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ORIGINAL RESEARCH

Association Analysis Between Catechol-O-Methyltransferase Expression and Cognitive Function in Patients with Schizophrenia, Bipolar Disorder, or Major Depression

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Introduction: Schizophrenia, bipolar disorder (BD), and major depressive disorder are three common mental disorders. Although their diagnosis and treatment differ, they partially overlap.

Methods: To explore the similarities and characteristics of these three psychiatric diseases, an intelligence quotient (IQ) assessment was performed to evaluate cognitive deficits. Relative catechol-O-methyltransferase (*COMT*) expression in peripheral blood mononuclear cells was examined in all three groups compared with healthy controls (HCs).

Results: The results indicated that patients with any of the three psychiatric diseases presented IQ deficits, and that the first-episode schizophrenia (FES) group had even lower cognitive function than the other two groups. The relative *COMT* expression decreased in the FES group and increased in the BD group compared with the HC group. The correlation analysis of *COMT* expression level and IQ scores showed a positive correlation between relative *COMT* expression and full-scale IQ in the HC group. However, this correlation disappeared in all three psychiatric diseases studied.

Conclusion: In conclusion, this cross-disease strategy provided important clues to explain lower IQ scores and dysregulated *COMT* expression among three common mental illnesses.

Keywords: first-episode schizophrenia, FES, bipolar disorder, BD, first-episode major depressive disorder, MDD, catechol-O-methyltransferase, COMT, intelligence quotient, IQ

Introduction

Schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are three types of common mental diseases, which severely affect psychological, biological, and social functioning. Although their diagnosis and treatment are different, there is some overlap in symptoms and treatment.[1–3] Although symptoms are complex and heterogeneous, cognitive impairment is prevalent in SCZ, BD, and MDD.[4] Cognitive deficit is regarded as a core symptom of SCZ and BD.[5,6] Cognitive impairment is also one of the most common symptoms of MDD,[7] and approximately 90% of patients with MDD complained about cognitive issues.[8] The intelligence quotient (IQ) score refers to the intelligence level, which can rate the subjects' cognitive ability, is an important indicator of cognitive assessment.[9] Numerous studies have shown that the aforementioned mental diseases can lead to an impaired IQ.[10–12] Although higher childhood IQ may predict increased risk of

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adult mania,[13] IQ impairments in childhood and adolescence are often observed in individuals who later develop SCZ, BD, and MDD.[14]

Mental disorders are multifactorial diseases influenced by both genetic and environmental factors.[15–17] All three common mental disorders have a high heritability,[18–20] which means that genes play a crucial role in the pathophysiology of these psychiatric diseases. Furthermore, disease-related susceptible genes/loci provide some clues for diagnosis and treatment.[21–23] The catechol-O-methyltransferase (*COMT*) gene has been widely investigated because of its high correlation with the risk of common psychiatric diseases, especially SCZ.[24–26] *COMT* is located on chromosome 22q11.226[27] and its single nucleotide polymorphisms (SNPs) are regarded as promising candidates for understanding the genetic basis of many common psychiatric disorders, especially rs4680, which can affect COMT activity.[28] COMT transfers a methyl group from S-adenosylmethionine to catecholamines to degrade dopamine, epinephrine, and norepinephrine.[28] Therefore, abnormal *COMT* expression or activity may cause dopaminergic dysfunction, which may, in turn, lead to common mental disease symptoms such as impaired cognition.[29–31] A large number of studies focused on the relationship between the *COMT* gene and cognitive function in SCZ, BD, and MDD,[32–35] while others have indicated that the relative risk of SCZ is 20 to 25 times higher in patients with 22q11.2 deletion syndrome (one *COMT* copy is deleted) than in the general population.[36] Patients with a 22q11.2 deletion syndrome SCZ form also showed a lower IQ.[37] In studies on BD, however, there are contradictory findings on the correlation between *COMT* and cognitive function.[38] This inconsistency may be due to the fact that some studies did consider factors that may influence the cognitive performance of BD patients, such as disease stage or medical treatment at the time of assessment.[39,40] Antypa et al proposed a tentative pathway whereby the *COMT* gene may influence cognitive vulnerability to depression.[41] In healthy research participants, the *COMT* genotype could help predict a small proportion of the variance in baseline cognition and neurophysiology,[42] but the association is modest and inconsistent.[43] Therefore, it is very important to explore the correlation between *COMT* expression and IQ defects with cross-disease strategies among different mental illnesses.

Studies have suggested that both relative *COMT* expression and IQ assessment could dynamically change according to the state of the episode and pharmacologic treatment.[30,39,40,44–46] To exclude the possible influence of pharmacologic treatment, the patients with SCZ and MDD included in this study were all drug-naïve first-episode subjects, and patients with BD did not take any medication 3 months before enrollment. In this cross-disease study, the combination of relative *COMT* expression and IQ assessment was considered to be a powerful approach to identify the potential path between the expression of risk genes and phenotype. We hypothesized that *COMT* expression was different in patients with mental disorders, and that the correlation between *COMT* expression and IQ scores may not be consistent.

Methods

Demographic Characteristics and General Cognitive Function Assessment

This study recruited 150 patients with FES (in acute or post-acute phase), 182 patients with BD (in depressive and manic as well as mixed phase), and 183 first-episode patients with MDD (in acute or post-acute phase) from the Mental Health Center of West China Hospital of Sichuan University. All patients were interviewed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Patient edition (SCID-P). Both patients with FES and MDD were drug-naïve, and patients with BD were not medicated in the 3 months prior to enrollment. All subjects were followed up for at least 6 months to further confirm the initial diagnosis. We also recruited 261 healthy controls (HCs) by poster advertisements within the local community in Chengdu, Sichuan Province, China. The HCs were interviewed using the SCID-NP. All subjects were recruited over the period from 2012–2016. IQ was tested using the short version of the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) according to the WAIS-RC manual.[47] The IQ assessment included seven subtests: information, digital span, digital symbol, picture completion, block design, similarities, and arithmetic. Verbal IQ, performance IQ, and full-scale IQ were calculated referring to the weighted formulas previously described.[47,48] This study was conducted in accordance with the Declaration of Helsinki. Approval for this study was granted by the Ethics Committee of the West China Hospital of Sichuan University. All participants signed an informed consent form, and patient's demographic characteristics are shown in Table 1.

Table 1 Demographic Data and IQ Scores of All Subjects Among Different Groups of Patients and Controls

	HC	FES	BD	MDD	F/χ^2	P value	FES vs HC	BD vs HC	MDD vs HC	FES vs BD	FES vs MDD	MDD vs BD
Gender (n)	261	150	182	183	6.899	0.075						
Male (%)	97 (37.2)	72 (48.0)	75 (41.2)	64 (35.0)								
Female (%)	164 (62.8)	78 (52.0)	107 (58.8)	119 (65.0)								
Age (years)	25.6±7.5	23.4±7.1	25.2±7.8	28.3±9.6	30.077	<0.001***	<0.001***	0.212	0.020*	0.028*	<0.001***	0.001***
Education years	15.1±3.1	12.2±2.8	13.7±2.8	13.8±3.1	88.082	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	0.526
BMI	21.0±2.9	20.6±3.1	21.9±3.3	21.4±3.3	14.403	0.002**	0.240	0.005**	0.207	<0.001***	0.028***	0.160
Verbal IQ	114.0±15.2	99.7±14.2	109.4±13.1	107.1±14.6	91.171	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	0.217
Performance IQ	111.4±13.8	93.0±16.8	103.0±15.0	104.7±13.8	118.992	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	0.375
Full-scale IQ	114.1±14.5	96.6±14.2	107.2±13.3	106.7±13.8	49.477	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	>0.999

Notes: Data were presented as mean±SD (standard Deviation); the difference of gender was analyzed by the χ^2 test among four groups. The data distribution of age, education years, and BMI deviated from normality; the Kruskal–Wallis ANOVA test was used to compare their differences among groups followed by post hoc Bonferroni correction for multiple comparisons; *indicate P<0.05; **indicate P<0.01; ***indicate P<0.001.

Abbreviations: HC, healthy controls; FES, first-episode schizophrenia; BD, bipolar disorder; MDD, first-episode major depressive disorder; BMI, body mass index; IQ, intelligence quotient.

Total RNA Extraction and Relative *COMT* Expression

Patients not treated with any medication after cognitive function assessment were scheduled for peripheral blood mononuclear cell (PBMC) collection at 8:00–9:00AM. For the patients and healthy controls, whose demographic characteristics are shown in Table 2, and could attend the PBMC collection, peripheral blood samples (3 mL) were collected. For total RNA extraction, whole blood samples were immediately preserved in Tempus Blood RNA Tubes (Applied Biosystems, Foster, USA). To avoid blood coagulation, the tubes were vigorously mixed for ≥10 seconds. All tubes were preserved at −80°C until use. According to the manufacturer's instruction, total RNA was extracted from the sample with MagMAX for Stabilized Blood Tubes RNA Isolation Kit (Thermo Fisher Scientific, Waltham, USA). cDNA was generated using the iScript cDNA Synthesis Kit (Bio-Rad, Hercules, USA) with 1 μg total RNA. Quantitative polymerase chain reaction (qPCR) was performed with the SsoFast EvaGreen^{TM} Supermix Real-time PCR kit (Bio-Rad, Hercules, USA). Relative mRNA expression was measured using the CFX96TM Real-Time System (Bio-Rad, Hercules, USA). The PCR cycling parameters were: 95°C for 1 min for denaturing, followed by 40 cycles of a two-step PCR (melting for 10 s at 95°C, annealing for 20 s at 60°C). Relative *COMT* mRNA expression was analyzed using the $2^{-\Delta\Delta Ct}$ method and normalized by GAPDH expression. The corresponding primer sequences are listed as follows:

COMT, Sense Primer: 5′–CGACTGTGCCGCCATCA

Anti-sense Primer: 5′–GCAGCAGGCCACATTCCTC

GAPDH, Sense Primer: 5′–GTCTCCTCTGACTTCA ACAGCG

Anti-sense Primer: 5′–ACCACCCTGTTGCTGTA GCCAA.

Statistical Analyses

All statistical analyses were performed using SPSS version 24 (IBM, Armonk, USA). The chi-square (χ^2) test was conducted to compare the frequency difference in qualitative characteristics (ie, gender) among the four groups. The Shapiro–Wilk test was employed for the normal distribution test, and equal variance was tested by Levene's test. Statistical analysis was performed using Welch's ANOVA test followed by the post hoc Tamhane's T2 test when normal distribution was

Table 2 Demographic Data and IQ Scores of Subjects with *COMT* Expression Analysis in HC, FES, BD, and MDD Groups

	HC	FES	BD	MDD	F/χ^2	P value	FES vs HC	BD vs HC	MDD vs HC	FES vs BD	FES vs MDD	MDD vs BD
Gender, (n)	53	32	47	25	3.724	0.293						
Male (%)	27 (50.9)	18 (56.2)	24 (51.1)	8 (32.0)								
Female (%)	26 (49.1)	14 (43.8)	23 (48.9)	17 (68.0)								
Age (years)	24.2±6.7	22.8±6.4	26.7±7.9	30.1±10.9	11.486	0.009**	0.291	0.115	0.020*	0.016*	0.003**	0.317
Education years	15.4±2.8	11.8±3.4	13.7±3.5	14.1±2.7	21.772	<0.001***	<0.001***	0.014*	0.169	0.017*	0.008**	0.522
BMI	20.7±3.5	21.0±3.1	22.6±3.1	21.8±3.1	11.432	0.010*	0.542	0.001**	0.070	0.032*	0.270	0.408
Verbal IQ	115.9±12.4	101.1±15.1	112.1±11.6	110.0±12.7	21.339	<0.001***	<0.001***	0.119	0.075	0.002**	0.024*	0.627
Performance IQ	112.4±12.7	91.8±17.7	100.8±16.4	102.7±14.0	32.359	<0.001***	<0.001***	<0.001***	0.010*	0.040*	0.025*	0.607
Full-scale IQ	115.8±11.8	96.5±15.5	107.9±13.5	107.4±12.5	14.027	<0.001***	<0.001***	0.022*	0.062	0.002**	0.015*	>0.999

Notes: Data were presented as mean±SD (standard Deviation); the difference of gender was analyzed by the χ^2 test among four groups; the data distribution of age, education years, and BMI deviated from normality; the Kruskal–Wallis ANOVA test was used to compare their differences among groups followed by post hoc Bonferroni correction for multiple comparisons; *indicate P<0.05; **indicate P<0.01; ***indicate P<0.001.

Abbreviations: HC, healthy controls; FES, first-episode schizophrenia; BD, bipolar disorder; MDD, first-episode major depressive disorder; BMI, body mass index; IQ, intelligence quotient.

assumed, but equal variance was not. When the data distribution deviated from normality, the Kruskal–Wallis ANOVA test was used to compare differences among groups followed by post hoc Bonferroni correction for multiple comparisons. The statistical methods for each statistical result are detailed in Supplementary Tables 1 and 2. Correlation between IQ and relative *COMT* expression in each group was examined by a partial correlation analysis with age, education years, and BMI as covariates.

Results

Demographic Characteristics

The demographic data of all subjects are shown in Table 1. A total of 776 subjects participated in this study, including 261 HC (97M/164F), 150 FES (72M/78F), 182 BD (75M/107F), and 183 MDD (64M/119F). There was no significant difference in gender among groups (χ^2=6.899, p=0.075). However, age (χ^2=30.077, p<0.001), education years (χ^2=88.082, p<0.001), and BMI (χ^2=14.403, p=0.002) were significantly different among groups. Patients with FES had the lowest average age at onset and education years, which was significantly lower than that of the HC group (age: p<0.001; education years: p<0.001) and patients with BD (age: p<0.001; education years: p<0.001) or MDD (age: p=0.028; education years: p<0.001). With respect to BMI, patients with BD had a significantly higher BMI than HC (p=0.005) and FES (p<0.001).

Lower IQ Scores of Patients with Psychiatric Disease

As shown in Table 1, there were significant differences in verbal IQ score (χ^2=91.171, p<0.001), performance IQ score (χ^2=118.992, p<0.001), and full-scale IQ score ($F_{(3,\ 772)}$=49.477, p<0.001) among the four groups. Compared with the HC group, all psychiatric groups showed lower verbal IQ, performance IQ, and full-scale IQ. Among psychiatric groups, all IQ scores of the FES group were significantly lower than those of the BD group (verbal IQ score: p<0.001, performance IQ score: p<0.001, and full-scale IQ score: p<0.001) and MDD group (verbal IQ score: p<0.001, performance IQ score: p<0.001, and full-scale IQ score: p<0.001). However, no difference in any IQ scores was found between the BD and MDD groups.

Dysregulated *COMT* Expression in Patients with Psychiatric Disease

Consistent with the overall demographic data, the subjects with analyzed *COMT* expression well represented the demographic distribution of all subjects (Table 2). Meanwhile, the IQ score distribution in the subgroup with analyzed *COMT* expression was also very similar to the overall results of all subjects (Table 2). There were significant differences in relative *COMT* expression among all groups ($F_{(3, 153)} = 40.120$, $p<0.001$). Compared with the HC group, there was a significantly lower *COMT* expression in the FES group ($p<0.001$) while *COMT* expression was upregulated in the BD group ($p=0.001$), and no difference was observed in the MDD group ($p=0.248$) (Figure 1A). The partial correlation analysis results of IQ scores and relative *COMT* expression in all groups are listed in Table 3. As shown in Figure 1B, the full-scale IQ score was positively correlated with relative *COMT* expression in the HC group ($r=0.301$, $p=0.040$).

Discussion

There is certain overlap in symptoms and treatment among the three common mental diseases examined here: SCZ, BD, and MDD. It is therefore of great significance for the objective diagnosis and precise treatment of these mental diseases to explore their similarities and characteristics. In this study, we identified consistent IQ impairment and different *COMT* expression in PBMCs among patients with FES, BD, and MDD, suggesting that a cross-disease strategy could provide important clues for the phenotypic and mechanistic characterization of mental diseases.

As an effective indicator of state assessment, IQ scores were used to evaluate the cognitive function of patients with different psychiatric diseases.[9–12] In this study, we found that the IQ scores of all three groups of patients with psychiatric diseases were significantly decreased, especially in the FES group, consistent with the severe cognitive impairment of FES patients observed in clinical practice.[49,50] Worse cognitive impairment and earlier age at onset[51–53] are possible explanations for the younger age and fewer education years of FES patients in this study.

Interestingly, the relative *COMT* expression in FES and BD groups presented an opposite trend compared with the HC group, that is, *COMT* expression significantly decreased in the FES group and increased in the BP group. According to previous studies, *COMT* is a risk gene for SCZ, BD, and MDD, and its risk effects are not consistent in different mental illnesses.[54,55] The inconsistent relative *COMT* expression in

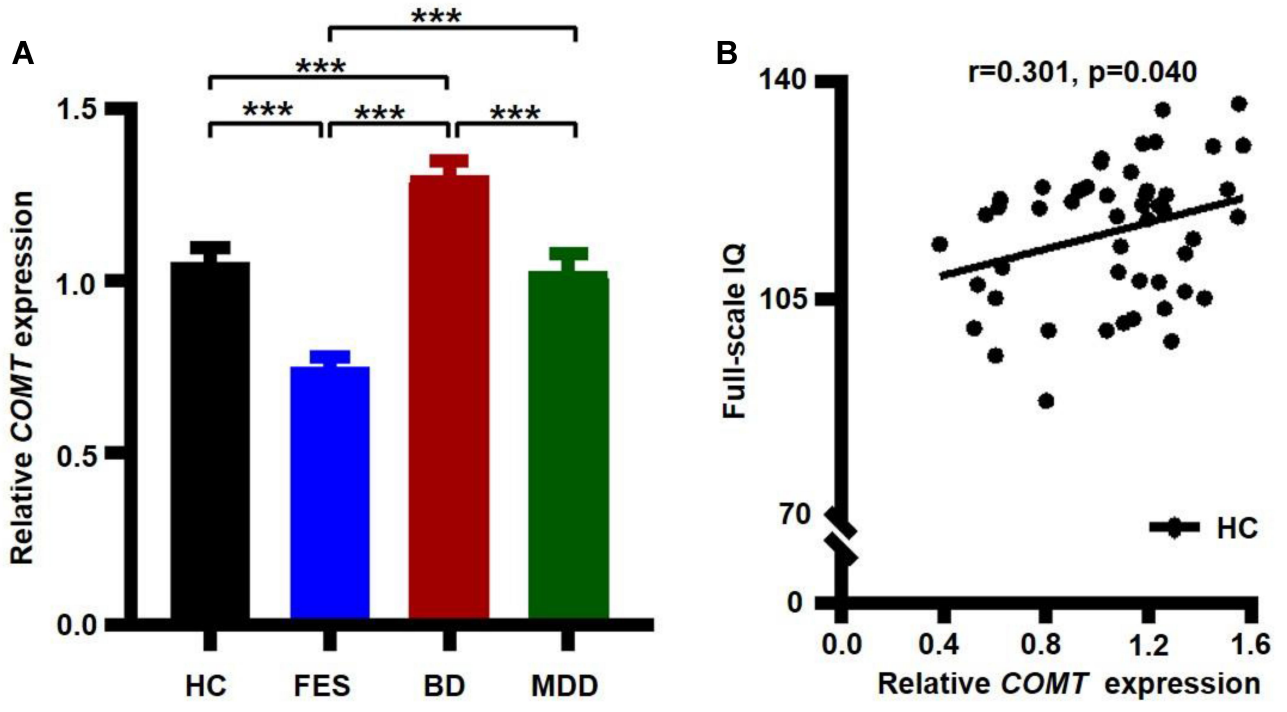

Figure 1 Full-scale IQ score positively correlated with relative *COMT* expression in the HC group. (**A**) Relative *COMT* expression among different groups of patients and controls. (**B**) Correlation analysis of *COMT* expression and full-scale IQ score in the HC group. Gene expression data normalized by *GAPDH* expression. Data are presented as mean±SEM. Asterisks indicate P<0.001.

Table 3 The Correlation of Verbal IQ, Performance IQ, Full Scale IQ with Relative *COMT* Expression in All Groups

IQ	HC		FES		BD		MDD	
	r	p	r	p	r	p	r	p
Verbal IQ	0.285	0.052	−0.129	0.539	0.031	0.843	−0.164	0.466
Performance IQ	0.199	0.179	0.078	0.711	−0.080	0.605	−0.066	0.769
Full scale IQ	0.301	0.040*	−0.035	0.867	−0.027	0.861	−0.124	0.582

Notes: Data were analyzed by Partial correlation analysis after adjusting for age, education years and BMI; *indicate P<0.05.
Abbreviations: HC, healthy controls; FES, first-episode schizophrenia; BD, bipolar disorder; MDD, first-episode major depressive disorder; IQ, intelligence quotient.

PBMCs among patients with SCZ and BD in this study might be due to genetic risk,[56] the disease course,[57,58] or the sample size, which may also be another important factor.[30,58] COMT is known to play an important role in the biological process of dopamine degradation through methyl transfer.[28] The relationship between dopamine levels and cognitive function presents an inverted U-shaped pattern,[59] thus implying the existence of an optimal dopamine level, and those with lower and higher predicted dopamine levels perform worse,[60] which has fundamental implications for the effects of dopaminergic treatment on cognition,[61] and also suggests that the expression level of *COMT* has meaningful implications for cognitive impairment and its potential biological mechanisms. To explore this significance, a correlation analysis of *COMT* expression level and IQ score was performed. The results showed that there was a positive correlation between relative *COMT* expression and full-scale IQ only in the HC group. This correlation disappeared in all groups with psychiatric diseases. As mentioned above, the U-shaped pattern between dopamine concentration and cognitive function[59] might mean that abnormal *COMT* expression may lead to its negative correlation with lower IQ in the three groups with psychiatric diseases.

Some limitations of the current study should be mentioned. The present observations await replication with a larger sample size in future studies, and more cognitive domains such as executive functions and working memory should be considered. Although PBMCs are more accessible, considering the tissue/cell specificity of *COMT* expression, research based on postmortem samples and/or specific neurons differentiated from induced pluripotent stem cells (iPSCs) will provide a more deliberate opportunity to explore the biological mechanism. Even though all patients in the FES and MDD groups were drug-naïve first-episode, the patients with BD may have taken some medications that affect *COMT* expression or cognitive responses during previous episodes of mania or depression, such as dopamine agonists.[62] Considering that such treatment can change the relative *COMT* expression,[30] it is difficult to rule out whether the abnormal *COMT* expression observed in the BD group corresponded to disease-innate abnormalities or was a side-effect of drug treatment. As a cross-sectional study, this study did not examine the effects of drug treatments on relative *COMT* expression. Therefore, subsequent longitudinal studies might provide evidence to support relative *COMT* expression as a biological marker for psychiatric diseases.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no potential conflicts of interest to disclose.

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