
BSRT delayed recall	13	7.8 (2.8)	14	7.2 (3.4)	25	6.2 (3.1)	24	7.2 (2.8)	17	5.8 (3.0)	15	6.3 (3.2)
COWAT	13	39.0 (13.9)	14	39.6 (13.1)	25	34.5 (12.4)	24	39.1 (12.8)	17	32.6 (15.1)	15	33.2 (11.7)
CIGT	13	47.4 (13.9)	14	49.9 (14.1)	25	42.9 (14.1)	24	45.6 (11.7)	17	42.9 (16.0)	15	41.2 (10.3)
WAIS-R DSST	12	6.7 (1.9)	13	7.4 (2.3)	25	7.2 (2.7)	24	7.8 (2.7)	16	7.3 (2.8)	15	6.6 (2.1)
WCST categories	13	3.5 (2.3)	14	3.1 (2.5)	25	2.6 (2.5)	24	2.3 (2.2)	17	2.1 (2.1)	15	2.1 (2.2)
WCST perseverative errors	13	19.0 (14.7)	14	14.9 (7.7)	25	26.0 (18.1)	24	26.2 (15.3)	17	27.7 (17.7)	15	27.3 (14.7)
WISC-R mazes subtest	12	8.0 (3.0)	14	9.3 (4.2)	25	8.4 (3.4)	24	9.6 (4.4)	17	7.6 (4.4)	15	6.3 (3.3)

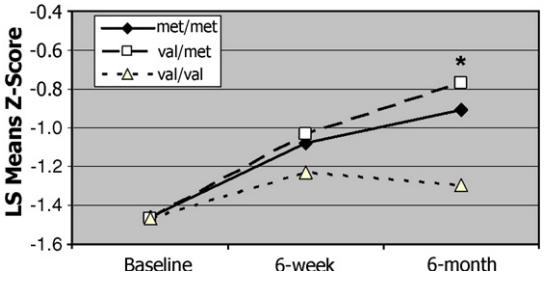

Fig. 2. Change in attention and verbal fluency domain scores with clozapine treatment in COMT val108/158met homozygous and heterozygous schizophrenia patients. *met/met and val/met groups significantly greater than val/val group; ANCOVA genotype by time interaction ($p<.05$) with baseline entered as a covariate.

subjected to a linear mixed model analysis in order to determine if the changes over time and interaction was observed on all or just a specific test(s) within this domain. A main effect of time was observed on all three measures included within this domain (all F statistics >9.41, $p<.001$); however, the interaction term only reached significance for the COWAT ($F(4,99)=4.40$, $p<.003$). Post-hoc contrasts indicated that met/met and val/met groups had higher COWAT scores, compared to the val homozygous group, at both the 6 week ($t(99)=3.45$, $p<.001$; and $t(99)=2.45$, $p<.017$, respectively) and 6 month evaluations ($t(99)=3.36$, $p<.002$; and $t(99)=4.24$, $p<.001$, respectively).

With respect to the ACTT and WCST percent perseverative errors scores, a main effect of time was observed only on the ACTT ($F(2,102)=7.05$, $p<.002$) due to the fact that ACTT scores decreased over time. No main effects or interactions were observed on the WCST percent perseverative errors scores (all F statistics <0.57, p-values $<.573$). Post-hoc contrasts indicated that, compared to baseline, patients with the met/met genotype demonstrated lower ACTT scores at 6 weeks ($t(102)=2.13$, $p<.036$) and 6 months ($t(102)=2.66$, $p<.001$). Patients with the val/met genotype also demonstrated a reduction in ACTT scores at 6 weeks ($t(102)=2.32$, $p<.023$). Conversely, patients with the val/val genotype did not demonstrate any changes in ACTT scores at either 6 weeks ($t(102)=1.39$, $p<.167$) or 6 months ($t(102)=0.71$, $p<.482$), relative to baseline.

4. Discussion

The current results provide further evidence of an association between COMT val108/158met genotype, cognitive function, and cognitive improvement with antipsychotic treatment in schizophrenia. As anticipated, at baseline patients homozygous for the met allele made fewer perseverative errors on the WCST and demonstrated superior performance on the ACTT compared to val allele homozygous patients. Moreover, the effect of genotype remained significant after covarying for global cognitive function suggesting that the relationship between COMT genotype and cognition is specific to working memory and executive function. The differences observed at baseline on the WCST replicates previous studies that have, for the most part, also identified an association between COMT genotype and performance on the WCST in patients with schizophrenia and healthy controls (Egan et al., 2001; Joober et al., 2002; Malhotra et al., 2002; Rosa et al., 2004; Bruder et al., 2005). However, in contrast to previous investigations in schizophrenia, the current findings observed at baseline were obtained in a largely unmedicated sample of patients. In fact, the main effect of genotype on the WCST percent perseverative errors score was substantially more robust in unmedicated patients; however, the small number of medicated patients at baseline precluded a formal comparison between medicated and unmedicated patients. Nonetheless, this observation suggests that the association between genotype and WCST might be slightly attenuated when subjects receiving typical APDs are included in a study. Conversely, the difference between met and val homozygous subjects appeared to slightly increase over assessments following treatment with clozapine. Combined, these observations suggest that medication status of patients at the time of testing might explain why several prior studies did not identify a significant genotype effect on the WCST in schizophrenia patients and that atypical APDs might augment the differences observed between genotypes, perhaps as a consequence of differential change over time within groups. Larger patient samples followed prospectively with a greater proportion of medicated, relative to unmedicated patients at baseline, are likely required to confirm these speculations.

The relationship between working memory and COMT genotype has not been examined before with the ACTT, although the current results are in agreement with several prior studies that found met homozygous subjects performed better on working memory tasks such as the N-back and letter–number span than val homozygous subjects (Goldberg et al., 2003; Bruder et al., 2005). The version of the ACTT used in the current study required subjects to recall three consonants read to them following a 15 second interference delay period during which subjects counted backwards aloud (Peterson and Peterson, 1959). Lesion studies using this version of the ACTT and imaging studies of working memory tasks that included a distraction task during the delay period

strongly suggest that the ACTT relies on the integrity of the PFC (Postle, 2005; Sakai et al., 2002; Stuss et al., 1982). It is noteworthy that studies that have identified an association between COMT genotype and working memory, including the present study, all included free recall, as opposed to recognition, working memory tasks that significantly tapped executive sub-processes such as manipulation and updating of information, and resistance to distraction (Goldberg et al., 2003; Bruder et al., 2005). Conversely, studies that included recognition working memory and/or tasks that do not tax executive processes have not found an association between COMT and working memory (Bruder et al., 2005; Stefanis et al., 2004). Pharmacological studies suggest that recall working memory tasks that tap executive processes are especially sensitive to PFC DA activity (Mattay et al., 2000, 2002), whereas recognition working memory tasks that do not tax executive sub-components are not (Kimberg et al., 2001; Bartholomeusz et al., 2003). As such, it is plausible that the effect of COMT genotype observed in the current and previous studies relates more to the executive components of the task than simply the on-line maintenance of information.

Consistent with two previous smaller studies, a significant interaction between COMT genotype and cognitive improvement with atypical APDs was observed. Specifically, met carriers improved to a greater degree on the attention and verbal fluency domain than val homozygous patients following treatment with clozapine. The attention and verbal fluency domain consisted of the DSST, COWAT, and CIGT. Inspection of the individual tests within this domain indicated that the interaction between genotype and cognitive improvement with clozapine was most apparent on the COWAT test, although met carriers also improved substantially more than val homozygous patients on the CIGT as well. The magnitude of the difference in change between met carriers and val homozygous patients was notable as the improvement detected in the met homozygous and heterozygous patients was approximately 9 and 8 words on the COWAT and CIGT, respectively, compared to a 4 word improvement and no change on the COWAT and CIGT, respectively, in val homozygous patients. With few exceptions (Buchanan et al., 1994; Bilder et al., 2002a), improvement in verbal fluency with clozapine has been consistently found in both double-blind, random assignment (Lee et al., 1999; Potkin et al., 2001), and naturalistic open label trials (Hagger et al., 1993; Zahn et al., 1994; Purdon et al., 2001). The interaction between improvement with clozapine and COMT genotype suggests that the failure of a minority of studies to identify a significant improvement in verbal fluency with clozapine might have related, in part, to the genotype of the subjects included in the studies. It is noteworthy in this regard that one such study may have included up to 3 times more val homozygous than met homozygous patients (Bilder et al., 2002b,a).

The finding that the COMT val108/158 met genotype was associated with improvement in the attention and verbal fluency domain but not the memory function domain, which included the most specific test of working memory, the ACTT, and the executive function domain, which includes the WCST categories and percent perseverative error scores, indicates that the relationship of COMT genotype to response to treatment goes beyond working memory (Weickert et al., 2004; Bertolino et al., 2004; Mattay et al., 2003). The failure to find an association between improvement in working memory and val108/158met genotype might relate to the difference in medication and subject population, compared to previous studies. The potential to improve any domain of cognition would be expected to be, in part, a function of baseline DAergic activity and the extent of enhancement by further release. Clozapine produces much larger increases in cortical DA efflux in rat cortex than olanzapine (Kuroki et al., 1999), which was used in a previous study (Bertolino et al., 2004). Moreover, although the current results conflict with previous reports in patients that found olanzapine improves working memory in met homozygous patients, they are entirely consistent with evidence that amphetamine significantly reduces N-back working memory accuracy in healthy subjects homozygous for the met allele and has a slight, non-significant negative effect in val homozygous subjects (Mattay et al., 2003).

The observation that on the one hand clozapine improves verbal fluency, but on the other reduces working memory performance in met homozygous patients has several implications. First, it indicates that as in healthy subjects, and in accordance with the inverted U-curve hypotheses of DA function, too much PFC DA activity impairs working memory performance in schizophrenia patients. At baseline when most patients were unmedicated, met homozygous patients performed better than val homozygous patients on the ACTT and, therefore, might have been operating at, or near the peak of the DA U-curve. The addition of clozapine, which evokes robust DA release in the PFC, could have increased cortical DAergic activity in these subjects beyond the optimal point for working memory. Second, it implies that the optimal level of DA function required for one task is not necessarily the same as that required for another task. Such a hypothesis is not unexpected given evidence that: 1) mesocortical DA dysfunction impairs some cognitive functions, such as working memory, but can actually enhance some aspects of attention in rodents and

primates (Granon et al., 2000; Roberts et al., 1994); and 2) findings from factor analytic studies in humans, including the current study, indicating that neuropsychological tests of "frontal" lobe function, such as the COWAT, WCST, and the ACTT, do not load onto a single unitary factor, but appear to rely on unique cognitive process (Miyake et al., 2000; Boone et al., 1998). As such, it is not unreasonable to expect that different cognitive tasks might be differentially sensitive to DA and require different levels of DA activity for optimal performance.

There are several caveats that may limit the conclusions that can be drawn from the current study. It is possible that the different ethnic compositions of the genotype groups influenced the current results. Specifically, the val/val group was comprised of significantly more African Americans than the met/met and val/met groups. However, it seems unlikely that ethnicity influenced the current results given evidence that the COMT val108/158met SNP accounts for the same variance in COMT activity in both African Americans and Caucasians (Chen et al., 2004). Nonetheless, the results for the WCST could not be confirmed after covarying for ethnicity. In addition, the patients included in this study were largely treatment refractory, hence the initiation of clozapine, thus it remains to be determined if the same results would be obtained in a more general schizophrenia sample. The current results are informative, but will require replication, particularly with respect to the interactions identified between COMT genotype and longitudinal changes in cognition with clozapine.

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