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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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