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COMT genotype and response to cognitive remediation in schizophrenia☆

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ABSTRACT

Background: A functional polymorphism of the catechol-*O*-methyltransferase (*COMT*) gene (Val158Met) partially appears to influence cognitive performance in schizophrenia subjects and healthy controls by modulating prefrontal dopaminergic activity. This study evaluated the association of the *COMT* Val108/158 Met genotype with response to computerized neurocognitive remediation (CRT).

Method: 145 subjects with DSM-IV-TR schizophrenia or schizoaffective disorder were genotyped via saliva sampling. Subjects were evaluated on neurocognitive assessments (MATRICS) and clinical symptoms (PANSS) at baseline and endpoint after 12 weeks of CRT. "Improvement" was defined as ≥67% of cognitive domains (≥4) showing performance increases. If ≤67% (≤2) of domains improved, the change was defined as "minimal improvement." A general linear model was conducted for change of each cognitive domain.

Results: Of 145 subjects, data from 138 subjects were usable. Distribution of *COMT* genotype: Met/Met: 28 (20.29%), Val/Met: 61 (44.20%), and Val/Val: 49 (35.51%). No significant differences were seen among genotype groups at baseline or across genotype group for "Improvement" vs. "Minimal Improvement." GLM analysis showed significant differences in Verbal Learning ($p = 0.003$), Visual Learning ($p = 0.014$) and Attention/Vigilance ($p = 0.011$) favoring Met/Met and Val/Met groups.

Conclusions: The low activity Met allele (Met/Met; Val/Met) was associated with significantly greater improvements in the MATRICS domains of Verbal Learning, Visual Learning and Attention/Vigilance after CRT.

1. Background

Impaired cognitive functioning has high relevance in schizophrenia because of its strong relationship with poorer functioning in areas such as work, school, self-care, independent living skills, and social relationships (Green, 1996; McGurk and Mueser, 2004). Effective treatment of cognitive impairments in schizophrenia has the potential to improve some of these important targets. Cognitive remediation programs providing structured, time limited restorative task practice of cognitive functioning using computerized software have demonstrated cognitive benefits in subjects with schizophrenia (Lindenmayer et al., 2008; McGurk et al., 2007; Wykes et al., 2011).

Dopamine (DA) modulates both working memory performance and task-dependent neuronal firing rates within the prefrontal cortex (PFC) in a complex manner (Arnsten, 2007; Weinberger et al., 2001). Abnormalities of prefrontal dopaminergic activity mediating information processing are found both in subjects with schizophrenia and in unaffected individuals who are genetically at risk for schizophrenia, suggesting that genetic polymorphisms affecting prefrontal dopaminergic function may represent susceptibility alleles for schizophrenia. One such candidate is a functional polymorphism of the catechol-o-methyl-transferase (*COMT*) gene that markedly affects enzyme activity in the prefrontal area. A single nucleotide polymorphism (SNP), Val 108/158 Met, in the coding region of the *COMT* gene, has been studied extensively (Lachman et al., 1996; Lotta et al., 1995). The *COMT* Met allele is associated with a lower activity form of COMT, decreased catabolism and increased availability of catecholamines and better performance on a cognitive measure of prefrontal functioning (Wisconsin Card Sorting Test (WCST)) (Egan et al., 2001; Ira et al., 2013; Malhotra et al., 2002;

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Weinberger et al., 2001; Wirgenes et al., 2010). In contrast, the Val allele is associated with a more active form of COMT and poorer executive cognition (Egan et al., 2001),

The differential *COMT* genotype effects on working memory functions have been used as a predictor of pharmacological treatment response in subjects with schizophrenia (Bertolino et al., 2004; Weickert et al., 2004), but few studies have examined the *COMT* genotype as predictor of cognitive interventions (Bosia et al., 2014a; Panizzutti et al., 2013) and results have been inconsistent (Greenwood et al., 2011). Hence, the question of this possible association requires further examination.

The *COMT* genotype was examined as a predictor of response after a 12-week, computerized cognitive remediation intervention (CRT) in subjects with chronic schizophrenia. It was hypothesized that the *COMT* Met/Met genotype would be associated with better response as compared to subjects with the *COMT* Val/Val genotype.

2. Method

Inpatients and outpatient subjects with DSM-IV-TR schizophrenia or schizoaffective disorder were consecutively enrolled from the parent study assessing the effectiveness of CRT (Lindenmayer et al., 2008) and were genotyped. All subjects were on stable antipsychotic medications during the 12 week duration of CRT. Inpatient subjects enrolled in the CRT program were in the sub-acute illness phase awaiting placement into a community residence. All subjects, inpatients and outpatients, were enrolled in rehabilitation programs which included treatment groups on understanding mental illness, coping skills, nutrition, and understanding medications and symptoms. Inpatients were enrolled during their post-acute state while in rehabilitation. All subjects were required to be stable, and inpatients were not dissimilar to outpatients who had been recently discharged. The protocol was approved by the local IRB (Nathan S. Kline Institute for Psychiatric Research; clinicaltrials.gov identifier: NCT00664274) and all subjects signed an informed consent.

2.1. Inclusion criteria

(1) Age 18–55 years; (2) Inpatients or outpatients; (3) DSM-IV-TR schizophrenia or schizoaffective disorder, with an illness duration ≥5 years; (4) Auditory and visual acuity adequate to complete cognitive tests; (5) Stable dose of atypical antipsychotic medication for at least 4 weeks prior to enrollment; (6) Good physical health determined by physical examination and laboratory tests; (7) Capacity and willingness to give written informed consent; (8) at least an 8th grade reading level as evidenced from psychological assessment during the chart review or the Wide-Range Achievement Test–Third Edition (WRAT-3) (Wilkinson, 1993).

2.2. Exclusion criteria

(1) Inability to read or speak English; (2) Documented disease of the central nervous system (CNS); (3) History of intellectual disability predating onset of symptoms of psychosis; (4) Clinically significant or unstable cardiovascular, renal, hepatic, gastrointestinal, pulmonary or hematologic conditions; (5) HIV +; (6) Subjects diagnosed with substance dependence.

The CRT program included a standardized curriculum of exercises drawn from the CRT computerized software Cogpack (Professional Version Marker Software Klaus Marker, 2004), providing broad based practice of working memory, attention, cognitive flexibility, and verbal learning with a programmed increase in difficulty in one-hour sessions occurring three times per week over 12 weeks (Lindenmayer et al., 2008; McGurk et al., 2009, 2005; Sartory et al., 2005). The groups were run by two staff members (MA or PhD level psychologists, MA or PhD level psychology interns/externs, and/or research associates). Training for the staff members was performed by a PhD level neuropsychologist with over 10 years of experience in Cognitive Remediation in severe mental illness. The staff members' role was to supervise navigation of the software by patients, orient new members, troubleshoot if a patient had difficulty performing the cognitive exercises, monitoring and recording progress.

3. Neurocognitive and clinical assessments

Interviewers assessed psychiatric diagnoses at baseline with the Structured Clinical Interview for DSM-IV and reading level based on chart review or with the WRAT III Reading Subtests. At baseline and 12 weeks, interviewers assessed cognitive functioning with the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery-defined indices (MCCB) (Nuechterlein et al., 2008), and symptoms with the Positive and Negative Syndrome Scale (PANSS). MCCB assessments were administered by 1 of 3 trained MA/MS or PhD level staff with psychology training who were blind to the study hypothesis and who were supervised by a senior PhD level neuropsychologist for inter-rater reliability and test administration fidelity.

4. The COMT codon 158 genotyping

Saliva samples were collected in Oragene DNA collection kits (DNA Genotek) and batch processed. DNA was extracted using a PureGene DNA isolation kit (Gentra systems, Minneapolis, MN). The *COMT* codon 158 polymorphism (rs4680) was analyzed using a Taqman assay, which is based on the 5′-exonuclease activity of AmpliTaq Gold DNA Polymerase, according to the manufacturer's protocol (reviewed by De la Vega et al., 2005) (Life Technologies).

PCR reactions were carried out and analyzed in 384 well plates on an ABI Prism 7900HT Sequence Detection System. Three patterns of fluorescence are generated and captured by the instrument: homozygotes to both allele and heterozygotes. Genotype calls are made using the SNP auto-caller feature and the data are displayed in one of several convenient formats.

5. Statistical analysis

All subjects were sampled and analyzed, as long as they had a baseline and endpoint evaluation, and completed at least 18 (i.e., ≥ 50%) CRT sessions (McGurk et al., 2007). Demographic characteristics, baseline clinical and neurocognitive measures were examined for group differences between the three genotype groups (Met/Met, Val/Met, Val/Val) using Chi Square or Fisher's Exact Test for dichotomous variables and Analysis of Variance (ANOVA) for continuous variables. The confirmatory statistical comparisons of all data was carried out at a significance level of $p = 0.05$, two tailed.

Changes were examined for the MCCB Global Cognitive Index, and the individual domain scores (Processing Speed, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning and Reasoning and Problem Solving) following CRT. In order to assess whether a priori levels of improvement in cognitive domains were similar across genotypes, proxy effect sizes were computed for each domain and the Global Composite Index, which was the change in the domain score divided by the standard error of the whole sample at baseline. This effect size allowed improvements across different domains for each subject to be equated within a category (Wykes et al., 1999). “Improvement” was defined as greater than 4 domains (67%) showing performance increases (defined as an increase of at least one standard error of the whole sample's baseline scores for that test). If less than 67% (i.e., ≤ 2 domains) improved, the improvement was defined as “minimal.” This definition of improvement was previously reported by Wykes et al. (1999). Chi Square analysis was used to examine the association of the three genotype groups Met/Met, Val/Met and

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Val/Val with subjects categorized as "Improvers" vs. "Minimal Improvers". Fisher's Exact Test was used instead of Chi Square Tests if there were fewer than 5 subjects per group.

To further assess response to CRT, a General Linear Model was performed with genotype (Met/Met, Met/Val and Val/Val) as categorical predictors, the proxy effect size measure of Wykes et al. (1999) as dependent variable and age and education used as covariates. Post hoc analysis using Fisher LSD and HSD Test for Unequal Numbers was performed. HSD Test was performed due to the unequal distribution of the samples for each group. Change in PANSS scores were analyzed with General Linear Mixed Model, repeated measures (GLMM-RM) analysis (Littell et al., 1996).

The standard Bonferroni procedure was used with alpha set at 0.05, and six domain comparisons. The required p-value was $0.05/6 = 0.008$. It should be noted that the use of Bonferroni procedures reduces power and increases Type II error, therefore by also presenting effect sizes we are able to compare results across studies (Jennions and Møller, 2003; Stoehr, 1999).

Following the results of Bosia et al. (2014b) who reported an interaction between pharmacological treatment (clozapine vs. typical/atypical D2 blockers) and *COMT* polymorphism, as an exploratory analysis, we analyzed the interaction between pharmacological treatment (clozapine vs. other typical/atypical antipsychotics) and *COMT* rs4680 polymorphism using a General Linear Model to assess interaction of pharmacological treatment and *COMT* polymorphism.

5.1. Results

A total of 145 subjects were enrolled. Seven saliva samples were excluded due to technical difficulties in the sample preparation, resulting in a total of 138 subjects. The mean age was 41.50 (SD = 9.35) years with a predominance of males (91.8%). 63.0% of the sample was African-American as is representative of the population of subjects at a large urban tertiary care facility in New York, NY. Mean total PANSS score was 77.8 (SD = 12.45) at baseline. Distribution of *COMT* genetic markers for the population was as follows: Met/Met: 28 (20.29%), Val/Met: 61 (44.20%), and Val/Val: 49 (35.51%). This genotype frequency distribution is consistent with the one expected in a predominantly African American sample (Wonodi et al., 2003).

All subjects were receiving antipsychotic treatments, which included one or more antipsychotic: Aripiprazole (n = 10), clozapine (n = 26), quetiapine (n = 16), risperidone (oral (n = 28)) and intramuscular (n = 19), olanzapine (n = 12), haloperidol (oral (n = 12)) and decanoate (n = 8), paliperidone ER (oral (n = 6) and depot (n = 6)) and chlorpromazine (n = 5). Demographic, neurocognitive and clinical variables among genotypes are presented in Table 1. The analyses did not show any significant differences among genotype groups (Met/Val, Met/Met, Val/Val) at baseline, except Fisher's Exact Test showed significant differences in genotype frequencies for primary diagnosis, hospitalization status, gender and ethnic distribution ($p < 0.001$). Due to the small number of subjects diagnosed with

Table 1
Baseline demographic, clinical characteristics, and neurocognitive measures of the sample.

	Genotype				
	Met/Met (n = 28)	Met/Val (n = 61)	Val/Val (n = 49)	F/Fisher's Exact/X^2	p value
	Mean (SD)	Mean (SD)	Mean (SD)		
Age (years)	42.235 (9.200)	40.468 (8.278)	42.136 (7.457)	F (1, 137) = 0.639	0.523
Education (years)	9.569 (5.236)	13.124 (2.459)	12.189 (3.758)	F (1, 137) = 0.968	0.422
Length of stay for inpatients (months)	13.231 (2.345) Range: 7, 18	15.239 (3.457) Range: 7, 21	13.468 (4.002) Range: 6, 18	F (1, 104) = 0.906	0.411
Length of stay for outpatients (months)	5.123 (1.230) Range: 2, 6	4.123 (1.323) Range: 1, 5	3.456 (1.478) Range: 2, 6	F (1, 32) = 0.979	0.430
Chronicity of illness (years)	14.231 (3.461)	13.36 (2.364)	15.239 (3.005)	F (1, 137) = 0.909	0.389
	%	%	%		
Gender					
Male	96.429%	85.246%	93.878%	Fisher's = 32.088	<0.001
Female	3.571%	14.754%	6.122%		
Antipsychotic treatment					
Oral antipsychotics	61.234%	59.436%	57.362%	Chi Square (6) = 7.426	0.794
Intramuscular depot	38.766%	40.564%	42.638%		
Ethnicity					
African American	75.000%	59.016%	55.102%	Fisher's = 66.431	<0.001
Asian	0.000%	3.279%	2.041%		
Caucasian	10.714%	18.033%	16.327%		
Hispanic	14.286%	19.672%	24.490%		
Primary diagnosis					
Schizophrenia	64.286%	80.328%	77.551%	Chi Square (6) = 23.124	<0.001
Schizoaffective	35.714%	19.672%	22.449%		
Hospitalization status					
Inpatients	100.00%	90.164%	81.633%	Chi Square (6) = 25.365	<0.001
Outpatients	0.00%	9.836%	18.367%		
PANSS positive	17.285 (5.460)	18.257 (5.152)	18.112 (4.785)	F (1, 137) = 1.234	0.201
PANSS negative	21.286 (4.076)	20.458 (4.639)	22.127 (3.598)		
PANSS total	76.053 (13.011)	78.001 (12.489)	79.596 (11.286)		
	Mean (SE)	Mean (SE)	Mean (SE)		Bonferroni corrected p
Speed of Processing	13.926 (1.093)	14.135 (0.741)	14.024 (0.826)	F (1, 137) = 0.668	0.514
Attention/Vigilance	17.536 (2.299)	19.867 (1.571)	17.327 (1.738)	F (1,136) = 0.694	0.501
Working Memory	10.571 (1.502)	11.623 (1.018)	9.000 (1.136)	F (1, 137) = 0.689	0.500
Verbal Learning	25.964 (0.487)	26.131 (0.330)	26.388 (0.368)	F (1,137) = 0.267	0.766
Visual Learning	23.321 (0.799)	22.738 (0.541)	24.347 (0.604)	F (1, 137) = 1.979	0.142
Reasoning & Problem Solving	30.036 (0.832)	29.705 (0.564)	29.020 (0.629)	F (1,137) = 0.561	0.572
Global Composite	18.571 (0.599)	19.261 (0.409)	18.235 (0.452)	F (1, 136) = 1.474	0.233

SD = Standard Deviation, SE: Standard Error; SAFE: Social Adaptive Functional Evaluation; PANSS: Positive and Negative Syndrome Scale. Bonferroni corrected p value for neurocognitive data is $p \leq 0.007$. Fisher's Exact Test was used, if cells contained 5 or less subjects.

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schizoaffective disorder (n = 33; 22.7%; Met/Met = 10; Met/Val = 12; Val/Val = 11) an exploratory analysis of this subgroup was not conducted at this time. Additionally, because of the small number of outpatient subjects enrolled, (n = 15), further analyses were not performed to assess level of psychopathology or neurocognitive status of these 15 subjects. It should be noted, of the 15 outpatient subjects enrolled in the study, 8 (53.3%) were hospitalized as inpatients ≤ 3 months prior to enrollment in the study, thereby having a similar patient profile as enrolled inpatients. All outpatients enrolled in the study were directly discharged from the same inpatient facility. The length of stay ranged from 6 months to 21 months for inpatients and 1 month to 6 months for outpatients. Additionally, the number of hospitalizations per subject for the entire sample ranged from 5 inpatient hospitalizations to 18 inpatient hospitalizations (including current) over the course of their illness with an overall chronicity of illness of 14.24 (SD = 3.1) years.

A majority of the sample were males (91.0%). In terms of genotype distribution for this predominantly African American sample (Met/Met = 75.0% were African American, Met/Val = 59.0% were African American and Val/Val 55.1% were African American), 1 subject classified as Met/Met was female (3.5%; the 1 subject was also African American), 9 subjects classified as Met/Val were females (14.7%, with 6 African Americans and 2 Hispanics), and 3 subjects classified as Val/Val were female (6.1%, with 2 African Americans and 1 Hispanic). Given the small sample size of females, further analysis was not undertaken.

Subjects categorized as "Improved" vs. "Minimal Improved" did not show significant differences across genotype groups (Chi Square = 0.159, p = 0.971). 67.85% (n = 19) of the Met/Met group, 68.85% (n = 42) of the Val/Met group and 65.30% (n = 32) of the Val/Val group were classified as improvers, with a total of 67.39% (n = 93) showing improvement. As an exploratory analysis we combined the Met/Met and Val/Met groups, but results were not significantly different (Val/Met + Met/Met, n = 61, 68.61%; Val/Val, n = 32, 65.31%) with no significant differences observed across the two genotype groups (Chi Square = 0.153, p = 0.711).

Using the proxy effect size measure of Wykes et al. (1999) and GLM for each neurocognitive domain (Processing Speed, Attention/vigilance, Working Memory, Verbal Learning, Visual Learning, Problem Solving), significant differences were observed in Verbal Learning after Bonferroni correction (F (2,129) = 6.112, p = 0.003) for genotype group. Prior to Bonferroni correction, Visual Learning (F (2,129), p = 4.446, p = 0.014) and Attention/Vigilance (F (2, 129) = 1.754, p = 0.011) were significant for genotype group, while no effects were observed for age (F (2,129) = 0.086, p = 0.869), or education (F (2,129) = 0.089, p = 0.870).

For Verbal Learning, Fisher LSD post hoc analysis revealed significant differences for the Met/Met (p = 0.006) and Met/Val groups (p = 0.002) with the Met/Met group showing higher difference scores (0.137, SE = 0.049), followed by the Met/Val group (0.127, SE = 0.041) for improvement compared to the Val/Val group.

For Visual Learning, Fisher LSD post hoc analysis revealed significant differences for the Met/Met (p = 0.005) and Met/Val groups (p = 0.048) for Visual Learning with the Met/Met group showing higher difference in proxy effect scores (0.218, SE = 0.076), followed by the Met/Val group (0.2125, SE = 0.063) for improvement compared to the Val/Val group.

For Attention/Vigilance, Fisher LSD post hoc analysis revealed significant differences for the Met/Met (p = 0.006) and Met/Val group (p = 0.010) showing higher difference scores (0.407, SE = 0.145). Additionally, there was a significant difference in mean scores between the Met/Met and Met/Val genotype (p = 0.07; 0.390, SE = 0.141).

Post-hoc HSD for unequal numbers confirmed a significant difference between *COMT* Met carriers and *COMT* Val/Val for Attention/Vigilance, Verbal Learning and Visual Learning.

Examining the effect sizes of change for each genotype, we found a small effect size for the Met/Met genotype for Verbal Learning (ES = 0.18) and a moderate effect size for Visual Learning (ES = 0.31) (see Table 2).

Table 2
Mean effect size of improvement in cognitive function by COMT genotype.

Dependent variable effect size	COMT genotype	Mean effect size	Std. error	F (*p*)
Processing Speed	Met/Met	0.310	0.078	F (2,129) = 1.320
	Val/Met	0.327	0.055	(*p* = 0.271)
	Val/Val	0.442	0.059	
Attention/Vigilance	Met/Met	0.021	0.115	F (2,129) = 0.864
	Val/Met	−0.369	0.082	(*p* = 0.011)**
	Val/Val	−0.386	0.087	
Working Memory	Met/Met	0.028	0.122	F (2,129) = 0.864
	Val/Met	−0.054	0.086	(*p* = 0.424)
	Val/Val	0.112	0.092	
Verbal Learning	Met/Met	0.183	0.039	F (2,129) = 6.116
	Val/Met	0.173	0.028	(*p* = 0.003)*
	Val/Val	0.045	0.030	
Visual Learning	Met/Met	0.314	0.060	F (2,129) = 4.446
	Val/Met	0.222	0.043	(*p* = 0.014)**
	Val/Val	0.097	0.046	
Reasoning & Problem Solving	Met/Met	0.029	0.064	F (2,129) = 0.111
	Val/Met	0.066	0.045	(*p* = 0.895)
	Val/Val	0.054	0.048	
Global Composite Index	Met/Met	0.024	0.060	F (2,129) = 0.108
	Val/Met	0.064	0.046	(*p* = 0.898)
	Val/VAl	0.055	0.050	

* Bonferroni corrected $p \leq 0.008$ (i.e., p value of 0.05/6 domains).
** Uncorrected p value $p \leq 0.05$.

No significant differences were observed in PANSS Total change (F (1,137) = 1.234, p = 0.201) across the three groups (Met/Val, Met/Met and Val/Val).

For the interaction between clozapine vs. other typical/atypical antipsychotics and *COMT* rs4680 polymorphism, GLM showed a significant interaction of pharmacological treatment and *COMT* polymorphism on the improvement in the Processing Speed domain (Bonferroni corrected p = 0.008). Post-hoc analysis revealed a significant difference between COMT genotypes, when treated with clozapine, with better results among Met/Met subjects (p = 0.010).

5.2. Discussion

Our results showed that the Val/Met and Met/Met genotype groups were associated with a better response to CRT intervention with greater improvements in three MCCB domains: Verbal Learning, Visual Learning, and Attention/Vigilance as compared to the Val/Val group, with Verbal Learning showing statistically significant improvements after Bonferroni correction. The Met/Met genotype associated effect was most notable for measures of Verbal Learning indicating the importance of this genotype in learning and memory processes. The superior effect on Verbal Learning may also have been mediated by our CRT intervention, which provides comprehensive auditory and visually presented material for practice of learning and memory processes, and is associated with performance benefits on various measures of Verbal Learning (Lindenmayer et al., 2008; McGurk et al., 2009, 2005; Sartory et al., 2005), similar to those observed in the present study with a greater improvement observed for the Met/Met group compared to Val/Val group.

The examination of the relationship of the three *COMT* genotypes with the categorically dichotomous response to CRT did not show significant differences among the three genotypes. These negative results may have been due to our using the dichotomous variable of "Improvement" vs. "Minimal Improvement" across genotype groups. Subjects were categorized as improvers as long as 4 domains showed improvement regardless of the specific improved domain. Therefore, a significant change in the categorical analysis may not always have produced significant findings, yet a GLM analysis looking at specific domain

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changes per genotype group would be more sensitive to show significant changes across domains.

The effect size of the selective enhancing effect of the Met/Met allele on change after CRT was significant for Verbal Learning, while the largest effect size associated with the Met/Met genotype was found for Visual Learning at 0.314. More recent evidence indicates that training with visual stimuli can cause long-term changes in how sensory signals are processed in the later stages of decision making and result in learning-related plasticity (Hironori and Takanori, 2013).

Our findings expand and confirm the results of Bosia et al. (2007) who genotyped a much smaller sample consisting of 27 schizophrenia subjects and reported that subjects with the Met allele made fewer perseverative errors of the WCST after CRT, but not in other neurocognitive functions. The difference between the two studies may be due to the difference in neurocognitive assessments used (BACS vs. MCCB). The MCCB includes only one measure of executive function (NAB mazes), a measure of planning, as opposed to WCST, which is a measure of problem solving. Additionally, the dependent measure, speed of completion, of NAB Maze performance may impede detection of improvements in planning in subjects having profound information processing speed impairments. Thus, this task has notable limitations in its sensitivity to detect changes in executive functioning compared to the WCST, which is not timed. Using an auditory based CRT intervention, Panizzutti et al. (2013) genotyped the *COMT* Val158Met polymorphism of 48 schizophrenia subjects who completed CRT and analyzed the association between DNA variants in the *COMT* gene and improvement in global cognition. The analysis performed focused on the *COMT* variant rs165599, which does interact with the *COMT* Met allele (rs4680) (Meyer-Lindenberg et al., 2006). They found a significant relationship between rs165599 and improvement of global cognition.

In contrast to these positive findings Greenwood et al. (2011) more recently did not find an association of the *COMT* Met/Met genotype with greater improvement after CRT. There are a number of significant differences between their study and ours. First their sample size was much smaller than ours (N = 61) reducing the statistical power and making it less likely to find small effects of potential genotype differences. The neuropsychological assessments were more limited, including only the WCST and Digit Span test. The ethnic composition of their sample was predominantly Caucasian, while our sample was predominantly African-American. Allelic frequency of *COMT* polymorphism shows significant variation in the Met allele (Harrison and Tunbridge, 2007) with Caucasians having nearly equal frequencies of the Met and Val alleles while the Val allele is much more common in all other ethnic groups. In addition, the mean IQ of the Greenwood sample was 96.5. Most of our participants were inpatients with an overall lower level of education as compared to the Greenwood sample.

Our exploratory analysis showed a significant interaction of pharmacological treatment with clozapine and *COMT* polymorphism on the improvement of Processing Speed, with better results among Met/Met subjects. We did not find the reversal of the negative Val/Val effect in patients as reported by Bosia et al. (2014b). As expected the *COMT* genotype did not show any effect on the PANSS.

The results of our study have to be interpreted in the context of some limitations. First, our sample size is small, which may have led to a type 1 error. While our sample size of subjects genotyped for the *COMT* polymorphism and treated with CRT is the largest to date, this limitation cannot be ruled out. Second, other than examining the interaction of *COMT* genotype with CRT response of subjects on clozapine, we were not able to examine the interaction of specific antipsychotics with both the *COMT* polymorphism and the effects of CRT as the subjects were on various antipsychotics preventing a systematic analysis. Finally, our results may also be affected by other loci in the genome (Bosia et al., 2014a; Wonodi et al., 2003). Associations between single genes and single cognitive processes may be more complex.

In conclusion, our findings support the hypothesis that *COMT* polymorphism influences improvement of cognitive functioning during a course of systematic CRT. The presence of a low activity Met allele (Met/Met and Val/Met) was associated with greater improvements in Verbal Learning, Visual Learning and Attention/vigilance after 12-weeks of CRT.

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Contributors

Jean-Pierre Lindenmayer and Anzalee Khan participated in the development of the concept for the study. Jean-Pierre Lindenmayer, Susan R. McGurk, Herbert Lachman, and Anzalee Khan participated in the design of the study. Anzalee Khan performed the statistical analysis and drafted the manuscript. Jean-Pierre Lindenmayer and Susan R. McGurk assisted with the statistical analysis and helped draft the manuscript. Jean-Pierre Lindenmayer and Anzalee Khan along with Saurabh Kaushik coordinated the implementation of the study and helped to draft the manuscript. All remaining authors participated in the design, coordination and draft of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

I would like to declare grant support from Neurocrine, Forum, Alkermes, Pfizer, and Roche, as well as consultancy from Otsuka, Janssen, and Alkermes. The remaining authors have declared that they have no conflicts of interest in relation to the subject of this study. I am the corresponding author and can be reached at Lindenmayer@nki.rfmh.org or 646 672 6004.

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