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Differential Association of the COMT Val158Met Polymorphism with Clinical Phenotypes in Schizophrenia and Bipolar Disorder

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Abstract

Schizophrenia and bipolar disorder, although diagnostically separate, likely share elements of their genetic etiology. This study assessed whether COMT Val158Met polymorphism has shared or specific associations with clinical phenotypes evident in schizophrenia and bipolar disorder. Schizophrenia and bipolar patients completed a clinical assessment encompassing premorbid functioning and current and lifetime symptomatology. Multivariate analyses yielded a three-way interaction of diagnosis, COMT genotype, and lifetime symptomatology. The COMT Val allele was associated with greater positive symptomatology in schizophrenia, whereas Met homozygosity was associated with greater positive symptomatology in bipolar disorder. Findings support the COMT Val158Met polymorphism conferring vulnerability for different clinical phenotypes in schizophrenia and bipolar disorder. Lifetime symptomatology may be particularly useful in determining the relationship between genes and clinical phenotypes across mental disorders.

Keywords

symptom dimensions; diagnosis; genes; dopamine; psychosis; mania; positive symptoms

Introduction

Schizophrenia and bipolar disorder share phenomenology but are differentiated in current diagnostic systems. Family studies of schizophrenia and bipolar disorder suggest there are common, as well as, disorder-specific aspects to genetic liability for the two disorders (e.g. Cardno et al., 2002). Unlike classification dichotomies, symptom dimensions may reflect neural and genetic contributions to disorder pathophysiology that span diagnostic categories. The catechol-O-methyl transferase (COMT) Val158Met polymorphism has been related to clinical manifestations of schizophrenia and bipolar disorder. Investigations of how the COMT polymorphism may affect the phenomenology of schizophrenia have usually investigated current symptoms and yielded varied results. In schizophrenia patients, a diplotype that includes the Val allele was associated with greater global, positive, and

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negative symptoms and worse response to neuroleptic treatment, though the Val158Met single nucleotide polymorphism failed to independently show the association (Molero et al., 2007). In contrast, the Met allele has been associated with greater negative symptoms (Bilder et al., 2002), delusions (Han et al., 2006), depression (Herken and Erdal, 2001), frequency of hospitalizations (Herken and Erdal, 2001), and higher dosage of neuroleptic medication (Inada et al., 2003) in schizophrenia. Other studies have found no association between COMT and clinical phenotypes in schizophrenia patients (Numata et al., 2007; Strous et al., 2006; Tsai et al., 2004). These discrepant findings may be the result of studies only incorporating measures of current symptoms that are dependent on the present phase of disorder.

Alternatively, two studies have utilized lifetime symptomatology to investigate the effects of the COMT polymorphism. Lifetime symptomatology may reduce the role of transient changes in clinical state as well as the effects of medication status on symptom dimensions, and perhaps increase sensitivity to genetic influences on disorder phenomenology. McClay and colleagues (2006) measured lifetime symptomatology in multiplex schizophrenia families and found preferential transmission of the Val allele for mania and depression. In a large sample of bipolar and depressed patients, Serretti and colleagues (2006) found no effect of the COMT polymorphism on lifetime symptomatology.

Given the diversity of findings in previous investigations, we attempted to clarify the association of the COMT polymorphism with clinical phenotypes in schizophrenia and bipolar disorder by characterizing current and lifetime symptomatology dimensions and premorbid function. A second goal was to assess whether lifetime symptomatology was more sensitive to the effect of COMT than current symptomatology.

Methods and Materials

Participants

Forty-eight schizophrenia, six schizoaffective bipolar subtype, and five schizoaffective depressive subtype patients (hereafter referred to collectively as schizophrenia patients) and 31 bipolar affective disorder patients were included in the study. Schizophrenia and bipolar patients were recruited from outpatient clinics at the Minneapolis VA Medical Center, community support programs, and a county mental health clinic. Exclusion criteria comprised of English being a second language, IQ less than 70, current alcohol or drug abuse, past drug dependence, current or past central nervous disease, and significant head injury (for full description see, Sponheim et al., 2006). COMT genotype was determined by a restriction fragment length polymorphism technique as described by Bergman-Jungstrom and Wingren (2001) and detailed in Goghari and Sponheim (2007). The study protocol was approved by the Minneapolis VA Medical Center and University of Minnesota Institution Review Boards. All subjects voluntarily participated and completed an informed written consent process.

Clinical Assessment

To obtain diagnostic information each participant completed the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and Premorbid Adjustment Scale (Cannon-Spoor et al., 1982). Patients' family members and medical records provided additional information. This information was used to confirm that participants met DSM-IV diagnosis for schizophrenia, schizoaffective disorder, or bipolar affective disorder. Two premorbid functioning dimensions, social and academic, were computed for the period prior to the patient's age of onset (Allen et al., 2001). Three current symptom dimensions were computed from the SANS and SAPS: psychosis symptoms (i.e., hallucinations and

delusions), formal thought disorder, and negative symptoms. To measure current overall symptom severity, the total score on the BPRS was computed. Extrapyramidal symptoms were assessed using the total score from the Simpson-Angus Scale (Simpson and Angus, 1970). Current anti-psychotic chlorpromazine-equivalence dosage was calculated. The five lifetime symptom dimensions of positive symptoms, negative symptoms, disorganization, mania, and depression, were computed by summing items in the factor structure generated by Serretti and Olgiati (2004) using the Operational Criteria for Psychotic Illness (OPCRIT; McGuffin et al., 1991). Clinical phenotypes are described in more detail in Table 1.

Statistical Analyses

Separate multivariate analysis of variance (MANOVAs) were used to assess the three domains of functioning (premorbid, current, and lifetime) for between group effects of diagnosis (schizophrenia, bipolar) and COMT genotype (Met/Met, Val/Met, Val/Val). A three-way interaction was investigated by including the symptom dimension factor for lifetime symptomatology. The lifetime negative dimension was not included in the between group MANOVAs, as Val homo- and heterozygotes bipolar patients did not demonstrate any of these symptoms. Only significant MANOVAs were followed by additional contrasts.

Results

Participants

Demographic information is presented in Table 1. Distribution of alleles for schizophrenia and bipolar patients were in Hardy-Weinberg equilibrium (p 's > 0.6). COMT allele frequencies did not differ by group ($X^2(2)=0.9$, $p=0.7$). The schizophrenia Met/Met group had no females. The groups did not differ for race. The schizophrenia and bipolar group did not differ for extrapyramidal symptoms. Current chlorpromazine-equivalence anti-psychotic dosage revealed a significant effect of diagnosis ($F(1, 54)=6$, $p=0.02$) with schizophrenia patients ($n=49$, mean=748, $sd=617.7$) have greater dosage than bipolar patients ($n=7$, mean=171.4, $sd=125.4$). There were no significant effects of COMT in the schizophrenia sample for extrapyramidal symptoms or chlorpromazine-equivalence anti-psychotic dosage, though a trend was observed for extrapyramidal symptoms ($F(2,49)=2.8$, $p=0.07$). Due to the small number of individuals with bipolar disorder on antipsychotics we did not carry out this analysis for the bipolar group.

Effect of Diagnosis, but not COMT Genotype on Premorbid Adjustment and Current Symptomatology

A MANOVA of specific symptom dimensions revealed a main effect of diagnosis ($F(2,82)=7$, $p=0.002$), with schizophrenia patients demonstrating worse premorbid social functioning than bipolar subjects ($F(1,83)=12.5$, $p=0.001$). Analyses failed to yield any main effects of COMT or interactions with COMT.

An ANOVA demonstrated an effect of diagnosis on BPRS total score ($F(1,83)=6.9$, $p=0.01$) with schizophrenia patients having more severe current overall symptomatology than bipolar patients. A MANOVA of current symptom dimensions revealed a main effect of diagnosis ($F(3,80)=18.4$, $p<0.001$), with schizophrenia patients demonstrating greater current psychotic ($F(1,82)=26.1$, $p<0.001$) and negative ($F(1,82)=35.9$, $p<0.001$) symptoms than bipolar patients. Analyses failed to yield any main effects of COMT or interactions with COMT.

Effects of Diagnosis and COMT Genotype on Lifetime Symptomatology

MANOVAs of lifetime symptomatology indices revealed a diagnosis main effect ($F(4,81)=26.9$, $p<0.001$). Schizophrenia patients had more positive ($F(1,84)=44.2$, $p<0.001$)

and disorganization ($F(1,84)=23.6$, $p<0.001$) symptoms, and bipolar patients had more mania ($F(1,84)=39.2$, $p<0.001$) and depression ($F(1,84)=10.3$, $p=0.002$) symptoms. In addition, the MANOVAs yielded a diagnosis by COMT interaction ($F(8,164)=2.1$, $p=0.04$) and a diagnosis by COMT by symptom dimension interaction ($F(6,166)=2.7$, $p=0.01$). The interactions derived from a prominent effect for positive symptoms ($F(2,84)=6.5$, $p=0.002$). Schizophrenia Val homozygotes ($p=0.04$, Cohen's $d=0.66$) and heterozygotes ($p=0.02$, Cohen's $d=0.71$) demonstrated greater positive symptomatology than Met homozygotes. Whereas, for bipolar patients, the Met homozygotes demonstrated greater positive symptomatology than heterozygotes ($p=0.02$, Cohen's $d=0.95$). There was also a trend for Met homozygote bipolar patients to demonstrate greater positive symptomatology than Val homozygotes ($p=0.1$, Cohen's $d=0.66$).

Because of an uneven gender distribution we conducted supplementary analyses investigating the effect of COMT polymorphism on the positive symptom dimension. Male schizophrenia Val homozygotes ($p=0.04$, Cohen's $d=0.72$) demonstrated greater positive symptomatology than male Met homozygotes. In addition, male heterozygotes ($p=0.06$, Cohen's $d=0.59$) tended to have greater positive symptomatology than male Met homozygotes. In contrast, male bipolar Met homozygotes demonstrated greater positive symptomatology than male Val homozygotes ($p=0.04$, Cohen's $d=1.17$) and heterozygotes ($p=0.02$, Cohen's $d=1.08$).

Because the schizophrenia group included patients with schizoaffective diagnoses we carried out supplemental analyses of only patients with a diagnosis of schizophrenia to test the robustness of findings. Individuals diagnosed with schizophrenia who were Val homozygotes tended to have greater positive symptomatology than their Met homozygotes counterparts ($p=0.1$, Cohen's $d=0.54$) (see Table 2, supplementary materials). Heterozygotes also had greater symptomatology than their Met homozygote counterparts ($p=0.05$, Cohen's $d=0.63$).

Discussion

We found COMT genotype effects on lifetime symptomatology in schizophrenia and bipolar disorder patients, whereas such effects were absent for current symptomatology suggesting that lifetime phenomenology may be more strongly associated with genetic influences than symptomatology characterizing at a single time point. Additionally, our findings suggest that the COMT Val158Met polymorphism is differentially related to lifetime symptom dimensions in schizophrenia and bipolar disorder. In schizophrenia Val homozygosity was associated with greater positive symptomatology while in bipolar disorder Met homozygosity was related to greater positive symptomatology.

Association of the Val allele with positive symptoms in schizophrenia is consistent with a current conceptualization of effects of the COMT Val158Met polymorphism on tonic and phasic dopamine in the striatum and prefrontal cortex in the disorder (Bilder et al., 2004). The Val allele may augment enzyme activity and decrease cortical dopamine transmission, but increase subcortical dopamine thus leading to positive symptomatology. Bilder and colleagues also posit that the Met allele may enhance cortical dopamine transmission and decrease subcortical dopamine, thereby increasing negative symptomatology. In a subsequent analysis of lifetime negative symptoms we found that schizophrenia Met homozygotes had greater negative lifetime symptomatology than the Val homozygotes and heterozygotes combined (Cohen's $d=0.65$). In contrast to these findings, McClay and colleagues (2006) measured lifetime symptomatology in multiplex schizophrenia families and found preferential transmission of the Val allele for mania and depression, but generally

not for psychosis. The lack of agreement may be due to the previous study using a less than ideal symptom factor structure to measure lifetime phenomenology.

In bipolar disorder we found the Met allele was associated with greater positive symptoms. The Met allele has been associated with greater symptomatology namely, rapid cycling in bipolar patients (Kirov et al., 1998; Papolos et al., 1998) and in 22q11.2 deletion syndrome (Lachman et al., 1996). In contrast, Serretti and colleagues (2006) using the same OPCRIT factor structure found no COMT genotype differences in any lifetime dimension in a combined sample of depressed and bipolar patients. The apparent inconsistency with our findings likely stems from Serretti and colleagues exclusive use of individuals with affective disorders.

The sample size for the current analyses was modest and replication is necessary. Nevertheless, results suggest that the COMT Val158Met polymorphism may have differential associations with lifetime clinical symptomatology across schizophrenia and bipolar disorder. Most importantly, future investigations may find lifetime symptom dimensions particularly helpful in determining the relationship between genes and clinical phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical information on participants. Mean and standard deviation unless otherwise noted.

	Schizophrenia				Bipolar	
	Met/Met	Val/Met	Val/Val	Met/Met	Val/Met	Val/Val
Demographics						
N	14	26	19	10	13	8
Age of Onset (years)	23.4 (5.8)	20.3 (6)	24.4 (7.9)	22.4 (8.9)	21.5 (8.3)	22.8 (6.7)
Current Age (years)	45.9 (9.6)	44.4 (11.1)	44.2 (7.5)	38.9 (9.2)	46.2 (10.3)	45.4 (9.3)
% Female	0	15	32	20	15	38
% Caucasian	93	89	68	100	85	100
Extrapyramidal Total	4.8 (3.8)	4.3 (4.0)	1.9 (3.2)	3.6 (3.3)	2.6 (4.2)	4.7 (2.7)
Clinical Phenotype						
Prenorbid Adjustment[§]						
Social	1.8 (0.9)	1.7 (1.2)	2 (1.1)	0.9 (0.6)	1.3 (0.9)	0.8 (0.7)
Academic	2.2 (1.2)	2.1 (1.2)	2.6 (1.4)	1.7 (1.1)	2.0 (1.1)	2.1 (1.4)
Current Symptomology[‡]						
Psychosis	1.6 (1.5)	1.9 (1.4)	2.2 (1.5)	0.5 (1.0)	0	0.7 (1.3)
Formal Thought Disorder	1.9 (1.1)	1.3 (1.4)	1.1 (1.1)	0.9 (1.2)	1.1 (1.1)	0.9 (1.2)
Negative	1.7 (0.8)	1.9 (0.9)	1.5 (0.8)	0.5 (0.5)	0.8 (0.7)	0.6 (0.5)
BPRS Total	42.3 (10.8)	45.2 (14.7)	41 (8.8)	37.1 (10.1)	35.8 (5)	35.4 (11.6)
Lifetime Symptomology[±]						
Positive	4.1 (2.7)	5.7 (1.7) ¹	5.6 (1.7) ²	3.4 (2.8) ³	1.2 (1.7)	1.8 (2.0)
Negative	1.1 (0.8)	0.4 (0.6)	0.7 (0.8)	0.1 (0.3)	0	0
Disorganization	1.6 (0.6)	1.2 (0.7)	1.4 (0.8)	0.6 (0.7)	0.5 (0.9)	0.5 (0.5)
Mania	2.1 (1.8)	2.2 (1.6)	2.4 (1.5)	4.7 (0.8)	3.8 (1.1)	4.4 (0.9)
Depression	2.8 (3.4)	3.3 (3.1)	4.8 (2.8)	5.6 (2.4)	5.5 (2.8)	6.1 (1.6)

¹ VM > MM;

² VV > MM;

³ MM > VM

Missing data: Extrapramidal total – 3 Met/Met schizophrenia patients, 3 Val/Met schizophrenia patients, 1 Val/Val schizophrenia patient, 2 Met/Met bipolar patients, 8 Val/Met bipolar patients, 2 Val/Val bipolar patients; Premorbid adjustment – 1 Val/Met bipolar patient; SAPS/SANS/BPRS – 1 Val/Val schizophrenia patients, 1 Val/Met bipolar patient

[§]Premorbid Adjustment Scale used to compute social and academic dimension (Allen et al., 2001; Cannon-Spoor et al., 1982). Higher numbers denote worse functioning.

[†]Current symptom dimensions: psychosis symptoms (the average global score for delusions and hallucinations); formal thought disorder (the global score for positive formal thought disorder); and negative symptoms (the average global score for alergia, affective flattening, avolition-apathy, and anhedonia-asociality) from the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981) and Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983). Brief Psychiatric Rating Scale, 24-item, used to compute total (Ventura et al., 2000). Simpson-Angus Scale used to compute total extrapyramidal symptoms (Simpson and Angus, 1970). Chlorpromazine-equivalence for current anti-psychotic medication dosage.

[‡]Lifetime symptom dimensions: positive symptoms (composed of persecutory delusions, organized delusions, delusions of influence, bizarre delusions, widespread delusions, abusive accusatory voices, delusions and hallucination last for 1 week, jealous delusions, and primary delusional perception items); negative symptoms (composed of negative thought disorder and blunted affect items); disorganization (composed of bizarre behavior and positive thought disorder item); mania (composed of distractibility, agitated activity, irritable mood, dysphoria, increased sociability, increased self-esteem, and grandiose delusions items); and depression (composed of loss of energy, loss of pleasure, poor concentration, slowed activity, self-reproach, suicidal ideation, poor appetite, diminished libido, diurnal variation items) (McGuffin et al., 1991; Serretti and Olgiati, 2004).