

Increased Plasma Kynurenic Acid Levels are Associated with Impaired Attention/Vigilance and Social Cognition in Patients with Schizophrenia

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Objective: Preclinical studies have reported that abnormal kynurenic acid (KYNA) may play a role in cognitive deficits. Schizophrenia (SCZ) is characterized by a wide range of cognitive deficits that may evolve from abnormal KYNA. This study aimed to explore the relationship between KYNA and cognitive impairment in SCZ, which has not yet been reported.

Methods: We recruited 30 SCZ patients and 34 healthy controls, measured clinical symptoms by using the Positive and Negative Syndrome Scale and performed cognitive tests using the MATRICS Consensus Cognitive Battery (MCCB). Plasma levels of tryptophan, kynurenine, and KYNA were determined by high-performance liquid chromatography–tandem mass spectrometry.

Results: We found that plasma KYNA levels were significantly higher in patients than in healthy controls ($p=0.009$). The cognitive performance of patients in the total MCCB scores and the scores of all subscales were significantly lower than those in healthy controls (all $P < 0.01$). Correlation analysis showed that KYNA levels were negatively correlated with attention/vigilance ($r=-0.457$, $p=0.019$) and social cognition ($r=-0.481$, $p=0.013$) only in SCZ patients.

Conclusion: Our results indicate that elevated plasma KYNA levels may serve as a biomarker of cognitive impairment in SCZ patients.

Keywords: schizophrenia, kynurenic acid, cognitive impairment, symptom

Introduction

Cognitive deficit is the key feature of schizophrenia (SCZ), and includes a range of domain deficits such as executive function, learning, memory, attention, and social cognition.¹⁻⁴ These may emerge long before illness onset and remain unchanged with improvement of clinical symptoms in SCZ patients.⁵ Cognitive impairments are correlated with poor clinical outcome and rehabilitation of social function.^{6,7} However, the pathophysiological mechanisms underlying the cognitive deficits in SCZ patients are currently unknown.

Kynurenic acid (KYNA) is an exogenous product of the kynurenine (KYN) pathway of tryptophan degradation, which antagonizes the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) and ionotropic glutamate receptors.^{8,9} Moreover, among the ionotropic glutamate receptors, KYNA preferentially inhibits the N-methyl-D-aspartate receptor (NMDAR).¹⁰⁻¹² Some studies have found that KYNA affects several neurotransmitters. For example, studies have reported that increased KYNA resulted in decreased glutamate levels, whereas decreased KYNA leads to increased glutamate.^{13,14} Also, KYNA levels are negatively correlated with dopamine,

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gamma-aminobutyric acid and acetyl choline.^{15–17} All of these neurotransmitter abnormalities are thought to play important roles in the pathogenesis of SCZ.^{18,19}

In recent years, KYNA has also been reported to be associated with cognitive function. In animal studies, increased KYNA levels were found to induce cognitive impairments, such as impaired spatial working memory, and broad monitoring deficits.^{20–22} In human studies, the relationship between KYNA and cognition has been reported to be inconsistent. For example, Fazio and colleagues reported that KYNA levels were negatively correlated with speed of processing.²³ However, another study found that KYNA levels were not correlated with processing speed or working memory.²⁴ The inconsistent results may be explained by the relationship between peripheral and central KYNA levels. Sellgren and colleagues found no association between central and peripheral KYNA levels in bipolar disorder patients and healthy controls.²⁵

Interestingly, KYNA levels were reported to be increased in cerebrospinal fluid and post-mortem brain tissue of SCZ patients.^{26,27} Moreover, KYNA was found to be associated with psychopathological symptoms. For example, Fazio and colleagues reported a negative association between KYNA levels and positive symptom score as measured by the Positive and Negative Syndrome Scale (PANSS).²³ However, whether there is a significant correlation between KYNA and cognitive deficits in SCZ patients has not been explored yet.

In this study, we compared the cognitive function between SCZ patients and healthy controls using the MATRICS Consensus Cognitive Battery (MCCB), a widely used tool for cognition approved by the US Food and Drug Administration.²⁸ More importantly, we examined the correlation between plasma KYNA and MCCB performance in patients with SCZ. We hypothesized that SCZ patients would have greater KYNA levels, which may be implicated in their cognitive deficits.

Materials and Methods

Participants

Thirty patients with SCZ (15 males, 15 females) were recruited from the inpatients at Guangzhou Huiai hospital, a public psychiatric hospital in Guangzhou city. Inclusion criteria included: (1) fulfilling the DSM-IV criteria for SCZ; (2) aged 17 to 50 years; (3) at least 6 years of education, and (4) a score of more than 60 on PANSS. Meanwhile, exclusion criteria were: (1) history of brain

injury or mental retardation, and (2) history of electric shock treatment within the past 6 months.

Thirty-four healthy individuals (13 males, 21 females) were enrolled from the local community, who were matched for age, sex, and education to the patients. All participants were Han Chinese, who entered this study at the same period. None of them had serious physical diseases, or alcohol or other substance abuse/dependence, except for nicotine.

This study was approved by the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki.

Clinical Assessment

Symptom severity of patients was measured using the PANSS. PANSS was evaluated by four raters, who undertook training before this study. Their inter-observer correlation coefficient reached more than 0.80 for the PANSS total score at repeated measurement after training.

Neuropsychological Assessment

All participants were tested using the MCCB for cognition. The MCCB consists of 10 tests: Trail Making Test A (TMT-A), Symbol Coding, Hopkins Verbal Learning Test (HVLT), Wechsler Memory Scale–Spatial Span, the University of Maryland Letter Number Span Test (LNS), Mazes, Brief Visuospatial Memory Test (BVMPT), Category Fluency, Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), and the Continuous Performance Test (CPT). These 10 tests cover the following seven cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning/Problem Solving, and Social Cognition.

The MCCB was translated into Chinese, and the psychometric properties of Chinese MCCB were good (Cohen's *d* from 0.02 to 0.49). For test-retest reliability, the reliability was good (interclass correlation coefficient from 0.73 to 0.94).²⁹

KYN Metabolite Measurement

All blood samples were collected in the morning after fasting overnight. Peripheral blood samples were collected in EDTA-containing anticoagulant tubes and then centrifuged at 3000 r/min for 10 min. The supernatant was transferred into polypropylene tubes and immediately frozen at –80 °C

until further use. Plasma TRP, KYN, and KYNA levels were measured using high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS), as described in our previous study.³⁰ The time intervals between blood collection and clinical/cognitive assessments were not more than 2 days.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. The χ^2 test was used for categorical variables. For those variables without normal distribution and those with unequal variances, we used the Mann–Whitney *U*-test to compare group differences between patients and controls. For those variables with normal distribution, we used analysis of variance (ANOVA). Whenever the ANOVA result was significant, we tested the effects of age, sex, and education by adopting them as the covariates. Correlation analyses were performed for relationships between KYN metabolites and clinical characteristics or cognitive domain scores in patients and healthy controls, respectively. Bonferroni corrections were utilized to control for multiple tests. Lastly, stepwise multiple regression analysis was performed to investigate associations of KYN metabolites and cognitive tests by adjusting for various confounders. Two-tailed significance values were used, and statistical significance was set at $p < 0.05$.

Results

Demographic Data

Table 1 shows no significant differences in age, sex, and years of education between the patients and healthy controls (all $p > 0.05$). Correlation analysis showed that age, sex and years of education were not associated with KYNA levels in either SCZ patient group or healthy control group (all $p > 0.05$).

Plasma KYN Metabolite Levels in Patients with SCZ and Controls

Table 2 shows that patients with SCZ had higher plasma KYNA levels than controls ($F = 10.211$, $p = 0.002$). Further, after controlling for age, sex and education as covariates, we still found significantly higher blood KYNA levels in patients than in controls ($F = -2.617$, $p = 0.009$). In addition, we found significantly higher KYN/TRP ratios in patients than in controls ($F = 8.739$, $p = 0.004$). However, we did not find significant differences in TRP or KYN between the two groups (all $p > 0.05$).

Cognition Domain Scores in Patients with SCZ and Controls

Table 3 shows significantly lower scores for the MCCB total and its domains in SCZ patients than in controls (all $p \leq 0.01$).

Table 1 Demographic and Clinical Data of Patients with SCZ and Controls

Variables	SCZ (n=30)	Controls (n=34)	Z/χ^2	df	p
Age	27.63±7.23	29.59±8.36	-0.964 ^a	1,63	0.335
Male/female	15/15	13/21	0.896 ^b	1	0.344
Education (y)	10.87±2.81	12.09±1.93	-1.677 ^a	1,63	0.093
Onset age (y)	24.73±7.28				
Antipsychotics					
Drug-naïve	21				
Atypicals	8				
Typicals	1				
Antipsychotic dose (mg/d) (chlorpromazine equivalent)	497.22±148.01				
PANSS total score	88.97±14.09				
Positive Subscale	24.47±3.37				
Negative Subscale	22.23±6.36				
General Subscale	42.27±7.00				

Notes: ^aMann–Whitney *U*-test. ^b χ^2 test

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia.

Table 2 Plasma KYN Metabolite Levels in Patients with SCZ and Controls

Variables	SCZ (n=30)	Controls (n=34)	F	df	p
Tryptophan (ng/mL)	8441.96±2463.42	8726.13±1644.24	1.430 ^a	1,63	0.236
Kynurenine (ng/mL)	312.01±86.80	274.18±65.97	2.421 ^a	1,63	0.125
Kynurenic acid (ng/mL)	7.46±2.44	5.80±1.70	-2.617 ^b	1,63	0.009*
KYN/TRP	0.04±0.08	0.03±0.01	8.739 ^a	1,63	0.004

Notes: ^aANOVA. ^bMann-Whitney U-test. *p<0.05.

Abbreviations: KYN, kynurenine; SCZ, schizophrenia; TRP, Tryptophan.

Table 3 MCCB Scores in Patients with SCZ and Controls

Variables	SCZ (n=30)	Controls (n=34)	F/Z	df	p
Speed of Processing	28.90±13.82	46.79±9.91	31.111 ^a	1,63	<0.001
Attention/Vigilance	34.40±10.75	50.35±8.70	35.208 ^a	1,63	<0.001
Verbal Learning	37.20±15.88	49.12±10.25	11.254 ^a	1,63	0.001
Visual Learning	37.77±11.37	46.79±11.25	-3.143 ^b	1,63	0.002
Working Memory	33.47±10.50	41.74±11.07	7.758 ^a	1,63	0.007
Reasoning and Problem Solving	37.23±9.51	51.29±11.05	22.911 ^a	1,63	<0.001
Social Cognition	41.43±10.24	53.76±9.58	23.251 ^a	1,63	<0.001

Notes: ^aANOVA. ^bMann-Whitney U-test.

Abbreviations: MCCB, MATRICS Consensus Cognitive Battery; SCZ, schizophrenia.

Table 4 Correlation Between Plasma KYN Metabolite Levels and PANSS Scores in Patients with SCZ

Variables	Tryptophan		Kynurenine		Kynurenic Acid		KYN/TRP	
	r	p	r	p	r	p	r	p
PANSS	-0.244	0.194	-0.062	0.746	0.125	0.510	0.174	0.356
Positive	-0.088	0.644	-0.146	0.440	0.032	0.868	-0.43	0.822
Negative	-0.190	0.315	0.168	0.376	0.088	0.644	0.313	0.092
General	-0.276	0.140	-0.206	0.274	0.157	0.408	0.087	0.646

Abbreviations: KYN, kynurenine; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; Positive, Positive Subscale scores; Negative, Negative Subscale scores; General, General Subscale scores.

Correlation Between KYN Metabolite Levels and PANSS Scores or Cognition

Table 4 shows no significant association between KYN metabolite levels and PANSS scores. Pearson correlation analysis revealed a significantly negative association between KYNA levels and attention/vigilance ($r=-0.477$, $p=0.008$), and social cognition ($r=-0.624$, $p=0.010$).

Stepwise multiple regression analysis identified KYNA levels ($\beta=-0.477$, $t=-2.871$, $p=0.008$) as the influencing factor for attention/vigilance in patients with SCZ. Similarly, stepwise multiple regression analysis identified KYNA levels ($\beta=-0.462$, $t=-2.760$, $p=0.010$) as the influencing factor for social cognition in patients with SCZ (Figure 1).

In addition, we did not find any association between KYN levels and cognitive tests in healthy controls (all $p>0.05$).

Discussion

This study had three major findings. (1) Plasma KYNA levels and KYN/TRP ratios were significantly higher in SCZ patients than in healthy controls. (2) Patients showed significantly impaired cognitive performances, as assessed by the MCCB, compared with healthy controls. (3) Plasma KYNA level was negatively correlated with attention/vigilance and social cognition only in patients with SCZ. To our best knowledge, this is the first study to find an association between KYNA and attention/vigilance or social cognition in SCZ patients.

In this study, we found that plasma KYNA levels were significantly higher in SCZ patients than in healthy controls, which is consistent with three previous studies.^{23,31,32} In contrast, two studies reported a decrease in blood KYNA levels in untreated SCZ patients,^{33,34} and two other studies

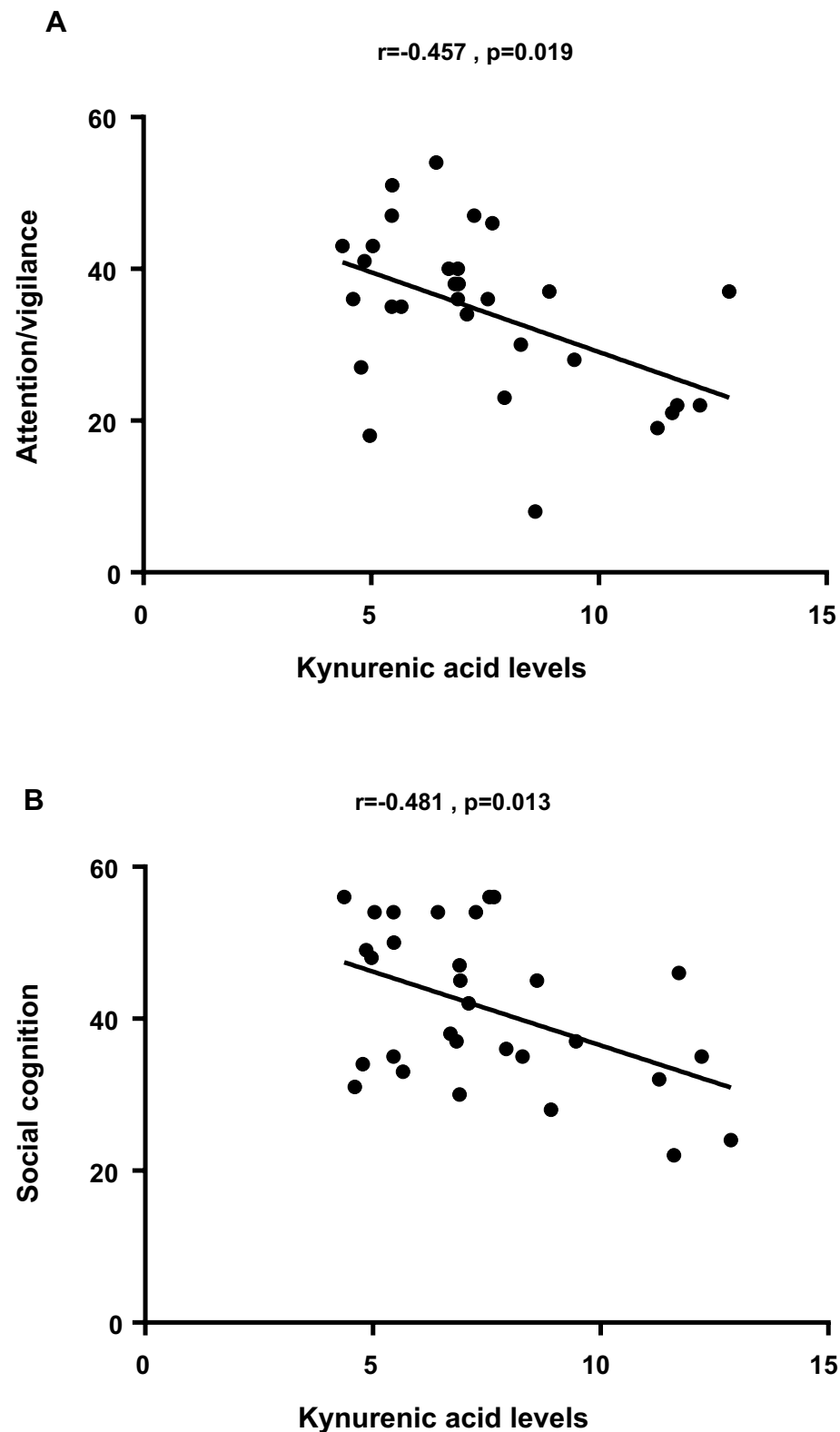


Figure 1 Correlation analysis revealed a significantly negative association between kynurenic acid levels and attention/vigilance (**A**) and social cognition (**B**).

reported no significant differences in blood KYNA levels between medicated SCZ patients and controls.^{35,36} Several factors, such as differences in demographic data (sex, age),

technical differences in measuring KYN metabolite levels, and differences in tested materials or antipsychotic treatments, may have an impact on blood KYNA levels, and

lead to differences in study results. Taking age into consideration, some studies have reported a positive correlation between age and KYNA in SCZ patients.^{37,38} However, in our study, we did not find that age had a significant effect on plasma KYNA level in both patients and healthy controls (both $p > 0.05$). Next, with regard to sex, a previous study found that the KYNA level was higher in the female than that in the male healthy controls.³⁹ However, we did not find a sex difference in KYNA levels in either patients or healthy controls (both $p > 0.05$). Consistent with some previous studies, the KYN/TRP ratio was also increased in the plasma of individuals with SCZ in our study, and an elevated KYN/TRP ratio is associated with immune activation in individuals with SCZ.^{40,41} In the brain, immune activation can activate astrocytes, where KYN can be transaminated to KYNA through KYN aminotransferases (KATs).^{42,43} Thus, we speculate that elevated plasma KYNA levels and KYN/TRP ratio may indicate higher KYNA levels in the brain.

Cognitive impairment is a key feature in SCZ patients. In this study, SCZ patients had significantly lower MCCB scores than healthy controls, which are consistent with previous studies.^{4,44} Evidence concerning the role of KYNA in cognitive dysfunctions in SCZ has mainly arisen from preclinical studies. In animal studies, animals that overexpressed KYNA showed cognitive impairments similar to those observed in SCZ patients, including impaired sensorimotor gating, working memory, and cognitive flexibility.^{22,45–47} Nevertheless, human studies have shown inconsistent results. One study found a negative correlation between KYNA levels and the processing speed in first-episode SCZ,²³ while another study found no correlation between KYNA levels and processing speed or working memory.²⁴ Compared with simple cognitive assessment, the MCCB assessment covers more cognitive domains. To our best knowledge, this study is the first to investigate the correlation between blood KYNA levels and MCCB scores, and we found that plasma KYNA levels were negatively correlated with attention/vigilance or social cognition in SCZ patients.

Sustained attention is the ability to maintain a consistent focus on certain continuous stimuli or activity. Attention deficit is one of the most common cognitive impairments in SCZ patients.^{48,49} It appears to be a major type of cognitive deficit in SCZ and is separable from other neurocognitive factors. Sustained attention is frequently measured by the Continuous Performance Test (CPT), a subtest of the MCCB. In this study, we found that patients with SCZ had significantly lower

CPT scores than healthy controls. In addition, our study is the first to find a correlation between plasma KYNA levels and attention/vigilance in SCZ patients. Previous studies have reported the role of NMDAR in attention. A preclinical study found that an NMDAR antagonist-induced robust decrease in synaptic responses was correlated with attention deficits.⁵⁰ In an animal study, Kazak and colleagues found that reduced brain KYNA levels improved performance in a sustained attention task.⁵¹ Furthermore, a clinical study found that anti-NMDAR encephalitis-induced white matter damage was correlated with attention deficits, and another human study reported that the NMDAR-glycine site obligatory co-agonist D-serine (DSR) improved attention/vigilance in healthy volunteers.^{52,53} As a previous study reported, KYNA is the only endogenous NMDAR antagonist.⁵⁴ Therefore, an increase in KYNA may influence the attention/vigilance of SCZ patients through the NMDAR.

Social cognitive impairment in SCZ has been reported in many studies.^{55,56} Consistent with previous studies, our study found significant lower scores of social cognition assessed by the MCCB in SCZ patients than in healthy controls. We also found a correlation between plasma KYNA levels and social cognition in SCZ patients. The decline of NMDAR function may be one of the causes of social cognition impairment. One study found that social cognition was impaired in patients with anti-NMDAR encephalitis.⁵⁷ Another study reported that the NMDAR agonist DSR reversed impaired auditory emotion recognition, a critical component of social cognitive impairment in SCZ.⁵⁸ Therefore, as an NMDAR antagonist, KYNA may be involved in impaired social cognition in SCZ by inhibiting the NMDAR.

Our research had some limitations. First, the sample size was comparatively small. We recruited 30 SCZ patients and 34 healthy controls in this study, which to some extent may have affected statistical ability. Second, the use of antipsychotic drugs may affect both cognitive performance and KYNA levels. Finally, elevated peripheral KYNA levels may not be representative of an increase in KYNA in the brain. Although KYN does cross the blood-brain barrier, and elevated peripheral KYN may lead to elevated brain KYNA, central and peripheral KYNA levels may be inconsistent. As previously mentioned, KYNA degenerates from KYN through KATs. We speculated that increased plasma KYNA may indicate increased levels of KATs activity in the periphery and

brain. However, no studies have detected both central and peripheral KYNA levels or KATs activity in SCZ patients.

In conclusion, we found that elevated plasma KYNA levels were associated with impaired attention/vigilance and social cognition of SCZ, suggesting that KYNA seems to be a promising biomarker for cognitive investigations in SCZ. To confirm the role of KYNA in cognitive deficits in SCZ, more studies should be conducted by measuring both blood and CSF KYNA simultaneously, together with cognitive performance in a large sample of first-episode drug-naïve SCZ patients using a longitudinal and prospective design.

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Disclosure

All authors declare no potential conflicts of interest.

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