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Linda Li April 8, 2019

The Interplay Between Inflammation and Kynurenines on Symptoms of Schizophrenia

by

Linda Li

David Goldsmith
Adviser

Biology

David Goldsmith

Adviser

Erica Duncan

Committee Member

Brad Pearce

Committee Member

Victor Corces

Committee Member

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Linda Li

David Goldsmith

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Abstract

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Schizophrenia is a chronic, debilitating psychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive impairment. Although antipsychotics are effective against positive symptoms, few clinical treatment options are available for negative and cognitive symptoms, which contribute more to poor functional outcome. Several studies have investigated possible biological mechanisms that underlie this pathophysiology. The NMDA receptor hypothesis suggests that hypofunction of this glutamate receptor may contribute to symptoms. Increased inflammation has also been repeatedly linked to abnormal brain circuitry in schizophrenia patients. In particular, inflammation may affect brain circuitry through its stimulation of the peripheral kynurenine pathway, to increase neuroactive compounds called kynurenine metabolites, some of which act as agonists or antagonists of the NMDA receptor. We hypothesized that inflammatory markers and kynurenine metabolites would be higher in concentration for patients relative to controls, and would be positively correlated with each other, as well as with symptom severity and poor cognitive test performance.

After recruiting participants, we assessed the symptom severity of those diagnosed with schizophrenia and assessed cognition in all participants using ten neuropsychological tests. Concentrations of kynurenine metabolites (tryptophan, kynurenine, kynurenic acid, anthranilic acid, and 3-hydroxyanthranilic acid) and of inflammatory markers (cytokines, receptor factors, chemokine MCP1, and acute phase reactant CRP) were measured from blood collected from participants. We compared patients and controls via descriptive statistics for all characteristics and plasma concentrations. Before and after grouping kynurenine metabolites and inflammatory markers into factor groups for simplified analysis, we calculated Pearson correlation coefficients and conducted linear regression analyses to evaluate the relationship between symptoms, kynurenine metabolites, and inflammatory markers.

We found that inflammatory markers were not only highly correlated with but also highly predictive of kynurenine metabolites in schizophrenia patients. However, the relationship between kynurenine metabolites and symptoms was less clear, suggesting that much research has yet to be done to illuminate the complex relationship between kynurenine metabolites and schizophrenia symptoms. Our findings suggest that the interaction of inflammation and kynurenine metabolites may indeed affect symptoms of schizophrenia and may lead to a promising solution to treating negative and cognitive symptoms for schizophrenia patients.

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Tables and Figures

INTRODUCTION

Schizophrenia is a chronic, debilitating psychiatric disorder affecting ~1% of the world's population [1, 2]. Because of its broad effects on brain development, schizophrenia has a profound effect on affected individuals and is a socioeconomic burden on society, with high rates of homelessness and unemployment, and with life expectancy reduced by approximately 20 years [1–6]. Additionally, affected individuals have difficulty leading productive lives in society due to discrimination and social isolation from others [2]. Patients are diagnosed with schizophrenia and begin to be treated after their first episode of psychosis (FEP) in mid adolescence to early adulthood, typically around 18-25 years of age [1, 2]. The FEP usually follows an at-risk, prodromal period during childhood or adolescence, during which sub-diagnostic psychotic experiences occur [1]. For most patients, schizophrenia has life-altering consequences, leaving them at risk for persistent symptoms of psychosis and episodic decompensations for the remainder of their lives [1]. The precise cause of the disease is unknown, but multiple genetic and environmental factors interact to contribute to its pathophysiology [1, 3].

The psychopathology of the disease is characterized by positive symptoms (delusions and hallucinations), negative symptoms (decreased speech expression, impaired motivation, social withdrawal, and loss of pleasure in normally rewarding activities), and cognitive impairment (deficits in attention, working memory, processing speed, and executive function) [1, 3]. Antipsychotic drugs, which primarily work as dopamine D2 receptor antagonists, are the basis of current clinical treatment [1, 3, 7]. Antipsychotics appear to be effective in treating positive symptoms [1, 3]. However, one particular challenge to these drugs is that they are largely ineffective in treating negative and

cognitive symptoms [1, 3]. Notably, these symptoms are thought to contribute more to poor functional outcomes, as an inability to interact with the environment and struggles with attention and memory may make interacting within society challenging [1, 3]. Though the current treatments for schizophrenia are often effective against positive symptoms, there are few treatment options for those negative and cognitive symptoms that are more important for real-life function [3]. Therefore, to improve quality of life for affected individuals, it is crucial to consider alternative potential mechanisms and treatments underlying such symptoms that do not appear to respond to dopamine D2 receptor antagonism.

Two leading hypotheses regarding the disease pathophysiology involve dopamine and glutamate. The dopamine hypothesis suggests that symptoms of schizophrenia result from dopaminergic dysfunction [7, 8]. As stated above, antipsychotic drugs act as antagonists of dopamine D2 receptors [7]. However, some schizophrenia patients do not respond to these antipsychotics [3, 7]. This suggests that mechanisms other than dopamine D2 antagonism may contribute to disease pathophysiology. Other possible mechanisms of schizophrenia should be explored to account for the limitations of the dopamine hypothesis, especially regarding the causality of negative and cognitive symptoms [7].

An alternative mechanism is the glutamatergic hypothesis of schizophrenia. Glutamate is the primary excitatory neurotransmitter in the brain and is transmitted through both metabotropic and ionotropic glutamate receptors [7]. In particular, studies have suggested that hypofunction of the N-methyl-D-aspartate (NMDA) receptor, an ion-channel subtype of glutamate receptors, underlies the pathophysiology of schizophrenia [7, 9, 10]. Early clinical findings found that treatment with exogenous NMDA receptor

antagonists, phencyclidine (PCP) and ketamine, produced schizophrenia-like symptoms, including negative and cognitive symptoms, in healthy humans [7, 9, 11]. Therefore, understanding NMDA receptor antagonism may provide insight into future promising treatments of the disorder.

Studies have also demonstrated that the immune system, particularly inflammation, plays a critical role in schizophrenia. Several peripheral cytokines, or signaling molecules that regulate acute and chronic inflammation, are abnormally increased in the blood and cerebrospinal fluid of both FEP patients and patients with chronic schizophrenia [12]. In a meta-analysis, Goldsmith et al. noted increased levels of interleukin-6 (IL6), tumor necrosis factor alpha (TNFα), soluble interleukin-2 receptor (sIL2R), and interleukin-1 receptor antagonist (IL1Ra) in patients with acute schizophrenia, and increases in IL6, interleukin-1 beta (IL1β), and sIL2R in patients with chronic schizophrenia [13]. Levels of blood C-reactive protein (CRP), an acute phase protein that is induced by inflammation, has been shown to be elevated in some patients with schizophrenia [12]. In addition, there is an increased prevalence of autoimmune diseases in schizophrenia patients, as well as an increase in circulating autoantibodies, irrespective of whether patients had autoimmune disorders [12]. Based on these observations, determining the underlying mechanisms in which inflammation contributes to the pathophysiology of schizophrenia may lead to potential drug targets. For example, increased inflammatory cytokines are associated with abnormal brain circuitry that leads to deficits in motivation and psychomotor function in patients with depression [14]. As patients with schizophrenia also show deficits in motivation (negative symptoms) and psychomotor speed (cognitive symptoms), it is

possible that inflammation may impact brain circuitry via similar mechanisms in schizophrenia.

Another possible mechanism of inflammation's effects in patients with schizophrenia is via the kynurenine pathway, which is regulated by the immune system and may be a potential pathway to target for future treatment. One hypothesis as to why the kynurenine pathway may improve symptoms of schizophrenia is because of the interaction of some kynurenine metabolites with the NMDA receptor [11]. Kynurenine metabolites are produced through the kynurenine pathway from the essential amino acid, L-tryptophan [9–11]. Tryptophan is degraded in the rate-limiting step to form *N*-formylkynurenine by the enzyme indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, or tryptophan 2,3-dioxygenase (TDO2) [9–11]. Kynurenine forms after formamidase deformylates *N*-formylkynurenine, and is afterwards metabolized through one of three branches of the pathway: producing kynurenic acid by one of four kynurenine aminotransferases (KATs), producing 3-hydroxykynurenine (3-OHKYN) by kynurenine 3-monooxygenase (KMO), or producing anthranilic acid by kynureninase [9–11]. 3-hydroxyanthranilic acid (3-OHAA) forms from 3-OHKYN by kynureninase, and it is used as the substrate of 3-hydroxyanthranilic acid 3,4-dioxygenase (3-HAO) to form α-amino-α-carboxymuconic-ω-semialdehyde [11]. This compound spontaneously reacts to form quinolinic acid, a neurotoxin that acts as an NMDA receptor agonist, as well as a source of NAD+ [11]. The kynurenine pathway is illustrated in a figure below, from a review by Schwarcz et al. [11].

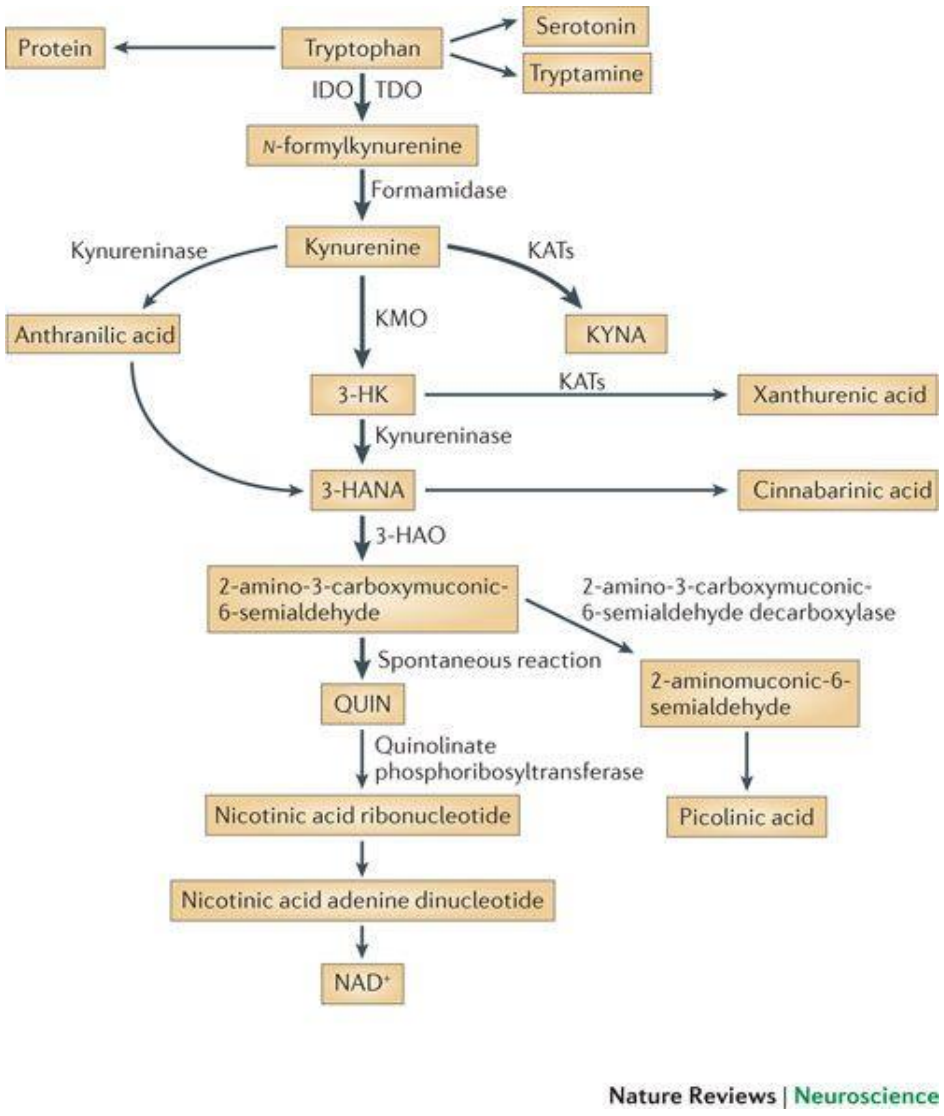

Fig. 1: Schematic of the kynurenine pathway, from a review by Schwarcz et al. [11]. Kynurenine metabolites such as kynurenine, kynurenic acid (KYNA), anthranilic acid, and quinolinic acid (QUIN) are produced through the kynurenine pathway from tryptophan. Here, 3-HK and 3-HANA are used to denote 3-hydroxykynurenine and 3-hydroxyanthranilic acid, respectively.

Enzymes in the peripheral kynurenine pathway are regulated by inflammation [10–12, 15]. Interferon gamma (IFNγ) and other pro-inflammatory cytokines have been shown

to stimulate IDO in the kynurenine pathway, thus increasing peripheral kynurenine and potentially contributing to elevated brain kynurenic acid [11, 15]. Administering IL6 to cultured astrocytes also increased kynurenic acid [10]. Elevated IL6 levels in the CSF and plasma, as well as elevated TNFα levels in plasma, have been found in schizophrenia patients [15]. These studies suggest that the regulation of the kynurenine pathway by cytokines and other inflammatory markers should be explored further to determine whether it may offer a potential treatment for schizophrenia.

Two kynurenine metabolites, quinolinic acid and kynurenic acid, interact with the NMDA receptor [11]. As stated above, quinolinic acid acts as an NMDA receptor agonist by selective stimulation of NMDA receptors in the forebrain [11]. Due to its excitatory properties, intracerebroventricular injection of quinolinic acid caused seizures in mice [11]. Its actions can be blocked by NMDA receptor antagonists, such as kynurenic acid [11].

As the only known endogenous NMDA receptor antagonist, kynurenic acid competitively inhibits the strychnine-sensitive glycine modulatory site on the NMDA receptor [9–11]. Kynurenic acid also acts as a competitive antagonist of the two other ionotropic glutamate receptors, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) receptors and kainate receptors [10, 11]. Additionally, it noncompetitively inhibits the α7 nicotinic acetylcholine receptor (α7nAChR) at the same allosteric potentiating site as that of galantamine, which stimulates the α7nAChR and has been shown to prevent cognitive deficits [9–11].

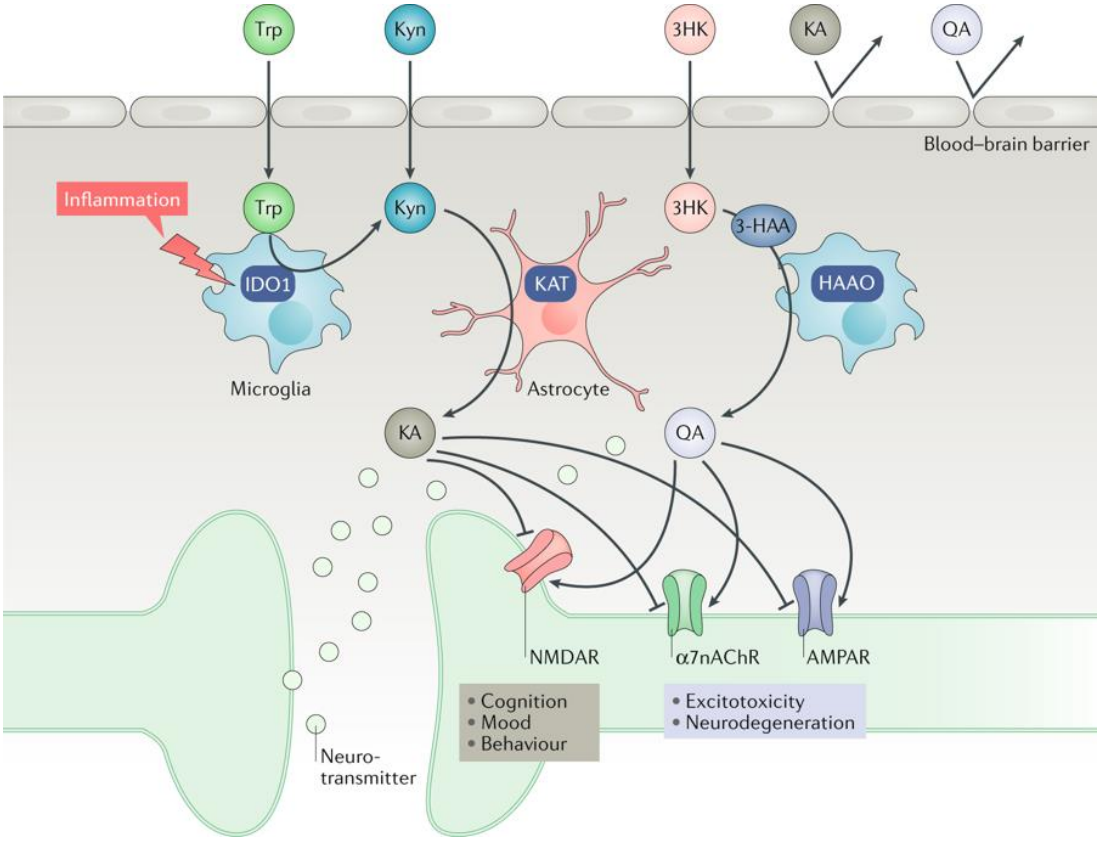

Fig. 2: Kynurenic acid is produced by astrocytes and inhibits multiple receptors, from a review by Platten et al. [16]. Astrocytes in the brain produce kynurenic acid (designated as KA in figure) from kynurenine (Kyn). Kynurenic acid then acts as an antagonist of α7nAChR and glutamate receptors NMDAR and AMPAR, whereas quinolinic acid acts as an agonist.

Due to its role in glutamatergic neurotransmission, there has been increased attention towards kynurenic acid as a possible target for treatment. Levels of kynurenic acid in the cerebrospinal fluid (CSF) and postmortem brain tissue, specifically the prefrontal cortex, are increased in schizophrenia patients [9–11, 15]. Reduced kynurenine 3-monooxygenase (KMO) levels and increased tryptophan 2,3-dioxygenase (TDO) levels in

frontal and anterior cingulate cortices, brain areas known to be affected in schizophrenia patients, suggest a possible mechanism of increasing kynurenic acid [11]. In preclinical studies, injections of L-kynurenine, a precursor to kynurenic acid, induced cognitive impairment in rats [9]. Conversely, administering an inhibitor of kynurenine aminotransferase II (KAT II) to reduce brain kynurenic acid improved cognitive performance in rats [17]. As a result, kynurenic acid is thought to play a causative role in the pathophysiology of schizophrenia.

Due to its polar structure, kynurenic acid cannot cross the blood-brain barrier [9–11]. Therefore, brain kynurenic acid is produced locally from brain kynurenine, of which 60% is transported from the periphery into glial cells [10, 11]. The branches of the kynurenine pathway are segregated in the glial cells, with microglia producing 3-OHKYN and further downstream kynurenine pathway metabolites, and with astrocytes synthesizing kynurenic acid [10, 11]. Though kynurenic acid in the periphery cannot cross the blood-brain barrier, the production of kynurenic acid is heavily influenced by the peripheral kynurenine pathway, which is influenced by inflammatory markers [11]. These studies suggest an association between peripheral inflammatory markers, kynurenine pathway metabolites, and schizophrenia pathophysiology, which therefore should be examined.

Chiappelli et al. explored this relationship in a recent study by analyzing the correlation of clinical characteristics of schizophrenia and plasma levels of kynurenine metabolites and cytokines in patients with schizophrenia spectrum disorder (SSD; including both schizophrenia and schizoaffective disorder) and controls [15]. Inconsistent with previous findings in the brain and CSF, plasma kynurenic acid levels were significantly

lower in SSD patients compared to controls. Other studies found similar results in patients with schizophrenia, as well as in patients with major depressive disorder, bipolar disorder, or schizoaffective disorder [18, 19]. These findings may be a result of measuring kynurenine and kynurenic acid only in the periphery, not in the brain and CSF [15]. In addition, no evidence was found to relate lowered plasma kynurenic acid levels with inflammatory cytokine IL6, and only a trend-level correlation was found between kynurenine levels and TNFα [15]. Chiappelli et al. concluded that increases in IDO and cytokine levels in SSD patients did not account for changes in kynurenine level [15].

We sought to replicate Chiappelli et al.'s findings with a larger group of kynurenine metabolites and inflammatory markers. Chiappelli et al. measured only peripheral kynurenine and kynurenic acid, as well as four cytokines (INFγ, TNFα, IL6, and interleukin-10 or IL10) [15]. We hypothesized that plasma kynurenine metabolites would be elevated in patients with schizophrenia relative to healthy controls, and that there would be an association between kynurenine metabolites and inflammatory markers. We also conducted exploratory analyses to explore the relationship between these inflammatory markers and positive, negative, and cognitive symptoms of schizophrenia.

METHODS

Participants

43 individuals with schizophrenia and 29 healthy controls were recruited from the Atlanta Veterans Affairs Medical Center (Atlanta VAMC) and the local community. Subjects were between 18 and 65 years old and either had a diagnosis of schizophrenia or schizoaffective disorder, or no history of major psychiatric disorder. Exclusion criteria

included a heart attack or heart failure within the last 6 months, antibiotic use within the last 60 days, hospitalization during the last 60 days, any condition requiring steroids within the last 60 days, neurologic disease, head trauma, central nervous system (CNS) infection, seizure disorder, mental retardation, active substance abuse as determined by urine toxicology, HIV infection, autoimmune conditions, or clinically significant hearing or visual impairment. All subjects signed an informed consent form approved by the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee. Information on demographics, smoking status, and medical/psychiatric history, and a blood draw were collected from these individuals. Toxoplasma intensity values were natural log transformed to achieve normality for statistical modeling.

Ratings

Participants with schizophrenia were assessed for symptom severity through the Positive and Negative Syndrome Scale (PANSS).

Neuropsychological Tests

Ten neuropsychological tests were conducted to assess cognition in all participants. Intelligence Quotient (IQ) was assessed using the Reynolds Intellectual Screening Test (RIST) [20]. Executive and frontal lobe function was tested by means of the Wisconsin Card Sorting Test (WCST), in which subjects matched cards based on a category (color, number, or symbol), which would change mid-test unknown to the subject [21]. A perseverative error was defined as a failure to move to a new category from the previously reinforced

one. A non-perseverative error was defined as a failure to maintain matching by the same category.

The Finger Tapping Test (FTT), in which subjects repeatedly pressed a key in a specified length of time, was used to measure psychomotor speed [22]. Psychomotor speed was measured as the number of taps subjects were able to complete in 60 seconds on both the dominant and the non-dominant hand.

Subjects were tested on selected components of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB) [23]. Three subtests were used to measure processing speed. In the Brief Assessment of Cognition in Schizophrenia (BACS), a symbol-coding test, subjects used a key to write digits that correspond to nonsense symbols, and processing speed was measured as the correct number of coded symbols over the course of 90 seconds. In the Fluency test, processing speed was measured as the total number of animal names subjects were able to say in 60 seconds. In the Trail Making Test (TMT), processing speed was measured as the time in which subjects finished drawing lines to connect consecutively numbered circles placed irregularly on a sheet of paper, without being corrected.

In addition to the three MCCB subtests, processing speed was measured in the reaction time test (RTT) as the time in which subjects pressed a key after a prompt appeared on the screen. RTT values were natural log transformed to achieve normality for statistical modeling.

Two subtests were used to measure working memory. The Spatial Span subtest of the Wechsler Memory Scale – Third Edition (WMS-III) assessed the ability of subjects to correctly recollect and reproduce a set of taps previously performed by the test

administrator on 10 irregularly spaced cubes on a board in either the same or the reverse order. The Letter Number Span test assessed the ability of subjects to repeat and reorder a string of letters or numbers presented to them.

One subtest of the MCCB was used to assess verbal learning. In the Hopkins Verbal Learning Test (HVLT), subjects were presented with a list of 12 words from three taxonomic categories. Verbal learning was measured by the number of words subjects were able to recall.

Kynurenine Metabolites

An analytical method capable of measuring tryptophan and its catalyzed products in human plasma and CSF samples was developed using liquid chromatography triple quadrupole mass spectrometry. The target compounds included tryptophan (TRYP), kynurenine (KYN), 3-hydroxykynurenine (3-OHKYN), kynurenic acid (KYNA), anthranilic acid (AA), and 3-hydroxyanthranilic acid (3-OHAA). Prior to analysis, 200 μL of each sample was spiked with a mixture of isotopic internal standard and mixed with 1 mL of 10% formic acid in water (v/v). The samples were loaded onto Strata C18 solid phase extraction cartridges (500 mg/6 mL) for cleanup. The extracts were evaporated to dryness and reconstituted with 100 μL of 1:49 methanol:water (v/v). A 2-μL volume of extract was injected onto a liquid chromatograph. The target compounds were separated using a Phenomenex Luna PFP analytical column (3 μM, 4.6x100 mm) and analyzed using a triple quadrupole mass spectrometer operated in positive electrospray ionization mode. The samples were quantified against a 7-point, matrix-matched calibration curve ranging from 3.91 nM to 3906 nM. In each analytical run, the samples were analyzed alongside an

analytical blank sample, and a low- and high-level quality control material. The method was validated and found to have acceptable degrees of accuracy and precision for all compounds, except for 3-OHKYN, largely due to matrix effects and a lack of the isotopic analog. The limits of detection (LODs) for TRYP, KYN, and 3-OHKYN were 3.91 μM, 0.39 μM, and 0.08 μM, respectively. The LODs for KYNA, 3-OHAA, and AA were 3.91 nM. This method is able to generate values of the target compounds that are comparable to the ranges normally found in the human population. KYN/TRYP, AA, and KYNA values were natural log transformed to achieve normality for statistical modeling.

Immune Biomarkers

Blood samples were obtained in chilled EDTA-coated tubes and spun at 1000g for 15 minutes at 4°C, and plasma was collected and stored at -80°C for later batched analysis of CRP and other inflammatory cytokines IL6, IL1β, and TNFα and their soluble receptors as well as monocyte chemoattractant protein 1 (MCP1). The immunoturbidimetric method was used to assure high sensitivity CRP concentrations with a Beckman AU480 chemistry analyzer and Ultra WR CRP kit (Sekisui Diagnostics). Concentrations of cytokines and their soluble receptors as well as the chemokine MCP1 were assessed in duplicate using high sensitivity multiplex bead-based assays (R&D Systems) and analyzed on a MAGPIX CCD imager (Luminix) as previously described [24]. Consistent with previous analyses, cytokine, cytokine receptor, and chemokine values were natural log transformed to achieve normality for statistical modeling.

Statistical Analyses

Descriptive statistics including means and standard deviations for the independent and dependent variables were calculated for the sample. Differences in demographic and clinical characteristics between patients and controls were analyzed using two-sample *t*-tests (for continuous variables) and chi-squared tests (for categorical variables). In addition, plasma levels of kynurenine metabolites and inflammatory markers were compared in patients and controls using two-sample *t*-tests.

Pearson correlation coefficients were calculated for the relationship among kynurenine metabolite and inflammatory marker concentrations. Correlations between these kynurenine metabolites and inflammatory markers with the symptom and cognitive measurements were also calculated. For data reduction, principal component analyses grouped kynurenine metabolites and inflammatory markers into their respective factor groups, and all correlations were repeated with the factor groups.

Linear regression analyses were performed to test which kynurenine metabolites and inflammatory markers (along with demographic covariables) predicted symptom scores and cognitive performance. Kynurenine metabolite factor groups were tested as the dependent variable, with demographic and clinical characteristics, as well as inflammatory marker factor groups, as the independent variables. Analyses were repeated with cognitive performance as the dependent variable and demographic and clinical characteristics, as well as kynurenine metabolite factor groups, as the independent variables.

RESULTS

Descriptive Statistics

Table 1. Summary of demographic and clinical characteristics and plasma measurements of kynurenine metabolites and inflammatory markers

	Control ($n = 29$)	SCZ ($n = 43$)	Test-statistic	p-value
Age (years)	53.1 ± 10.8	51.5 ± 9.4	$t = 0.672$	0.504
Sex (% male)	82.8	90.7	$\chi^2 = 0.998$	0.318
Race (% black)	79.3	95.3	$\chi^2 = 4.511$	0.034*
% smoker	51.7	55.8	$\chi^2 = 0.117$	0.733
% past cocaine use	31.0	34.9	$\chi^2 = 0.115$	0.734
% on antipsychotic	n/a	93.0	n/a	n/a
% on atypical antipsychotic	n/a	76.7	n/a	n/a
% on typical antipsychotic	n/a	23.3	n/a	n/a
KYN (μM)	2.72 ± 0.84	2.68 ± 1.04	$t = 0.192$	0.848
TRYP (μM)	61.63 ± 19.26	54.91 ± 11.99	$t = 1.825$	0.072
3OHAA (nM)	29.42 ± 18.34	25.92 ± 14.12	$t = 0.914$	0.364
AA (nM)	14.85 ± 18.41	12.85 ± 6.49	$t = 0.657$	0.514
KYNA (nM)	47.52 ± 40.91	31.88 ± 16.21	$t = 2.263$	0.027*
TNFα (pg/mL)	3.66 ± 1.06	4.03 ± 1.33	$t = -1.274$	0.207
IL1β (pg/mL)	0.62 ± 0.11	0.58 ± 0.06	$t = 1.572$	0.124
IL6 (pg/mL)	3.17 ± 0.83	3.27 ± 0.89	$t = -0.488$	0.627
IL10 (pg/mL)	0.48 ± 0.20	0.49 ± 0.25	$t = -0.113$	0.910
MCP1 (pg/mL)	167.37 ± 13.67	172.99 ± 16.77	$t = -1.464$	0.148
IL6sR (pg/mL)	40409 ± 9691	39640 ± 8315	$t = 0.353$	0.725
IL1Ra (pg/mL)	382.72 ± 197.43	508.89 ± 289.01	$t = -2.004$	0.049*
TNFR2 (pg/mL)	2324 ± 866	2331 ± 1259	$t = -0.027$	0.979
hsCRP (mg/L)	4.39 ± 5.79	4.78 ± 7.77	$t = -0.217$	0.829

Values recorded as mean ± standard deviation, or percentage of whole group.

In Table 1, descriptive statistical analysis of demographic and clinical characteristics showed that the percentage of schizophrenia patients who were black was significantly higher than the percentage of controls who were black ($p = 0.034$). Schizophrenia patients were also found to have significantly lower concentrations of KYNA than controls ($p = 0.027$), as well as marginally significantly higher concentrations of IL1Ra ($p = 0.049$). No significant differences were found between patients and controls for all other demographic

and clinical characteristics, as well as for plasma concentrations of kynurenine metabolites and inflammatory markers.

Correlation Analysis

Table 2. Significant Pearson correlations between kynurenine metabolites and cognitive test scores in whole group

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
WCST Non-perseverative Error	KYN	-0.262	0.026*
Fluency	3OHAA/AA	0.249	0.035*
TMT	3OHAA/AA	-0.277	0.019*
LNS	TRYP	0.234	0.048*
	3OHAA	0.340	0.004**
	KYNA	0.293	0.012*

Table 3. Significant Pearson correlations between kynurenine metabolites and cognitive test scores in controls

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
LNS	3OHAA	0.433	0.019*
	KYNA	0.426	0.021*

Table 4. Significant Pearson correlations between kynurenine metabolites and cognitive test scores in schizophrenia patients

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
FTT Dominant Hand Mean	3OHAA/AA	0.375	0.013*
Fluency	3OHAA/AA	0.348	0.022*
TMT	3OHAA/AA	-0.302	0.049*
HVLT	KYNA	0.311	0.042*

Table 5. Significant Pearson correlations between kynurenine metabolites and symptom severity in schizophrenia patients

Symptoms	Kynurenine Metabolite	Correlation Coefficient	p-value
PANSS negative symptoms score	3OHAA	-0.398	0.008**

Correlation analysis showed that concentrations of kynurenine metabolites were significantly positively correlated with cognitive performance in whole group, controls, and schizophrenia patients (Tables 2-4). High scores for most cognitive tests indicate better performance; for WCST, TMT, and RTT, lower scores indicate better performance. Kynurenine metabolite concentrations were also significantly negatively correlated with the negative symptoms score in PANSS for schizophrenia patients, thus indicating that higher kynurenine metabolite concentrations were associated with reduced negative symptom severity (Table 5).

Table 6. Significant Pearson correlations between inflammatory markers and kynurenine metabolites in whole group

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
TRYP	TNFα	-0.264	0.025*
KYN	IL10	0.333	0.005**
	IL1Ra	0.309	0.010*
	TNFR2	0.430	0.000**
KYN/TRYP	TNFα	0.311	0.008*
	IL10	0.267	0.025*
	MCP1	0.328	0.006**
	IL6sR	0.323	0.007**
	IL1Ra	0.409	0.001**
	TNFR2	0.584	0.000**
AA	IL10	0.325	0.006**
	IL6sR	0.270	0.025*
	TNFR2	0.326	0.007**
3OHAA	IL10	0.268	0.024*
	CRP	0.319	0.012*
3OHAA/AA	CRP	0.265	0.038*

Table 7. Significant Pearson correlations between inflammatory markers and kynurenine metabolites in controls

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
KYN/TRYP	TNFα	0.465	0.011*
	TNFR2	0.463	0.013*
3OHAA/AA	IL1Ra	0.389	0.041*

Table 8. Significant Pearson correlations between inflammatory markers and kynurenine metabolites in schizophrenia patients

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
TRYP	MCP1	-0.375	0.017*
KYN	IL10	0.403	0.008**
	IL1Ra	0.427	0.006**
	TNFR2	0.618	0.000**
KYN/TRYP	MCP1	0.453	0.003**
	IL6sR	0.333	0.034*
	IL1Ra	0.448	0.004**
	TNFR2	0.645	0.000**
KYNA	IL6sR	0.341	0.029*
	IL1Ra	0.316	0.047*
	TNFR2	0.333	0.036*
AA	IL1β	0.325	0.033*
	IL10	0.403	0.008**
	MCP1	0.366	0.020*
	IL6sR	0.512	0.001**
	TNFR2	0.424	0.006**
3OHAA	IL6sR	0.347	0.026*
	TNFR2	0.384	0.014*
	CRP	0.348	0.044*
3OHAA/AA	IL1β	0.376	0.013*
	MCP1	0.533	0.000**

All but one inflammatory marker were significantly positively correlated with kynurenine metabolites in whole group, controls, and schizophrenia patients, indicating that higher inflammatory marker concentrations were associated with higher concentrations of kynurenine metabolites (Tables 6-8). Only three significant correlations were found for controls (Table 7), whereas 21 significant correlations were found for patients (Table 8). In particular, in schizophrenia patients, TNFR2 was strongly correlated with both KYN and KYN/TRYP, and MCP1 was strongly correlated with 3OHAA/AA, with p-values below 0.0005 (Table 8).

Table 9. Factor groups for kynurenine metabolites and immune biomarkers for whole group

Factor Group	Variables
Kynurenine Factor 1	TRYP, 3OHAA, 3OHAA/AA
Kynurenine Factor 2	AA, KYNA
Kynurenine Factor 3	KYN, KYN/TRYP
Immune Biomarker Factor 1	IL6sR, TNFRII, MCP1
Immune Biomarker Factor 2	TNF, IL10
Immune Biomarker Factor 3	IL1β, IL6, IL1Ra

Principal component analysis grouped inflammatory markers into three factor groups: IL6sr, TNFR2, and MCP1 (factor 1); TNFα and IL10 (factor 2); and IL1β, IL6, and IL1ra (factor 3), as shown in Table 9.

Table 10. Significant Pearson correlations between inflammatory marker factors and kynurenine metabolites in whole group

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
KYN	Factor 1 (IL6sR, TNFR2, MCP1)	0.368	0.003**
AA	Factor 1 (IL6sR, TNFR2, MCP1)	0.352	0.004**
KYNA	Factor 1 (IL6sR, TNFR2, MCP1)	0.340	0.006**
KYN/TRYP	Factor 1 (IL6sR, TNFR2, MCP1)	0.439	0.000**
	Factor 2 (TNFα, IL10)	0.291	0.020*
3OHAA/AA	Factor 3 (IL1β, IL6, IL1Ra)	-0.276	0.027*

Table 11. Significant Pearson correlations between inflammatory marker factors and kynurenine metabolites in schizophrenia patients

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
KYN	Factor 1 (IL6sR, TNFR2, MCP1)	0.508	0.001**
AA	Factor 1 (IL6sR, TNFR2, MCP1)	0.522	0.001**
KYNA	Factor 1 (IL6sR, TNFR2, MCP1)	0.414	0.011*
KYN/TRYP	Factor 1 (IL6sR, TNFR2, MCP1)	0.627	0.000**
3OHAA/AA	Factor 3 (IL1β, IL6, IL1Ra)	-0.370	0.024*

Inflammatory marker factors were positively correlated with individual kynurenine metabolites in whole group and schizophrenia patients, with p-values ranging from below 0.0005 to 0.027 (Tables 10-11). These correlations indicate that higher concentrations of particular groups of inflammatory markers were associated with higher concentrations of kynurenine metabolites. In particular, factor 1 (IL6sR, TNFR2, and MCP1) was correlated with the most kynurenine metabolites; 4 out of 6 significant correlations in whole group (Table 10) and 4 out of 5 significant correlations in patients (Table 11) included factor 1.

Table 12. Significant Pearson correlations between inflammatory markers and kynurenine metabolite factors in whole group

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 3 (KYN, KYN/TRYP)	TNFα	0.290	0.014*
	MCP1	0.427	0.000**
	IL6sR	0.335	0.005**
	IL1Ra	0.375	0.002**
	TNFR2	0.588	0.000**

Table 13. Significant Pearson correlations between inflammatory markers and kynurenine metabolite factors in controls

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 3 (KYN, KYN/TRYP)	IL1β	0.373	0.046*
	IL1Ra	0.417	0.027*
	TNFR2	0.459	0.014*

Table 14. Significant Pearson correlations between inflammatory markers and kynurenine metabolite factors in schizophrenia patients

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	MCP1	-0.379	0.016*
Factor 2 (AA, KYNA)	MCP1	0.341	0.031*
	IL6sR	0.331	0.035*
	IL1Ra	0.333	0.035*
	TNFR2	0.397	0.011*
Factor 3 (KYN, KYN/TRYP)	TNFα	0.302	0.049*
	MCP1	0.467	0.002**
	IL6sR	0.399	0.010**
	IL1Ra	0.351	0.027*
	TNFR2	0.701	0.000**

Principal component analysis grouped kynurenine metabolites into three factor groups: TRYP, 3OHAA, and 3OHAA/AA (factor 1); AA and KYNA (factor 2); and KYN and KYN/TRYP (factor 3), as shown in Table 9. Similar to the results seen when grouping inflammatory markers, kynurenine metabolite factors were positively correlated with individual inflammatory markers in whole group, controls, and schizophrenia patients (Tables 12-14). These correlations indicate that higher concentrations of particular groups of kynurenine metabolites are associated with higher concentrations of inflammatory markers. In particular, factor 3 (KYN, KYN/TRYP) was a component of all significant correlations found for whole group (Table 12) and controls (Table 13) and for 5 out of 10 significant correlations found for patients (Table 14).

Table 15. Significant Pearson correlations between inflammatory marker factors and kynurenine metabolite factors in whole group

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	Factor 3 (IL1β, IL6, IL1Ra)	-0.262	0.036*
Factor 3 (KYN, KYN/TRYP)	Factor 1 (IL6sR, TNFR2, MCP1)	0.460	0.000**
	Factor 2 (TNFα, IL10)	0.308	0.013*

Table 16. Significant Pearson correlations between inflammatory marker factors and kynurenine metabolite factors in controls

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 3 (KYN, KYN/TRYP)	Factor 2 (TNFα, IL10)	0.404	0.037*

Table 17. Significant Pearson correlations between inflammatory marker factors and kynurenine metabolite factors in schizophrenia patients

Kynurenine Metabolite	Inflammatory Marker	Correlation Coefficient	p-value
Factor 2 (AA, KYNA)	Factor 1 (IL6sR, TNFR2, MCP1)	0.447	0.006**
Factor 3 (KYN, KYN/TRYP)	Factor 1 (IL6sR, TNFR2, MCP1)	0.616	0.000**

Positive correlations comparing factor groups of kynurenine metabolites to factor groups of inflammatory markers were significant across whole group, controls, and schizophrenia patients (Tables 15-17). However, the correlations were strongly significant in patients, with p-values below 0.01 (Table 17). In particular, factor 1 of inflammatory

markers IL6sR, TNFR2, and MCP1 was positively correlated with kynurenine metabolite factor 2 (AA and KYNA) and factor 3 (KYN and KYN/TRYP), as seen in Table 17.

Table 18. Significant Pearson correlations between kynurenine metabolite factors and cognitive test scores in whole group

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
Symbol Coding	Factor 2 (AA, KYNA)	0.249	0.035*
TMT	Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	-0.260	0.028*
LNS	Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	0.302	0.010**

Table 19. Significant Pearson correlations between kynurenine metabolite factors and cognitive test scores in controls

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
LNS	Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	0.533	0.003**

Table 20. Significant Pearson correlations between kynurenine metabolite factors and cognitive test scores in schizophrenia patients

Cognitive Variable	Kynurenine Metabolite	Correlation Coefficient	p-value
Symbol Coding	Factor 3 (KYN, KYN/TRYP)	0.330	0.030*

Correlation analysis of kynurenine metabolite factor groups with cognitive test scores yielded few significant correlations in whole group, controls, and patients (Tables 18-20). Factor groups of kynurenine metabolites were positively associated with most cognitive test scores and negatively associated with TMT scores, indicating that higher

concentrations of particular kynurenine metabolites were associated with better cognitive performance in all groups.

Linear Regression Analysis

Table 21. Linear regression analysis with kynurenine metabolite factors as dependent variable in whole group

Kynurenine Metabolite	Independent Variable	Beta Coefficient	p-value
Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	Inflammatory Marker Factor 3 (IL1β, IL6, IL1Ra)	-0.285	0.017*
	Race	-0.250	0.035*
	Toxoplasma Intensity	0.286	0.016*
Factor 2 (AA, KYNA)	Smoker	-0.254	0.043*
Factor 3 (KYN, KYN/TRYP)	Inflammatory Marker Factor 1 (IL6sR, TNFR2, MCP1)	0.441	0.000**
	Inflammatory Marker Factor 2 (TNFα, IL10)	0.263	0.017*

Table 22. Linear regression analysis with kynurenine metabolite factors as dependent variable in controls

Kynurenine Metabolite	Independent Variable	Beta Coefficient	p-value
Factor 3 (KYN, KYN/TRYP)	Age	0.437	0.015*

Table 23. Linear regression analysis with kynurenine metabolite factors as dependent variable in schizophrenia patients

Kynurenine Metabolite	Independent Variable	Beta Coefficient	p-value
Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	Race	-0.319	0.040*
Factor 2 (AA, KYNA)	Inflammatory Marker Factor 1 (IL6sR, TNFR2, MCP1)	0.339	0.017*
	Sex	-0.303	0.034*
	Smoker	-0.356	0.011*
Factor 3 (KYN, KYN/TRYP)	Inflammatory Marker Factor 1 (IL6sR, TNFR2, MCP1)	0.616	0.000**

Linear regression analyses were performed in all groups with kynurenine metabolite factor groups as the dependent variable, and inflammatory marker factor groups and demographic and clinical characteristics as the independent variables (Tables 21-23). In particular, factor 1 of inflammatory markers IL6sR, TNFR2, and MCP1 was highly significant ($p < 0.0005$) in a positive linear regression with factor 3 of kynurenine metabolites KYN and KYN/TRYP and less significant ($p = 0.017$) in a positive linear regression with factor 2 of kynurenine metabolites AA and KYNA in patients (Table 23). These relationships were plotted in partial regression plots in Figure 3.

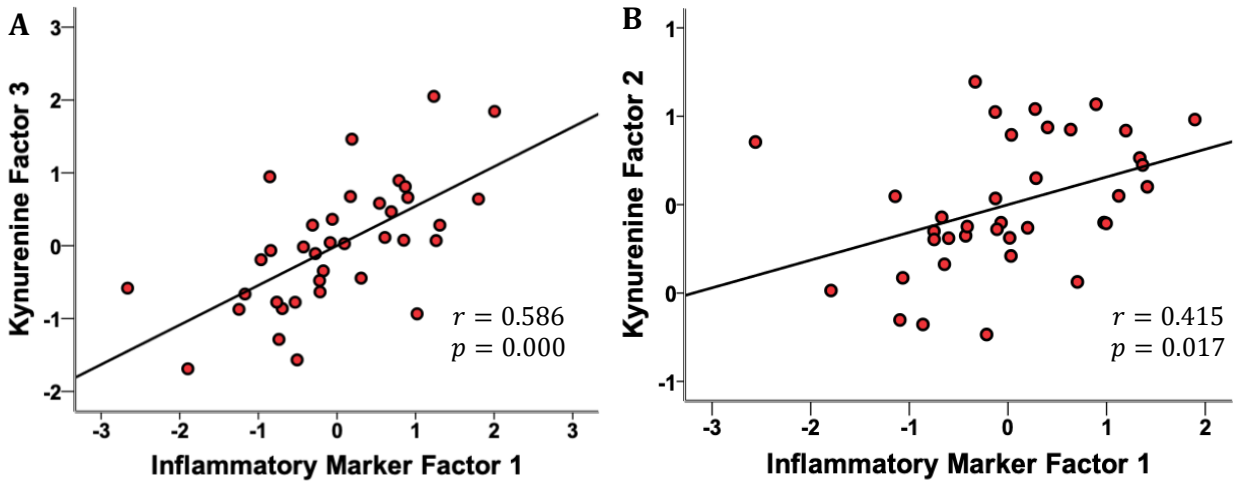

Fig. 3: Linear regression models evaluating the predictive relationships between kynurenine metabolite factors 3 (A) and 2 (B) with inflammatory marker factor 1.

Table 24. Linear regression analysis with cognitive test scores as dependent variable in controls

Cognitive Variable	Independent Variable	Beta Coefficient	p-value
RIST	Age	-0.616	0.000**
	Race	-0.580	0.000**
Symbol Coding	Age	-0.678	0.000**
	Race	-0.560	0.001**
	Smoker	-0.420	0.003**
	Toxoplasma Intensity	0.312	0.047*
Fluency	Age	-0.668	0.000**
TMT	Age	0.570	0.001**
	Race	0.304	0.045*
	Sex	0.353	0.020*
Spatial Span	Age	-0.562	0.008**
	Race	-0.555	0.008**
LNS	Kynurenine Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	0.433	0.002**
	Age	-0.463	0.001**
	Race	-0.269	0.036*
HVLT	Age	-0.631	0.000**

Table 25. Linear regression analysis with cognitive test scores as dependent variable in schizophrenia patients

Cognitive Variable	Independent Variable	Beta Coefficient	p-value
RIST	Race	-0.446	0.002**
WCST Perseverative Error	Race	0.322	0.028*
	Toxoplasma Intensity	0.508	0.001**
WCST Non-perseverative Error	Race	-0.347	0.023*
FTT Non-Dominant Hand Mean	Kynurenine Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	0.352	0.037*
	Toxoplasma Intensity	-0.353	0.036*
FTT Dominant Hand Mean	Kynurenine Factor 1 (TRYP, 3OHAA, 3OHAA/AA)	0.486	0.002**
	Sex	0.311	0.029*
	Toxoplasma Intensity	-0.502	0.002**
Symbol Coding	Kynurenine Factor 3 (KYN, KYN/TRYP)	0.289	0.029*
	Age	-0.498	0.000**
Fluency	Age	-0.312	0.029*
	Race	-0.287	0.044*
	Smoker	0.355	0.014*
RTT	Sex	-0.507	0.001**
LNS	Age	-0.391	0.007**
	Race	-0.300	0.041*
HVLT	Age	-0.324	0.034*

Linear regression analyses were also performed in controls and patients with cognitive test scores as the dependent variable, and kynurenine metabolite factor groups and demographic and clinical characteristics as the independent variables (Tables 24-25).

Kynurenine factor group 1 (TRYP, 3OHAA, 3OHAA/AA) was only predictive of LNS scores for controls (Table 24) and of FTT scores for patients (Table 25), indicating that higher kynurenine metabolite concentrations were predictive of better cognitive performance. Kynurenine factor group 3 (KYN, KYN/TRYP) also demonstrated a predictive relationship with symbol coding scores in patients, indicating their link to better cognitive performance as well (Table 25).

DISCUSSION

Our study explored the relationship between inflammatory markers and kynurenine metabolites, and how they may be linked to symptoms of schizophrenia. We hypothesized that inflammatory marker concentrations would be positively associated with kynurenine metabolite concentrations, and that higher concentrations of kynurenine metabolites would be associated with worse cognitive performance and increased symptom severity.

Our initial finding that KYNA concentrations were significantly lowered, rather than elevated, in schizophrenia patients relative to controls was not supportive of our hypothesis. This finding was inconsistent with findings of elevated KYNA concentrations in the CSF and postmortem brain tissue of schizophrenia patients [25-27]. However, our finding replicates those of several other studies [15, 18, 19]. Most recently, Chiappelli et al. found decreased plasma KYNA concentrations in patients with schizophrenia and schizoaffective disorder [15]. These mixed findings may be due to the inability of KYNA to cross the blood-brain barrier. In our study, as in the study by Chiappelli et al., KYNA was measured from blood plasma, rather than from CSF or brain tissue. Therefore, lower plasma measurements of KYNA may not be indicative of brain KYNA levels. In fact, there

may be higher concentrations of kynurenine metabolites in the brain that cannot be measured peripherally.

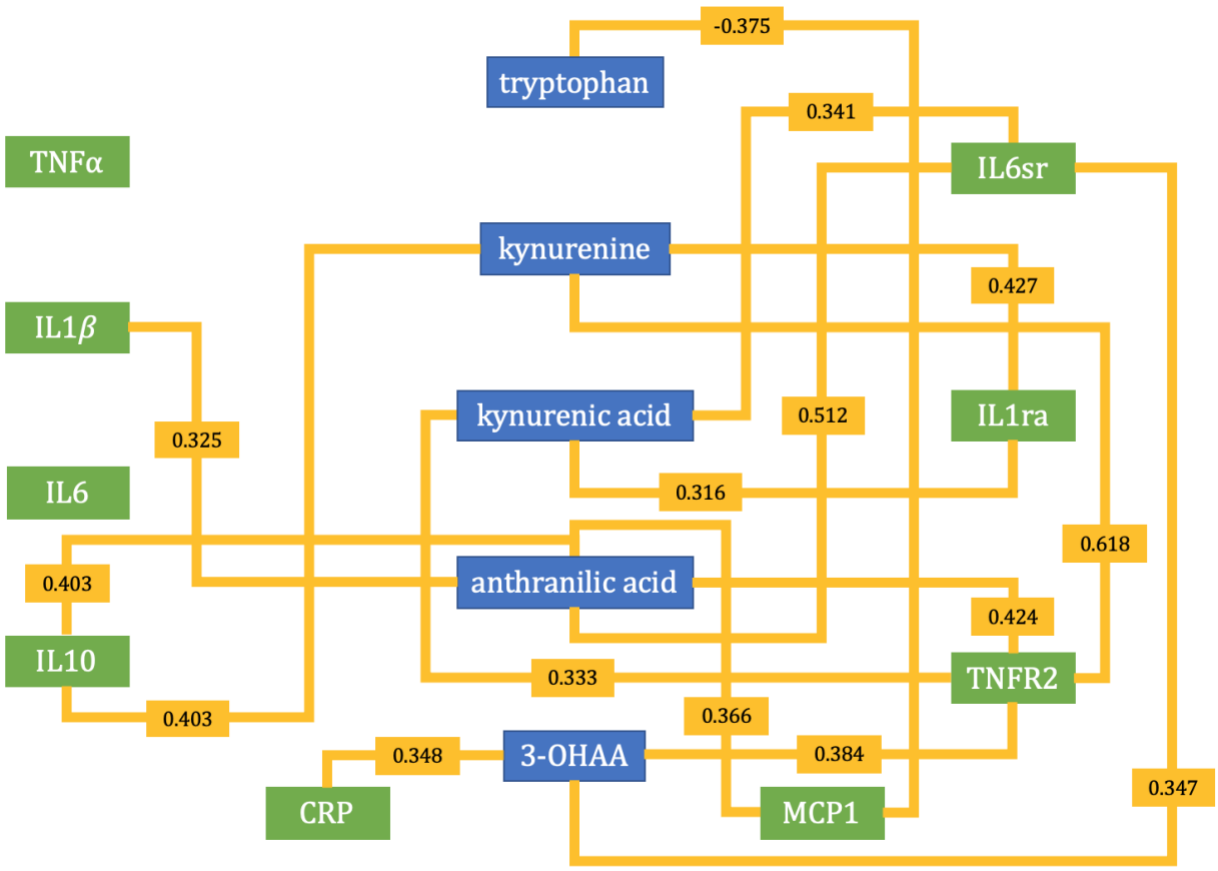

Fig. 4: Schematic summarizing the correlative relationships between the kynurenine metabolites and the inflammatory markers in schizophrenia patients. Pearson correlation coefficients listed in yellow boxes for each relationship.

Correlation analyses both with and without factor groups, as well as our linear regression models, support our hypothesis that inflammatory markers are positively associated with and predictive of kynurenine metabolites in schizophrenia. These

relationships are summarized in Figure 4. The strong positive correlations and regressions, particularly between inflammatory marker factor 1 (IL6sR, TNFR2, and MCP1) and kynurenine metabolite factor 3 (KYN and KYN/TRYP), give credence to the hypothesis that increased inflammation may lead to elevated kynurenine production, perhaps by affecting the enzyme IDO. These results are supported by other findings as well [28, 29]. Increased IL6 and KYNA were found in the CSF of schizophrenia patients [28]. In addition, patients with major depressive disorder were found to have positively correlated plasma IL6, CRP, and KYN/TRYP [29].

The relationship between kynurenine metabolites and symptoms, as shown through our correlations and linear regressions, is less clear. In general, kynurenine metabolites were positively associated with better cognitive performance in both controls and patients, contrary to previous findings linking increases in kynurenine metabolites to deficits in spatial working memory and sensory processing [30, 31]. However, other studies have found no significant relationship between baseline kynurenine metabolites and processing speed or working memory [32], as well as severity of schizophrenia symptoms as measured by the Brief Psychiatric Rating Scale [33]. The mixed results in our study, as well as in literature, indicate that much research has yet to be done in order to fully understand the complex relationship between kynurenine metabolites and symptoms of schizophrenia.

Several factors limit our understanding of these relationships in this study. First, there was no control of the baseline levels of tryptophan in participants. Differing levels of the precursor tryptophan would affect the production of kynurenine metabolites we measured. In addition, we did not account for physical exercise, which has been shown to increase plasma KYNA [34], and did not directly account for BMI, which has been

consistently associated with schizophrenia in previous studies [35, 36]. However, the results of our linear regressions did not appreciably change after adjusting for BMI in the smaller sample of subjects for whom we had BMI data.

The strengths of this study outweigh its limitations, however, thus allowing it to add significant findings to the current literature on inflammation and kynurenine in schizophrenia. This study includes a comprehensive panel of inflammatory markers—possibly larger than any other study evaluating the relationship between inflammation and kynurenine metabolites. In addition, a wide range of neurocognitive tests were included in this study to assess many components of cognition. Despite the extensive number of variables taken into consideration, however, our findings are still significant, as our use of principal component analysis reduced the data to simplify the complex interconnected biological mechanisms in play.

In conclusion, our study clearly demonstrates a positive association between inflammation and kynurenine metabolites, and that this interaction may affect symptoms of schizophrenia. Based off these findings we will continue to explore these relationships. We hope to increase the panel of kynurenine metabolites of future studies to include quinolinic acid. As a known neurotoxin and NMDA receptor agonist, quinolinic acid may interact with kynurenic acid or other kynurenine metabolites in symptoms of schizophrenia. In addition, we hope to examine the cognitive effects of administering kynurenic acid and quinolinic acid to the brain directly using animal models or gene knockdown, or examine these effects in humans by exploring pharmacologic targets for the kynurenine pathway. Through our investigation of these complex relationships between

inflammation and kynurenine metabolites, we may find a promising solution to treating symptoms affecting quality of life for schizophrenia patients.

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