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The role of *Toxoplasma gondii* and Kynurenine metabolism in cognitive impairments in Schizophrenia

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An abstract of
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Rollins School of Public Health of Emory University
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Abstract

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Around 85% of schizophrenic patients suffer from some form of cognitive impairment and the severity of these cognitive impairments correspond to the severity of impaired everyday functioning. The neurobiological mechanisms underlying these cognitive impairments is not well understood, impeding drug discovery efforts. Previous studies have shown an association between infection and immune dysfunction and cognitive deficits with higher levels of some cytokines corresponding to worse cognitive scores. Chronic inflammation linked to persistent infections can modulate tryptophan/ kynurenine metabolism. The aim of this study is to assess levels of various metabolites of the "Kynurenine Pathway of Tryptophan metabolism" and related biomarkers (neopterin, tyrosine and phenylalanine) in relation to cognitive deficits across domains including processing speed, working memory, verbal, and visual learning. The effect of Kynurenic Acid (KYNA) is determined by the characteristics of the specific receptors on which it acts, and we hypothesized that the relative potency of KYNA at GPR35 receptors to reduce inflammation may correspond to better cognition. Thus, KYNA may have either a deleterious or salutary effect on cognition in schizophrenia, but this has not been previously assessed. Demographic, biologic, and cognitive data from 71 patients recruited from the Atlanta Veterans Affairs Medical Center was assessed in this study. Linear regression analysis was conducted for each of the cognitive variables and immune biomarkers adjusted for covariates like age, sex, race, and smoking status. Results indicate that KYNA levels in blood were higher in controls and were significantly associated with better cognition as determined by the Letter Number Span (LNS), fluency, Brief Assessment of Cognition in Schizophrenia-Symbol Coding (BACS-SC), Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST), and RIST Index. The levels of Tryptophan were significantly higher in controls and corresponded to better scores on LNS, WCST and WMS. These findings may indicate the protective effect of KYNA through the GPR35 receptor in the periphery.

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CHAPTER 1. LITERATURE REVIEW AND BACKGROUND

Schizophrenia is a debilitating, heterogenous brain disorder currently affecting more than 21 million people in the world (71). It includes a cluster of positive and negative symptoms as well as neurocognitive and sensory motor disturbances. The positive symptoms include hallucinations, paranoid delusions, distortion of perception and bizarre behavior while the negative symptoms include avolition, alogia, anhedonia, and apathy (1). These patients also suffer from impaired everyday functioning like social and occupational functions, difficulties in maintaining residence and compliance with medication, the severity of which is related to the severity of cognitive impairment (2). The disease is thought to occur when a genetic predisposition occurs together with exposure to incompletely defined environmental factors like infection, stress, smoking, environmental pollutants, and toxins (3). Pathogens suspected to have a significant association with schizophrenia include Epstein-Barr virus, measles, Polio, and human herpes virus. However, the strongest association of schizophrenia is with the neurotropic parasite *Toxoplasma gondii (T. gondii)* (4-7).

T. gondii is perhaps the most prevalent human parasite in the world. It has been estimated that at least 30% of the world's population is infected with *T. gondii* (8). There are approximately 1 million new cases and 750 *T. gondii* related deaths in the US annually (9). It is an intracellular parasite with the ability to form cysts. Its sexual reproductive phase occurs in the intestinal epithelium of cats, which are the definitive hosts. Transmission between intermediate hosts occurs through ingestion of raw or uncooked meat containing tissue cysts (10) or by consuming food and water contaminated with

oocysts from infected cat feces (10). Congenital transmission can also occur. The parasite has an ability to cross barriers like the intestinal epithelium, placenta, endothelium, and blood-brain barrier (10).

An association between schizophrenia and *T. gondii* has been suspected since the 1950s. A meta-analysis of 23 studies reported that the seroprevalence of *T. gondii* is 2.7 times higher in schizophrenia patients than in controls (11). Toxoplasma infected patients have higher scores on the positive and negative syndrome scale (12-14). Also, grey matter density is reduced in schizophrenia subjects who are *T. gondii* seropositive compared to those who are seronegative (15). Further, antipsychotic drugs like fluphenazine, valproic acid are found to inhibit toxoplasma reproduction in vitro (16, 17).

Toxoplasma seropositivity is associated with poor cognitive performance (18). It has been suspected that persistent infections cause low-grade inflammation leading to subtle alterations in neurotransmission and synaptic plasticity, thus impairing cognition (19-21). Studies of cognition and cytokines indicate that worse cognitive performance is associated with higher levels of TNF (22). A long-term goal of Dr. Pearce's laboratory is to study cognition in relation to the GPR35 receptor mechanism that may connect infection and immune dysfunction to cognitive defects.

The cytokine Interferon gamma (IFNg) produced by peripheral immune cells and glia plays a crucial role in connecting the immune system and the nervous system (23, 24). It sets off the cascade of steps from tryptophan (Trp) down the kynurenine pathway, causing accumulation of various neuroactive metabolites such as quinolinic acid, L-kynurenine, and kynurenic acid. The kynurenine pathway plays an important role in infection and immunity (25-27). An imbalance in the metabolites of this pathway is

associated with a range of neuropsychiatric sequellae. Kynurenic acid (KYNA) is one of the end products of the kynurenine pathway (KP), and the increased levels of KYNA are associated with cognitive deficits (28, 29).

Three enzymes are responsible for catalyzing the first step in the KP (oxidative cleavage of Trp), namely tryptophan 2,3-dioxygenase (TDO), indolamine 2,3-dioxygenase 1 (IDO1) or indolamine 2,3-dioxygenase 2 (IDO2) which convert Trp to N-formylkynurenine which is then converted to L-kynurenine (KYN) by kynurenine formamidase (30). IDO1 and 2 are upregulated by IFNg produced in response to infection (31-34). KYN is then metabolized by either:

(1) kynurenine 3-monooxygenase (KMO) into 3-hydroxykynurenine (3-HK) which is then converted to 3-hydroxyanthranilic acid (3-HAA) and finally into quinolinic acid (QUIN)

(2) kynurenine aminotransferase (KAT) I, II, III or IV into Kynurenic Acid (KYNA) which occurs in astrocytes and microglia (35)

(3) kynureninase into anthranilic acid (AA)

QUIN increases neuronal activity, elevates intracellular calcium concentrations, activates NMDA receptor (36) and is also responsible for increased microenvironmental glutamate concentrations (37). Thus, QUIN is considered a neurotoxic and pro-inflammatory KP metabolite. KYNA suppresses inflammation (38) and elevated KYNA levels in response to inflammatory stimuli are essential to maintain the balance between pro-inflammatory and anti-inflammatory processes (38, 39). These two branches illustrate the opposing

roles of the KP in regulation of inflammation. Thus, the KP can be considered as a system under tension and can be perturbed easily.

KYNA was the first endogenous ligand discovered for GPR35 (40). GPR35 is a Class A (Rhodopsin) G Protein Coupled Receptor (41). There is some debate regarding its "orphan" status as endogenous ligands since KYNA, 2-oleyl lysophosphatidic acid, reverse T3, cyclic guanosine monophosphate (40, 42, 43) and more recently the chemokine CXCL17 (41) have been discovered. However, under normal physiological conditions, the estimated concentrations of these ligands in humans may be less than what would be required to modulate the activity of the receptor substantially (44, 45) so GPR35 might still be considered an orphan receptor. GPR35 has been observed in numerous organ systems including the immune system, central nervous system, cardiovascular system, and the gastro-intestinal tract (46). It is important in the functioning of the immune system, potentially in the neuro-inflammatory axis in that it is expressed at high levels in peripheral blood lymphocytes, neutrophils, CD14+ monocytes, dendric cells (40), mast cells, basophils, and eosinophils. It is also expressed in glia (40) and plays a role in mediating hyperalgesia, neurogenic inflammation, and neuropathic pain (45, 47, 48).

KYNA levels are elevated in inflammatory neurological diseases (49-51) and the expression of GPR35 predominantly in inflammatory cells implies that the GPR35-KYNA pair might be important in regulating immune function. KYNA is an agonist ligand for GPR35 and acts to reduce inflammation (39, 40, 52). Experiments on human peripheral blood cells as well as whole blood stimulated by Staph. Aureus or lipopolysaccharide (LPS) show that KYNA attenuates TNF-alpha production in a dose-

dependent manner (38, 40). It acts at the GPR35 receptor to modulate the activity of calcium channels and reduces calcium influx, mediated by adenylate cyclase inhibition and reduced intracellular cAMP (40, 53). This process contributes to decreased astrocytic glutamate output and excitatory neurotransmitter levels in brain extracellular space, thus explaining the anti-excitotoxic and neuroprotective effect of KYNA at GPR35 (53). Furthermore, KYNA decreased phosphorylation of the extracellular signal-regulated kinases 1/2 (ERKs), p38, and mitogen activated protein kinases (MAPK) which are targets of GPR signaling (54-56) and these effects of KYNA-GPR35 signaling may reduce inflammation (57).

The effect of KYNA on inflammation is determined by the characteristics of specific receptors located on immune cells and glia (38, 58). KYNA acts as an antagonist at the glycine co-agonist site of the N-methyl-D-aspartate (NMDA) receptor (39) and the allosteric potentiating site of the alpha 7 nicotinic acetylcholine (*a7nACh*) receptor (59) but, it acts as an agonist at the newly described GPR35 receptor (see above) (40). KYNA mediates its anti-inflammatory effect by action on GPR35 and NMDA receptors while its action on the *a7nACh* receptor is pro-inflammatory.

Under normal conditions, acetylcholine acts on *a7nACh* receptors to decrease TNF production and produce an anti-inflammatory effect (60). KYNA acts as an antagonist at the nicotinic receptor, leading to increased levels of TNF (61, 62). On the other hand, the action of KYNA on GPR35 is anti-inflammatory, leading to decreased TNF levels (40). NMDA and *a7nACh* receptors are essential in regulating neurodevelopment (63, 64) and inhibition of the receptors by increased levels of KYNA are associated with cognitive deficits (28, 65) in animal models. Also, the EC50 values of KYNA on GPR35 activation

are similar to the concentration required for KYNA to antagonize the NMDA receptor (40). Thus, the balance between pro- and anti-inflammatory processes and by extension cognition, are determined by the relative sensitivities and abundance of these receptors. We hypothesize that the relative potency of KYNA at GPR35 receptors to reduce inflammation would lead to better cognition.

In addition to tryptophan metabolism, tyrosine metabolism also affects cognition by synthesis of neurotransmitters. The tyrosine pathway is altered through activation of the guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) which in turn is induced by interferon gamma produced in reaction to inflammatory stimuli. This resembles the activation of the enzyme IDO by interferon gamma which further converts tryptophan to kynurenine as the first step in the KP. The activation of GTP-CH1 is responsible for the synthesis of neopterin in dendritic cells and astrocytes (66, 67). GTP-CH1 is also responsible for the production of tetrahydrobiopterin (BH4) which is a cofactor for phenylalanine 4-hydroxylase (PAH) (68, 69). The conversion of tyrosine(TYR) to phenylalanine(PHE) is mediated by PAH. Tyrosine is then metabolized by tyrosine 3-monooxygenase to dihydroxyphenylalanine which is responsible for the synthesis of the neurotransmitter dopamine. Thus, BH4 is essential to neurotransmitter synthesis. In chronic inflammatory conditions, the balance shifts towards production of neopterin instead of production of BH4. The deficiency of BH4 is associated with psychiatric disorders including schizophrenia (70).

CHAPTER 2. THESIS MANUSCRIPT

INTRODUCTION

Schizophrenia is a debilitating disorder affecting more than 21 million people worldwide (71). It has a point prevalence range of 2.6 to 6.7 per 1000 (72). Despite its low prevalence, schizophrenia was ranked among the top 15 causes of disability worldwide in 2016 (73). Its economic burden is estimated to range from 0.02% to 1.65% of the gross domestic product (74). In the US, the economic burden of schizophrenia is more than $60 billion per year (75).

Schizophrenia is associated with a range of positive and negative symptoms and neurocognitive and sensorimotor processing deficits. Around 85% of the patients experience some form of cognitive deficit (76) and the severity of cognitive impairment is associated with the severity of impaired everyday functioning (77). The mechanism behind these neurocognitive impairments is not well understood, thus limiting drug discovery efforts. We intend to study cognitive deficits in relation to the metabolites of the kynurenine pathway (KP) of tryptophan metabolism and other immune biomarkers like neopterin, tyrosine and phenylalanine that may connect infections and immune dysfunction with cognitive dysfunction in schizophrenia.

One of the pathogens suspected to have an association with schizophrenia is the parasite *T. gondii* (4-6, 11). Previous studies showed that individuals who were *T. gondii*

seropositive had relatively poor cognitive performance (18). These infections cause low-grade inflammation leading to alterations in neurotransmission and synaptic plasticity, thus impairing cognition (19-21). An important immune reaction against *T. gondii* infection is the production of interferon gamma (IFNg) which sets off the cascade of steps in the KP leading to elevations of kynurenine (KYN) and kynurenic Acid (KYNA) levels (32).

KYNA acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor and at the alpha-7 nicotinic acetylcholine receptor (a7nACh) (32) and as an agonist at the GPR35 receptor (40). These receptors are relevant to cognitive function. KYNA is elevated in response to inflammatory stimuli and while its action on GPR35 and NMDA is anti-inflammatory (38), its action on a7nACh is pro-inflammatory (61, 62). Under normal conditions, acetylcholine acts on the nicotinic receptor to decrease production of TNF (60), but KYNA's action as an antagonist of a7nACh can counteract the ACh anti-inflammatory effect.

The relative abundance and sensitivities of these receptors determine the anti- or pro-inflammatory response. This neuroimmune mechanism has not yet been examined in schizophrenia despite evidence of alterations in the KP in schizophrenia patients with cognitive impairments (78). We hypothesize that the relative potency of KYNA at GPR35 to reduce inflammation will correspond to better cognition. On the other hand, if cognitive deficits are associated with a stronger antagonism of the ac7nACh receptor and attenuated effect of KYNA on GPR35, the net effect would be pro-inflammatory. Moreover, we intend to study the levels of 3-hydroxyanthranilic acid (3HAA) and anthranilic acid (AA) in relation to cognitive function.

METHODS

Subject recruitment

Subjects were recruited from the Atlanta Veterans Affairs Medical Center (Atlanta VAMC) and from the local community through interfacing with Atlanta VAMC clinicians, targeted letters and advertisements. To be included in the study, subjects had to be between 18 and 65 years old and have a diagnosis of schizophrenia or schizoaffective disorder A separate group was recruited with no history of major psychiatric disorder to serve as controls. 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, CNS infection, seizure disorder, mental retardation, active substance abuse, HIV infection, autoimmune conditions (such as rheumatoid arthritis, lupus erythematosus), or clinically significant hearing or visual impairment. After receiving information about the study and being given a chance to ask questions, subjects indicated their informed consent by their signature on an informed consent form that had been approved by the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee. Subjects were also asked to participate in a blood draw.

A total of 612 individuals signed informed consent. 161 completed subjects were available for analysis after excluding screen failures, family members and subjects who

did not provide a blood sample. Information on demographics, smoking status, and medical and psychiatric history was collected from these individuals.

Toxoplasma Seropositivity

Serum specimens were analyzed for *T. gondii* IgG antibodies as per manufacturer's recommendations (Bio-Rad, Redmond, WA). Seropositivity was determined in an ELISA through a quotient of weakly positive single calibrator index value and its absorbance at 450nm, multiplied by the absorbance of the sample to find the sample index. An index value greater than 0.9 indicated *T. gondii* seropositivity.

Kynurenine Pathway metabolites

An analytical method capable of measuring tryptophan and its catalyzed products in human plasma and cerebrospinal fluid samples was developed using liquid chromatography triple quadrupole mass spectrometry (Parinya Panuwet and Dana Boyd Barr). The target compounds include tryptophan (TRYP), kynurenine (KYN), 3-hydroxy kynurenine (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 LODs for TRYP, KYN, and 3-OHKYN were 3.91 uM, 0.39 uM, and 0.08 uM, 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.

Cognitive Tests

Intelligence Quotient (IQ) was assessed using the Reynolds Intellectual Screening Test (79).

Executive and frontal lobe function was tested by means of the Wisconsin Card Sorting Test (80). This is a test of set-shifting (cognitive flexibility). Stimulus cards are presented to the subject. The cards differ in color, quantity and design. The subjects' task is to match cards in an additional deck to the stimulus cards by one of the categories, but no instructions are given on which category to match on. With each card the subject is just told whether their match was right or wrong. The category for matching changes at a time the experimenter knows but the subject does not know. The resulting score is the number of errors and a higher score indicated a lower executive and frontal lobe function. A perseverative error is defined as a failure to move to a new category from the previously reinforced one. A non-perseverative error is failure to maintain matching by the same category.

Finger Tap test: This is a motor test of the speed at which the subject is able to repeatedly press a key in a specified length of time (81). Studies show this is not only an indicator of motor function, but of general learning ability in schizophrenic subjects. Psychomotor speed in this test was measured as the number of clicks the subject was able to make on the counter in 60 s by pressing their finger. This measure was completed on the dominant and non-dominant hand.

Subjects were tested on selected components of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus battery (MCCB) (82).

Speed of Processing - This component is comprised of three subtests:

(a) Brief Assessment of Cognition in Schizophrenia (BACS): Symbol-Coding test. This is a timed visuomotor test in which respondent uses a key to write digits that correspond to nonsense symbols using pencil and paper. Processing speed in this test was measured as the correct number of coded symbols the subject was able to write in 90 seconds.

(b) Category Fluency: Animal naming; Oral test in which respondent names as many animals as she/he can in 1 minute as a verbal index of processing speed. Processing speed in this test was measured as the total number of animal names the subject was able to say in 60 seconds.

(c) Trail Making Test: This is a timed paper-and-pencil visuomotor test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper. Processing speed in this test was measured as the number of seconds it takes the subject to complete the connection of all the numbers.

The MATRICS software computes a composite score from these three subtests that served as a measure of processing speed.

Working memory - comprises of two subtests:

(a) Wechsler Memory Scale -Third edition: Spatial Span; The test administrator tapped 10 irregularly spaced cubes on a board and the subject had to tap them in the same or reverse order.

(b) Letter Number Span- the subject repeated strings of letters or numbers after mentally reordering them.

The MATRICS software computes a composite score from these two subtests that served as a measure of working memory.

Verbal learning- Hopkins Verbal Learning Test-Revised: it is an orally administered test. The subject was presented with a list of 12 words from three taxonomic categories and was asked to recall as many as possible after each of three learning trials.

Analysis

The analysis dataset consisted of 71 observations and variables taken into consideration included the kynurenine pathway metabolites, kyn-tryp ratio 3-HAA-AA ratio, neopterin, phenylalanine, tyrosine and Phe-Tyr ratio as predictors, the cognitive variables as outcome measures, toxoplasma status, schizophrenia status, and age, sex, race and smoking status as covariates. The immune biomarkers, cognitive variables and age were treated as continuous. The race variable was dichotomized with 1 corresponding to African Americans and 0 corresponding to other ethnicities. Toxoplasma status and schizophrenia status were coded as binary variables with 0 corresponding to those who

were seronegative (non-exposed) and 1 corresponding to those with a positive serology (exposed). The variables for the Trail Making Test and Wisconsin Card Sorting Test were log transformed to account for a non-normal distribution.

A partial correlation matrix adjusted for age was created using the immune biomarkers. A t-test was conducted to assess the association between schizophrenia status and the outcome variables. Logistic regression models were used to assess the association between schizophrenia status as the outcome and each of the immune biomarkers taken one at a time after adjusting for age, sex, race, and smoking status. Linear regression models were created to assess the correlation between each of the cognitive variables as the outcome and each of the immune markers taken one at a time after adjusting for age, sex, race and smoking status. A series of fully parameterized models were also created that included each of the cognitive variables as the outcome and all the immune markers taken together along with toxoplasma and schizophrenia status and the covariates. The regression models were assessed using backwards elimination. SAS 9.4 (Cary, North Carolina) was used to perform statistical analyses.

RESULTS

Selection of participants for this study is shown in figure 1. Our data consisted of 71 subjects who had complete demographic and cognitive data and data on all biomarkers. 42 participants (59.2%) had a diagnosis of schizophrenia and 16 (22.5%) were *T. gondii* seropositive. A majority of the total participants were African American (88.7%) and male (87.3%). Subject characteristics by schizophrenia status are presented in Table 1.

Wilcoxon Rank Sum tests for predictors

Many of the immune biomarkers showed a skewed distribution so, the Wilcoxon Rank Sum test was performed. Mean values, z-statistics, and p-values for each of the predictors by schizophrenia status are presented in Table 1. Mean values of tryptophan were significantly higher in controls than in schizophrenia subjects (p-value = 0.03). On performing a similar test by *T. gondii* status, the values of tryptophan (p=0.03), phenylalanine (p=0.02) and phenylalanine-tyrosine ratio (p=0.02) were significantly elevated for *T. gondii* seropositive individuals. These are shown in Tables 1 and 2.

T-test analysis for cognitive variables

The controls had significantly better scores on cognitive tests: FTT dominant-hand (p=0.002), FTT non-dominant hand (p=0.006), RIST Index (p=0.02), TMT (p=0.002), Fluency (p=0.004) and BACS-SC (p=0.004). The *T. gondii* seronegative individuals performed significantly better on the FTT dominant hand (p=0.02) and WCST (p=0.01) than the *T. gondii* seropositive subjects as shown in Tables 3 and 4.

Logistic Regression Analysis

Schizophrenia status was taken as the outcome variable in models with each of the biomarkers taken one at a time and adjusting for covariates (Tables 5-20). None of the models yielded a statistically significant ($p<0.05$) association between the biomarker and schizophrenia status.

Regression analysis

Tryptophan values were significantly elevated in controls and in *T. gondii* seropositive individuals (Table 2). Given the large number of variables, we performed two types of regression analysis: 1) by forcing demographic variables into the model (Tables 32-151) and 2) using a backward elimination starting with all predictors in the model and removing the least significant variable at each step. In regression models with tryptophan as the predictor and adjusting for age, race, sex and smoking status, tryptophan was significantly associated with LNS scores (Model F = 7.42, p-value <0.0001) (Table 108). It also had a significant effect on the WCST scores (Model F = 2.62, p-value = 0.03) (Table 54). Higher values of tryptophan predicted better scores for both these cognitive variables. On performing a backward selection with all biomarkers taken together with schizophrenia and *T. gondii* status and after adjusting for the covariates, tryptophan was significantly associated with scores on the LNS, WCST and WMS, with higher values predicting better cognition (Tables 24, 26, 28). *T. gondii* status remained significant ($p=0.007$) in the final model for WCST after backward selection. We examined individually each of the metabolites that were significant by the backward selection method of model selection. The correlation matrix showed significant correlations between many of the metabolites. But, the Variance Inflation Factors for all these

metabolites were less than 5 in the fully parameterized models (see appendix) indicating no impact of collinearity on the models.

Kynurenine levels did not differ by *T. gondii* status or schizophrenia status. When considered by itself in models after adjusting for covariates, kynurenine failed to predict any of the cognitive scores. However, in backward selection models, kynurenine was significantly associated with WCST and BACS-SC (Tables 23, 24, 31). The results here were inconsistent with higher levels of kynurenine predicting better scores for BACS-SC and worse scores for WCST.

KYNA levels were not significantly different by *T. gondii* or schizophrenia status (Tables 1 and 2). Models considering KYNA by itself and adjusting for covariates significantly predicted LNS scores (model $F=7.31$, $p<0.0001$) (Table 110), Fluency (Table 132) (model $F = 5.63$, $p<0.001$) and BACS-SC scores (model $F= 10.65$, $p<0.0001$) (Table 143). Higher levels of KYNA were associated with better cognition for all these variables. After performing backward selection on models containing all biomarkers taken together along with *T. gondii* and schizophrenia status and covariates, KYNA was found to significantly predict WCST scores, TMT scores and RIST Index scores (Tables 23,25,27). Again, higher levels of KYNA indicated better cognition on all these tests.

3HAA levels did not differ by schizophrenia or *T. gondii* status. When considered by itself in models adjusting for covariates, 3HAA failed to predict the scores for cognitive variables. On backward selection, 3HAA was found to be significantly associated with WCST with higher levels predicting better cognition (Table 23,24). AA levels too did not differ by schizophrenia or *T. gondii* status. On backward selection, AA levels were

significantly associated with the TMT scores with higher levels predicting worse cognition (Table 27)

Neopterin, tyrosine and phenylalanine failed to predict cognitive scores when taken individually in models containing covariates. Age and race were associated with many of the cognitive variables including BACS-SC, fluency, LNS, TMT however our findings were not confounded by these variables, as observed by backward selection (Tables 97-151).

DISCUSSION

The role of infection is well established in cognitive deficits. Many studies have demonstrated that viral infections like cytomegalovirus, Human Simplex Virus (HSV1), Hepatitis A, Human Immunodeficiency Virus correspond to worse cognition (19, 83, 84). Among parasitic infections, *T. Gondii* has been studied in relation to cognitive deficits (18). Our results showed higher levels of tryptophan in *T. Gondii* seropositive individuals. This is contrary to the findings of previous experiments where IDO activation led to lowering of tryptophan levels (85). We also found elevated Phe levels in *T. Gondii* seropositive patients. Cognitive variables like FTT, RIST index, TMT, fluency, and BACS-SC were significantly different between schizophrenia patients and controls. This is similar to findings from previous studies that found that schizophrenia patients performed worse compared to controls on tests of general intelligence (76), verbal fluency (86), and working memory (87). T-test analyses showed no difference in cognitive scores between *T. Gondii* seropositive and negative individuals. However, we found a statistically significant association between *T. Gondii* seropositivity and FTT and WCST scores after adding all immune biomarkers in regression models and adjusting for

covariates. A similar study by Pearce et al indicated that *T. Gondii* seropositivity was associated with poor performance on the simple reaction time test, symbol coding speed and learning and working memory tasks (18). Another study found that *T. Gondii* seropositivity is associated with lower verbal intelligence in young adult men (88). Studies predicting the effect of Toxoplasma infection on cognitive deficits in schizophrenic individuals have produced conflicting results. One study found no significant difference in cognitive function in patients, but seropositive patients did worse on the Trail Making Test (20). Another study by Brown et al, reported that schizophrenic patients exposed to *T. gondii* prenatally, performed worse on the WCST and TMT (89).

Similar to findings from previous studies by Szymona et al, our results indicate lower blood levels of KYNA in those with a diagnosis of schizophrenia compared to controls (90). Conversely, increased KYNA levels are found in the cerebrospinal fluid of schizophrenic patients (91-93). The decrease of KYNA in blood and its increased level in brain in schizophrenia may indicate an increased transfer of KYN (92) or TRP to the brain for synthesis of KYNA. KYNA is protective against QUIN induced toxicity. It acts by blocking NMDA receptors. This antagonism of NMDA receptors by KYNA in brain can alter glutamatergic transmission and lead to cognitive deficits, as evidenced by animal studies (see below). Increased KYNA concentrations in rodent brain correspond to impairments in working and learning memory, sensory gating and cognitive flexibility (65, 94-96). This is consistent with the concept discussed above whereby decreased KYNA blood levels and potentially increased CSF levels may impair cognitive functioning. Controls in our study showed higher levels of KYNA in blood like previous studies (90). This corresponded to better performance on cognitive tests like LNS,

BACS-SC, fluency, RIST index, WCST and TMT. This might be due to the protective effect of GPR35 in the periphery. Moreover, studies in Alzheimers disease (AD) patients show that plasma KYNA levels correlated positively with cognitive function as assessed through Mini Mental State Examination. This study also found decreased plasma levels of KYNA in AD patients compared to controls (97). We also found higher levels of tryptophan in controls and they corresponded to better performance on LNS, WCST and WMS. A meta-analysis of over fifty tryptophan depletion studies conducted by Mendelson et al indicated that lowering tryptophan is associated with impairment of episodic memory for verbal information (98).

Strengths and weaknesses

The individuals in this study were very well phenotyped. To our knowledge, no previous human study has examined cognition in schizophrenia and infection across many domains and used the MATRICS battery. We also examined many KP metabolites in relation to these cognitive variables.

However, we do not have the cerebrospinal fluid levels of these metabolites which may help us better understand the neurocognitive mechanisms in the brain. We also do not have levels of QUIN which is considered to be a neuroexcitatory metabolite and it how it corresponds to cognition. Lastly, studies in the future may consider repeating these studies with a larger N.

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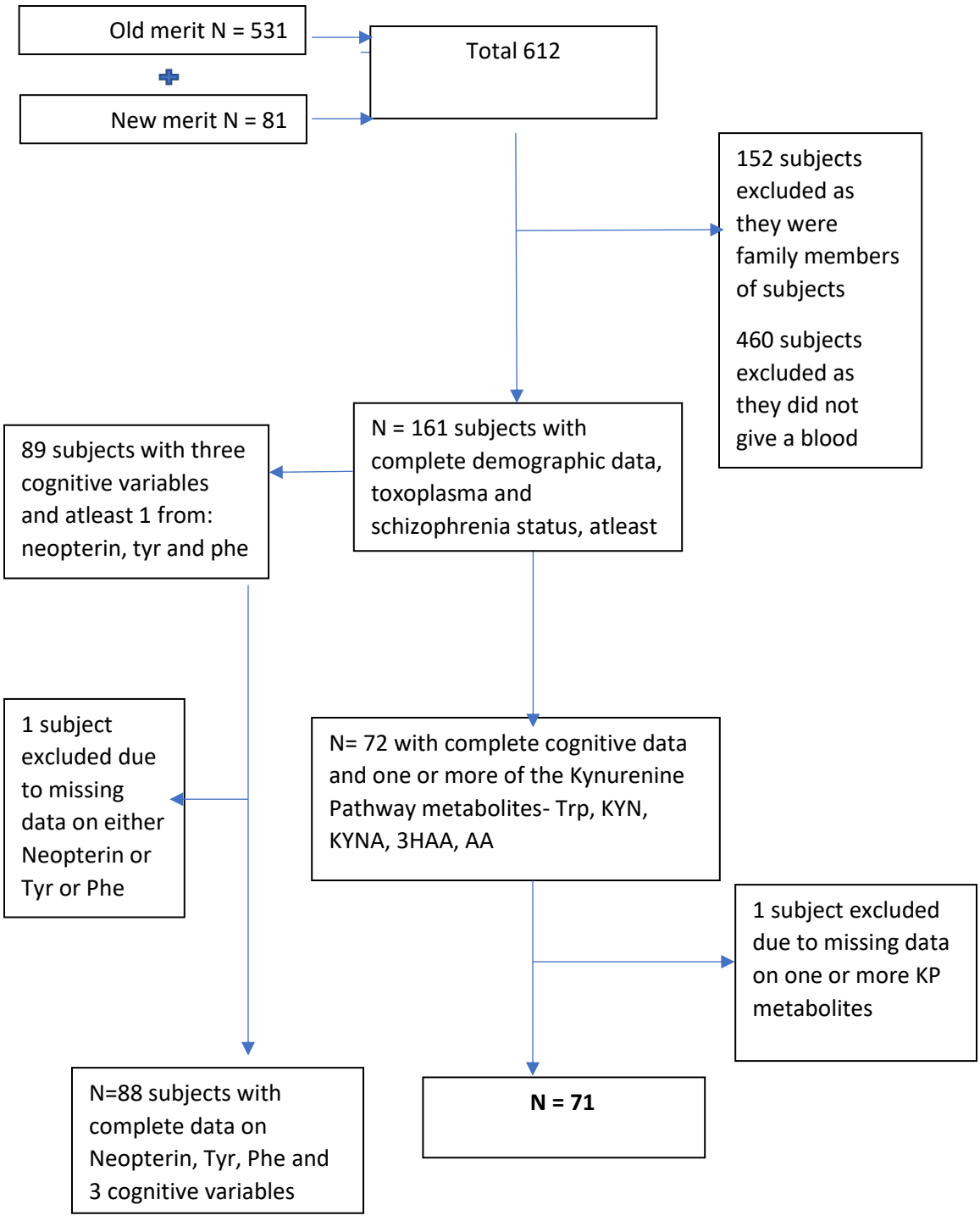
TABLES AND FIGURES



Flow diagram showing the process by which patients were selected into the final cohort

Table 1. Subject characteristics and average values of predictors by schizophrenia status

	Non-Schizophrenic		Schizophrenic			
	N	**%**	**N**	**%**	**Chi-sq or t-statistic**	**p-value**
	29		42			
Toxoplasma status						
Positive	6	20.69	10	23.81	0.1	0.76
Negative	23	79.31	32	76.19		
Gender						
Male	24	82.76	38	90.48	0.92	0.47
Female	5	17.24	4	9.52		
Race						
Black	23	79.31	40	95.24	4.35	0.06
Other	6	20.69	2	4.76		
Smoking status						
Smoker	14	48.28	19	45.24	0.06	0.8
Non-smoker	15	51.72	23	54.76		
Mean Age	53.07		51.43		0.68	0.5
SD	10.75		9.46			

Table 1 continued

Immune Biomarker	Mean value in non-schizophrenic control	Mean value in schizophrenia patient	z-statistic	p-value
Tryptophan (uM)				
Mean	61.63	54.52	2.24	0.03
SD	19.26	11.85		
Median	62.13	53.42		
Range	99.18	62.01		
KYN (uM)				
Mean	2.72	2.71	0.32	0.75
SD	0.84	1.03		
Median	2.89	2.54		
Range	3.32	4.80		
KYNA (nM)				
Mean	47.52	32.54	1.73	0.08
SD	40.91	15.82		
Median	45.60	29.66		
Range	218.15	62.25		
3HAA (nM)				
Mean	29.42	26.23	0.38	0.70
SD	18.34	14.15		
Median	26.80	22.12		
Range	68.14	61.10		
AA (nM)				
Mean	14.85	13.06	-0.44	0.66
SD	18.41	6.42		
Median	10.98	11.30		
Range	102.14	30.09		
KYN_Trp ratio				
Mean	0.05	0.05	-1.02	0.31
SD	0.03	0.02		
Median	0.04	0.05		
Range	0.13	0.01		
3HAA-AA ratio				
Mean	2.50	2.22	0.82	0.41
SD	1.45	1.21		
Median	2.09	1.74		
Range	5.89	4.93		

Table 1 continued

Immune Biomarker	Mean value in non-schizophrenic control	Mean value in schizophrenia patient	z-statistic	p-value
Neopterin (nM)				
Mean	6.49	6.15	1.33	0.09
SD	1.87	2.37		
Median	5.75	4.96		
Range	5.98	11.30		
Tyrosine (uM)				
Mean	62.19	60.76	0.13	0.89
SD	21.65	13.39		
Median	59.80	59.62		
Range	84.89	52.95		
Phenylalanine (uM)				
Mean	56.18	56.04	0.46	0.64
SD	15.03	13.39		
Median	58.49	52.76		
Range	68.85	57.43		
Phe-Tyr ratio				
Mean	0.95	0.94	-0.01	1.00
SD	0.21	0.19		
Median	0.97	0.93		
Range	0.93	0.78		

Table 2. Wilcoxon rank sum test by Toxoplasma Status

Immune Biomarker	Mean value in Toxoplasma Seronegative	Mean value in Toxoplasma Seropositive	Z-statistic	P-value
Tryptophan	55.43	64.26	2.22	0.03
Kynurenine	2.65	2.93	1	0.16
Kynurenic Acid	39.00	37.48	0.23	0.82
3HAA	26.56	30.88	1.2	0.23
AA	14.33	11.96	-0.58	0.56
Kyn-Tryp ratio	0.05	0.05	-0.5	0.62
OHAA-AA ratio	2.18	2.86	1.48	0.07
Neopterin	6.10	6.93	0.89	0.37
Phenylalanine	54.06	63.10	2.35	0.02
Tyrosine	61.05	62.35	0.5	0.62
Phe-Tyr ratio	0.91	1.03	2.29	0.02

Table 3. Difference in mean values of cognitive variables by Schizophrenia Status

Cognitive variable	Mean value in non-schizophrenic control	Mean value in schizophrenia patient	Difference in mean value	T-statistic	P-value
FTT Dominant hand	305.40	262.70	42.70	3.2	0.002
FTT Non-Dominant hand	270.60	236.40	34.20	2.9	0.006
WCST perseverative error	2.34	2.65	-0.31	-2.03	0.05
WCST non-perseverative error	2.28	2.28	0.00	0	1.00
RIST Index	99.07	92.48	6.59	2.43	0.02
WMS-III	13.41	12.57	0.84	1.09	0.28
logTMT	3.49	3.83	-0.34	-3.71	<0.001
LNS	12.45	11.52	0.92	1.06	0.29
HVLT-revised	21.79	20.21	1.58	1.33	0.19
Fluency	22.45	18.48	3.97	2.95	0.004
BACS-SC	47.41	38.33	9.08	2.97	0.004

Table 4. Difference in mean values of cognitive variables by Toxoplasma Status

Cognitive variable	Mean value in Toxoplasma Seronegative patients	Mean value in Toxoplasma Seropositive patients	Difference in mean value	T-statistic	P-value
FTT Dominant hand	288.8	250.3	38.44	2.37	0.02
FTT Non-Dominant hand	256.8	228	28.85	2	0.05
LogWCST pers	2.42	2.89	-0.47	-2.7	0.01
LogWCST nonpers	2.33	2.1	0.22	1.35	0.18
RIST Index	95.29	94.75	0.54	0.16	0.87
WMS-III	12.84	13.19	-0.35	-0.38	0.7
LogTMT	3.68	3.74	-0.05	-0.44	0.66
LNS	12.29	10.56	1.73	1.7	0.09
HVLT-revised	20.78	21.13	-0.34	-0.24	0.81
Fluency	20.15	19.94	0.21	0.12	0.9
BACS-SC	43.02	38.69	4.33	1.14	0.26

Correlation Matrix adjusted for age

	TRYP	KYN	KYNA	3-HAA	AA	Neopterin	Tyr	Phe	Phe/Tyr	KYN/TRYP	OHAA/AA
TRYP	1										
KYN	0.271**	1									
KYNA	0.288**	0.590**	1								
3-HAA	0.419**	0.593**	0.642**	1							
AA	-0.015	0.457**	0.431**	0.441**	1						
Neopterin	-0.144	0.393**	0.227	0.121	0.280**	1					
Tyr	0.468**	0.216	0.482**	0.548**	0.243**	0.054	1				
Phe	0.292**	0.165	0.444**	0.505**	0.258**	0.048	0.651**	1			
Phe/Tyr	-0.230	-0.117	-0.138	-0.179	-0.007	0.088	-0.489**	0.305**	1		
KYN/TRYP	-0.412**	0.593**	0.381**	0.239**	0.398**	0.495**	-0.120	-0.054	0.091	1	
OHAA/AA	0.450**	0.159	0.345**	0.720**	-0.261**	-0.143	0.347**	0.287**	-0.156	-0.198	1

Table 5. Logistic Regression of Diagnosis on Tryptophan adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	TRYP	-0.03	0.02	2.96	0.09	0.97	0.94	1.00
	age	-0.02	0.03	0.61	0.44	0.98	0.93	1.03
Diagnosis (1=Scz	Sex	0.65	0.78	0.69	0.40	1.91	0.42	8.78
0=Control)	smoker	0.12	0.54	0.05	0.82	1.13	0.39	3.25
	Race	1.47	0.88	2.81	0.09	4.36	0.78	24.44

Table 6. Logistic Regression of Diagnosis on Tryptophan adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	TRYP	-0.03	0.02	3.82	0.05	0.97	0.93	1.00
Diagnosis (1=Scz 0=Control)	age	-0.03	0.03	0.99	0.32	0.97	0.93	1.03

Table 7. Logistic Regression of Diagnosis on Kynurenine adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	KYN	0.11	0.28	0.17	0.68	1.12	0.65	1.93
	age	-0.01	0.03	0.28	0.60	0.99	0.94	1.04
Diagnosis (1=Scz	Sex	0.76	0.77	0.98	0.32	2.14	0.47	9.71
0=Control)	smoker	0.11	0.53	0.04	0.83	1.12	0.40	3.15
	Race	1.69	0.88	3.64	0.06	5.40	0.96	30.51

Table 8. Logistic Regression of Diagnosis on Kynurenine adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	KYN	0.00	0.26	0.00	0.99	1.00	0.60	1.67
Diagnosis	age	-0.02	0.03	0.47	0.50	0.98	0.94	1.03

Table 9. Logistic Regression of diagnosis on Kyunrenic Acid adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	KYNA	-0.02	0.01	2.96	0.09	0.98	0.95	1.00
	age	-0.01	0.03	0.19	0.66	0.99	0.94	1.04
Diagnosis	Sex_01	0.88	0.80	1.22	0.27	2.42	0.51	11.56
(1=Scz 0=Control)	smoker	-0.17	0.56	0.09	0.77	0.85	0.28	2.56
	Race_01	1.45	0.88	2.68	0.10	4.25	0.75	24.03

Table 10. Logistic Regression of diagnosis on Kyunrenic Acid adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	KYNA	-0.02	0.01	3.57	0.06	0.98	0.95	1.00
Diagnosis	age	-0.02	0.03	0.43	0.51	0.98	0.94	1.03
(1=Scz 0=Control)								

Table 11. Logistic Regression of diagnosis on 3HAA adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	3-HAA	-0.01	0.02	0.20	0.65	0.99	0.96	1.03
Diagnosis	age	-0.01	0.03	0.27	0.60	0.99	0.94	1.04
(1=Scz 0=Control)	Sex_01	0.66	0.77	0.73	0.39	1.94	0.43	8.85
	smoker	0.13	0.53	0.06	0.80	1.14	0.41	3.20
	Race_01	1.58	0.88	3.23	0.07	4.86	0.87	27.18

Table 12. Logistic Regression of diagnosis on 3-HAA adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	_OHAA	-0.01	0.02	0.77	0.38	0.99	0.96	1.02
Diagnosis	age	-0.02	0.03	0.54	0.46	0.98	0.94	1.03
(1=Scz 0=Control)								

Table 13. Logistic Regression of diagnosis on AA adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	AA	-0.01	0.02	0.42	0.52	0.99	0.95	1.03
	age	-0.01	0.03	0.29	0.59	0.99	0.94	1.04
Diagnosis	Sex_01	0.70	0.77	0.83	0.36	2.01	0.45	9.03
(1=Scz 0=Control)	smoker	0.10	0.53	0.03	0.85	1.10	0.39	3.12
	Race_01	1.65	0.87	3.59	0.06	5.23	0.94	28.96

Table 14. Logistic Regression of diagnosis on AA adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	AA	-0.01	0.02	0.41	0.52	0.99	0.95	1.03
Diagnosis	age	-0.02	0.03	0.56	0.45	0.98	0.93	1.03
(1=Scz 0=Control)								

Table 15. Logistic Regression of diagnosis on Neopterin adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Neopterin	-0.06	0.12	0.22	0.64	0.95	0.75	1.20
	age	-0.01	0.03	0.20	0.65	0.99	0.94	1.04
Diagnosis	Sex_01	0.71	0.76	0.86	0.35	2.03	0.45	9.08
(1=Scz 0=Control)	smoker	0.14	0.53	0.07	0.79	1.15	0.41	3.25
	Race_01	1.61	0.88	3.40	0.07	5.02	0.90	27.95

Table 16. Logistic Regression of diagnosis on Neopterin adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Neopterin	-0.07	0.11	0.35	0.55	0.94	0.75	1.17
Diagnosis	age	-0.02	0.03	0.39	0.53	0.98	0.94	1.03
(1=Scz 0=Control)								

Table 17. Logistic Regression of diagnosis on Tyrosine adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Tyr	0.00	0.02	0.09	0.76	1.00	0.97	1.03
	age	-0.01	0.03	0.26	0.61	0.99	0.94	1.04
Diagnosis	Sex_01	0.71	0.76	0.86	0.35	2.03	0.45	9.09
(1=Scz 0=Control)	smoker	0.11	0.53	0.04	0.84	1.11	0.39	3.17
	Race_01	1.63	0.87	3.48	0.06	5.08	0.92	28.05

Table 18. Logistic Regression of diagnosis on Tyrosine adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Tyr	-0.01	0.01	0.17	0.68	0.99	0.97	1.02
Diagnosis	age	-0.02	0.03	0.52	0.47	0.98	0.94	1.03
(1=Scz 0=Control)								

Table 19. Logistic Regression of diagnosis on Phenylalanine adjusting for covariates

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Phe	0.00	0.02	0.00	0.99	1.00	0.96	1.04
	age	-0.01	0.03	0.25	0.62	0.99	0.94	1.04
Diagnosis	Sex_01	0.72	0.77	0.89	0.34	2.06	0.46	9.28
(1=Scz 0=Control)	smoker	0.13	0.53	0.07	0.80	1.14	0.41	3.21
	Race_01	1.63	0.87	3.50	0.06	5.12	0.92	28.33

Table 20. Logistic Regression of diagnosis on Phenylalanine adjusting for age

Dependent variable	Independent variable	β	SE	Wald chi-sq	Pr>chi-sq	OR	95% CI	
	Phe	0.00	0.02	0.00	0.97	1.00	0.97	1.03
Diagnosis	age	-0.02	0.02	0.47	0.49	0.98	0.94	1.03
(1=Scz 0=Control)								

Table 21. Final Model for FTT Dominant hand after Backward selection

Dependent	Independent	β	SE	F	p-value
FTT dominant Hand	Toxo	-36.64	15.27	5.76	0.02
	Diagnosis	-41.60	12.98	10.27	0.00

Table 22. Final Model FTT non-dominant hand after Backward selection

Dependent	Independent	β	SE	F	p-value
FTT non-dominant Hand	Toxo	-27.41	13.77	3.96	0.05
	Diagnosis	-33.32	11.70	8.11	0.01

Table 23. Final Model for WCST perseverative error after Backward selection

Dependent	Independent	β	SE	F	p-value
Log WCST	KYN	0.18	0.08	4.39	0.04
	KYNA	-0.01	0.00	7.28	0.01
	3HAA	-0.01	0.01	4.70	0.03
	Tyr	0.01	0.01	4.33	0.04
	Toxo	0.45	0.16	7.83	0.01
	Race	0.45	0.22	4.41	0.04

Table 24. Final Model for WCST non-perseverative error after Backward selection

Dependent	Independent	β	SE	F	p-value
Log WCST	TRYP	-0.01	0.00	8.05	0.01
	KYN	-0.15	0.08	3.88	0.05
	3HAA	0.01	0.01	4.90	0.03

Table 25. Final Model for RIST Index after Backward selection

Dependent	Independent	β	SE	F	p-value
RIST Index	KYNA	0.16	0.06	6.70	0.01
	AA	-0.29	0.14	4.00	0.05
	age	-0.44	0.11	14.84	0.00
	Race	-17.54	3.58	23.95	<.0001

Table 26. Final Model for WMS after Backward selection

Dependent	Independent	β	SE	F	p-value
WMS	TRYP	0.07	0.03	7.33	0.01
	Tyr	-0.04	0.02	3.25	0.08
	age	-0.08	0.04	4.73	0.03
	Race	-2.77	1.11	6.24	0.02

Table 27. Final Model for TMT after Backward selection

Dependent	Independent	β	SE	F	p-value
Log TMT	KYNA	-0.01	0.00	5.43	0.02
	AA	0.01	0.01	4.94	0.03
	Diagnosis	0.25	0.09	8.05	0.01
	age	0.02	0.00	15.94	0.00
	Sex	0.28	0.12	5.27	0.02
	Race	0.24	0.13	3.31	0.07

Table 28. Final Model for LNS after Backward selection

Dependent	Independent	β	SE	F	p-value
LNS	TRYP	0.06	0.02	5.22	0.03
	KYNA	0.02	0.01	2.91	0.09
	Toxo	-1.63	0.88	3.48	0.07
	age	-0.15	0.04	17.27	<.0001
	Race	-2.64	1.12	5.55	0.02

Table 29. Final Model for HVLT-R after Backward selection

Dependent	Independent	β	SE	F	p-value
HVLT-R	age	-0.24	0.05	19.60	<.0001
	Race	-3.47	1.66	4.36	0.04

Table 30. Final Model for fluency after Backward selection

Dependent	Independent	β	SE	F	p-value
Fluency	TRYP	-0.09	0.04	4.18	0.05
	_OHAA	0.08	0.04	3.76	0.06
	DX_01	-4.21	1.22	11.91	0.00
	age	-0.29	0.06	22.95	<.0001
	Race_01	-4.24	1.88	5.07	0.03
	smoker	2.10	1.16	3.29	0.07

Table 31. Final Model for BACS-SC after Backward selection

Dependent	Independent	β	SE	F	p-value
BACS-SC	TRYP	-0.15	0.08	3.30	0.07
	KYN	3.90	1.34	8.40	0.01
	Neopterin	-1.13	0.57	3.95	0.05
	DX_01	-9.80	2.48	15.59	0.00
	age	-0.78	0.12	42.81	<.0001
	Sex_01	-6.80	3.43	3.92	0.05
	Race_01	-9.11	3.77	5.85	0.02

Table 32. The effect of Tryptophan on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	Tryp	71.00	0.42	0.47	0.89	0.37
	Age		-0.35	0.75	-0.47	0.64
	Sex		3.98	21.91	0.18	0.86
	Race		-31.84	22.83	-1.39	0.17
	smoker		-12.18	14.81	-0.82	0.41

Table 33. The effect of Kynurenine on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	KYN	71.00	4.08	7.70	0.53	0.60
	Age		-0.49	0.74	-0.66	0.51
	Sex		4.08	22.08	0.18	0.85
	Race		-32.58	23.01	-1.42	0.16
	Smoker		-13.23	14.95	-0.88	0.38

Table 34. The effect of Kynurenic Acid on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	KYNA	71.00	0.29	0.25	1.19	0.24
	Age		-0.47	0.73	-0.64	0.53
	Sex		0.60	21.85	0.03	0.98
	Race		-31.98	22.64	-1.41	0.16
	Smoker		-8.09	15.17	-0.53	0.60

Table 35. The effect of 3-HAA on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	3-HAA	71.00	0.57	0.45	1.26	0.21
	Age		-0.41	0.73	-0.56	0.58
	Sex		6.93	21.98	0.32	0.75
	Race		-30.51	22.72	-1.34	0.18
	Smoker		-12.07	14.72	-0.82	0.42

Table 36. The effect of AA on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	AA	71.00	0.07	0.57	0.11	0.91
	Age		-0.46	0.74	-0.62	0.54
	Sex		2.98	22.04	0.14	0.89
	Race		-34.57	22.80	-1.52	0.13
	Smoker		-12.18	14.98	-0.81	0.42

Table 37. The effect of Neopterin on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	Neopterin	71.00	-0.34	3.32	-0.10	0.92
	Age		-0.46	0.74	-0.62	0.54
	Sex		2.79	22.01	0.13	0.90
	Race		-34.60	22.82	-1.52	0.13
	Smoker		-12.34	14.90	-0.83	0.41

Table 38. The effect of Tyrosine on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	Tyr	71.00	-0.07	0.43	-0.17	0.86
	Age		-0.47	0.74	-0.64	0.52
	Sex		2.76	22.01	0.13	0.90
	Race		-34.45	22.78	-1.51	0.14
	Smoker		-12.83	15.13	-0.85	0.40

Table 39. The effect of Phenylalanine on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	Phe	71.00	-0.39	0.51	-0.76	0.45
	Age		-0.46	0.74	-0.63	0.53
	Sex		2.75	21.91	0.13	0.90
	Race		-34.29	22.68	-1.51	0.14
	Smoker		-12.83	14.84	-0.86	0.39

Table 40. The effect of Phenylalanine-Tyrosine ratio on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	Phe-Tyr ratio	71.00	-8.38	37.59	-0.22	0.82
	Age		-0.46	0.74	-0.62	0.54
	Sex		2.90	22.00	0.13	0.90
	Race		-34.08	22.84	-1.49	0.14
	Smoker		-11.70	15.18	-0.77	0.44

Table 41. The effect of Kynurenine-Tryptophan ratio on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	KYN-Tryp ratio	71.00	22.53	316.79	0.07	0.94
	Age		-0.48	0.75	-0.64	0.53
	Sex		2.86	22.01	0.13	0.90
	Race		-34.43	22.78	-1.51	0.14
	Smoker		-12.43	14.93	-0.83	0.41

Table 42. The effect of OHAA-AA ratio on FTT-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-dominant hand	OHAA-AA ratio	71.00	10.48	5.44	1.93	0.06
	Age		-0.45	0.72	-0.62	0.53
	Sex		4.70	21.42	0.22	0.83
	Race		-26.08	22.58	-1.16	0.25
	Smoker		-13.96	14.51	-0.96	0.34

Table 43. The effect of Tryptophan on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	Tryp	71.00	0.24	0.40	0.60	0.55
	Age		-0.80	0.64	-1.24	0.22
	Sex		17.52	18.94	0.93	0.36
	Race		-27.65	19.73	-1.40	0.17
	smoker		-17.58	12.80	-1.37	0.17

Table 44. The effect of Kynurenine on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	KYN	71.00	-1.10	6.65	-0.17	0.87
	Age		-0.86	0.64	-1.35	0.18
	Sex		16.52	19.06	0.87	0.39
	Race		-29.68	19.86	-1.49	0.14
	Smoker		-17.45	12.91	-1.35	0.18

Table 45. The effect of Kynurenic Acid on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	KYNA	71.00	0.12	0.22	0.56	0.58
	Age		-0.87	0.64	-1.36	0.18
	Sex		15.94	18.98	0.84	0.40
	Race		-28.17	19.66	-1.43	0.16
	Smoker		-15.95	13.18	-1.21	0.23

Table 46. The effect of 3-HAA on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	3-HAA	71.00	0.20	0.39	0.51	0.61
	Age		-0.85	0.64	-1.33	0.19
	Sex		18.29	19.13	0.96	0.34
	Race		-27.79	19.77	-1.41	0.16
	Smoker		-17.58	12.81	-1.37	0.17

Table 47. The effect of AA on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	AA	71.00	0.01	0.49	0.01	0.99
	Age		-0.87	0.64	-1.36	0.18
	Sex		16.87	18.99	0.89	0.38
	Race		-29.19	19.64	-1.49	0.14
	Smoker		-17.66	12.90	-1.37	0.18

Table 48. The effect of Neopterin on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	Neopterin	71.00	0.62	2.86	0.22	0.83
	Age		-0.88	0.64	-1.38	0.17
	Sex		16.93	18.95	0.89	0.37
	Race		-28.91	19.65	-1.47	0.15
	Smoker		-17.73	12.83	-1.38	0.17

Table 49. The effect of Tyrosine on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	Tyr	71.00	-0.34	0.37	-0.94	0.35
	Age		-0.90	0.63	-1.42	0.16
	Sex		16.51	18.83	0.88	0.38
	Race		-29.16	19.49	-1.50	0.14
	Smoker		-19.86	12.95	-1.53	0.13

Table 50. The effect of Phenylalanine on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	Phe	71.00	-0.43	0.44	-0.97	0.34
	Age		-0.86	0.63	-1.37	0.18
	Sex		16.76	18.82	0.89	0.38
	Race		-28.99	19.48	-1.49	0.14
	Smoker		-18.20	12.75	-1.43	0.16

Table 51. The effect of Phenylalanine-Tyrosine ratio on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	Phe-Tyr ratio	71.00	20.58	32.29	0.64	0.53
	Age		-0.89	0.64	-1.40	0.17
	Sex		16.70	18.90	0.88	0.38
	Race		-30.10	19.62	-1.53	0.13
	Smoker		-19.30	13.04	-1.48	0.14

Table 52. The effect of Kynurenine-Tryptophan ratio on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	KYN-Tryp ratio	71.00	-8.36	272.8	-0.03	0.98
	Age		-0.86	0.65	-1.34	0.18
	Sex		16.85	18.96	0.89	0.38
	Race		-29.18	19.63	-1.49	0.14
	Smoker		-17.66	12.86	-1.37	0.17

Table 53. The effect of OHAA-AA ratio on FTT-non-dominant hand while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
FTT-non-dominant hand	OHAA-AA ratio	71.00	4.33	4.78	0.90	0.37
	Age		-0.86	0.63	-1.36	0.18
	Sex		17.62	18.86	0.93	0.35
	Race		-25.72	19.87	-1.29	0.20
	Smoker		-18.35	12.77	-1.44	0.16

Table 54. The effect of Tryptophan on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	Tryp	71.00	0.00	0.00	0.55	0.58
	Age		0.01	0.01	1.57	0.12
	Sex		-0.14	0.22	-0.64	0.53
	Race		0.60	0.23	2.58	0.01
	smoker		0.32	0.15	2.15	0.04

Table 55. The effect of Kynurenine on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logWCST	KYN	71.00	0.03	0.08	0.44	0.66
	Age		0.01	0.01	1.47	0.15
	Sex		-0.14	0.22	-0.62	0.54
	Race		0.60	0.23	2.57	0.01
	Smoker		0.32	0.15	2.07	0.04

Table 56. The effect of Kynurenic Acid on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logWCST	KYNA	71.00	0.00	0.00	-1.36	0.18
	Age		0.01	0.01	1.51	0.14
	Sex		-0.12	0.22	-0.56	0.58
	Race		0.56	0.23	2.42	0.02
	Smoker		0.27	0.15	1.78	0.08

Table 57. The effect of 3-HAA on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	3-HAA	71.00	0.00	0.00	-0.91	0.37
	Age		0.01	0.01	1.44	0.15
	Sex		-0.18	0.22	-0.80	0.43
	Race		0.56	0.23	2.39	0.02
	Smoker		0.32	0.15	2.13	0.04

Table 58. The effect of AA on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	AA	71.00	-0.01	0.01	-1.39	0.17
	Age		0.01	0.01	1.42	0.16
	Sex		-0.17	0.22	-0.75	0.45
	Race		0.60	0.23	2.62	0.01
	Smoker		0.30	0.15	2.00	0.05

Table 59. The effect of Neopterin on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	Neopterin	71.00	-0.02	0.03	-0.54	0.59
	Age		0.01	0.01	1.54	0.13
	Sex		-0.15	0.22	-0.68	0.50
	Race		0.58	0.23	2.49	0.02
	Smoker		0.32	0.15	2.15	0.04

Table 60. The effect of Tyrosine on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	T	p-value
LogWCST	Tyr	71.00	0.00	0.00	0.66	0.51
	Age		0.01	0.01	1.53	0.13
	Sex		-0.15	0.22	-0.66	0.51
	Race		0.58	0.23	2.53	0.01
	Smoker		0.34	0.15	2.22	0.03

Table 61. The effect of Phenylalanine on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	Phe	71.00	0.00	0.01	0.19	0.85
	Age		0.01	0.01	1.49	0.14
	Sex		-0.15	0.22	-0.67	0.51
	Race		0.58	0.23	2.52	0.01
	Smoker		0.32	0.15	2.14	0.04

Table 62. The effect of Phenylalanine-Tyrosine ratio on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	Phe-Tyr ratio	71.00	-0.49	0.38	-1.29	0.20
	Age		0.01	0.01	1.58	0.12
	Sex		-0.15	0.22	-0.66	0.51
	Race		0.61	0.23	2.64	0.01
	Smoker		0.36	0.15	2.37	0.02

Table 63. The effect of Kynurenine-Tryptophan ratio on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	KYN-Tryp ratio	71.00	0.41	3.22	0.13	0.90
	Age		0.01	0.01	1.45	0.15
	Sex		-0.15	0.22	-0.67	0.51
	Race		0.58	0.23	2.53	0.01
	Smoker		0.32	0.15	2.12	0.04

Table 64. The effect of OHAA-AA ratio on WCST perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST	OHAA-AA ratio	71.00	0.00	0.06	0.09	0.93
	Age		0.01	0.01	1.49	0.14
	Sex		-0.15	0.22	-0.66	0.51
	Race		0.59	0.24	2.49	0.02
	Smoker		0.32	0.15	2.12	0.04

Table 65. The effect of Tryptophan on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non perserverative error	Tryp	71.00	-0.01	0.00	-2.26	0.03
	Age		0.00	0.01	-0.09	0.93
	Sex		0.06	0.21	0.28	0.78
	Race		0.01	0.22	0.03	0.98
	smoker		0.05	0.14	0.36	0.72

Table 66. The effect of Kynurenine on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	KYN	71.00	-0.14	0.08	-1.78	0.08
	Age		0.00	0.01	0.38	0.70
	Sex		0.05	0.22	0.22	0.83
	Race		0.01	0.23	0.04	0.97
	Smoker		0.09	0.15	0.58	0.57

Table 67. The effect of Kynurenic Acid on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	KYNA	71.00	0.00	0.00	-1.56	0.12
	Age		0.00	0.01	0.29	0.77
	Sex		0.12	0.22	0.54	0.59
	Race		0.04	0.23	0.17	0.87
	Smoker		0.00	0.15	0.00	1.00

Table 68. The effect of 3-HAA on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	3-HAA	71.00	0.00	0.00	0.28	0.78
	Age		0.00	0.01	0.31	0.76
	Sex		0.10	0.22	0.44	0.66
	Race		0.08	0.23	0.34	0.73
	Smoker		0.06	0.15	0.38	0.71

Table 69. The effect of AA on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	AA	71.00	-0.01	0.01	-0.97	0.34
	Age		0.00	0.01	0.23	0.82
	Sex		0.08	0.22	0.35	0.73
	Race		0.08	0.23	0.35	0.73
	Smoker		0.04	0.15	0.27	0.79

Table 70. The effect of Neopterin on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	Neopterin	71.00	0.02	0.03	0.74	0.46
	Age		0.00	0.01	0.23	0.82
	Sex		0.09	0.22	0.41	0.68
	Race		0.08	0.23	0.35	0.72
	Smoker		0.05	0.15	0.36	0.72

Table 71. The effect of Tyrosine on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	Tyr	71.00	-0.01	0.00	-1.22	0.23
	Age		0.00	0.01	0.23	0.82
	Sex		0.08	0.22	0.38	0.71
	Race		0.07	0.23	0.31	0.76
	Smoker		0.02	0.15	0.15	0.88

Table 72. The effect of Phenylalanine on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	Phe	71.00	-0.01	0.01	-1.14	0.26
	Age		0.00	0.01	0.30	0.77
	Sex		0.09	0.22	0.40	0.69
	Race		0.07	0.23	0.32	0.75
	Smoker		0.05	0.15	0.33	0.74

Table 73. The effect of Phenylalanine-Tyrosine ratio on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	Phe-Tyr ratio	71.00	0.11	0.38	0.30	0.77
	Age		0.00	0.01	0.27	0.79
	Sex		0.09	0.22	0.40	0.69
	Race		0.07	0.23	0.29	0.78
	Smoker		0.05	0.15	0.31	0.76

Table 74. The effect of Kynurenine-Tryptophan ratio on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LogWCST non- perseverative error	KYN-Tryp ratio	71.00	-0.12	3.20	-0.04	0.97
	Age		0.00	0.01	0.29	0.77
	Sex		0.09	0.22	0.40	0.69
	Race		0.07	0.23	0.31	0.76
	Smoker		0.06	0.15	0.38	0.71

Table 75. The effect of OHAA-AA ratio on WCST non- perseverative error while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
LogWCST non- perseverative error	OHAA-AA ratio	71.00	0.00	0.06	0.00	1.00
	Age		0.00	0.01	0.29	0.77
	Sex		0.09	0.22	0.40	0.69
	Race		0.07	0.23	0.30	0.76
	Smoker		0.06	0.15	0.37	0.71

Table 76. The effect of Tryptophan on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	Tryp	71.00	0.04	0.08	0.56	0.58
	Age		-0.42	0.12	-3.43	0.00
	Sex		3.54	3.57	0.99	0.32
	Race		-19.06	3.72	-5.13	<.0001
	smoker		-0.04	2.41	-0.02	0.99

Table 77. The effect of Kynurenine on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	KYN	71.00	-0.56	1.25	-0.45	0.66
	Age		-0.43	0.12	-3.55	0.00
	Sex		3.26	3.58	0.91	0.37
	Race		-19.58	3.73	-5.25	<.0001
	Smoker		0.06	2.43	0.03	0.98

Table 78. The effect of Kynurenic Acid on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	KYNA	71.00	0.06	0.04	1.61	0.11
	Age		-0.43	0.12	-3.64	0.00
	Sex		2.94	3.51	0.84	0.41
	Race		-18.78	3.64	-5.16	<.0001
	Smoker		0.87	2.44	0.36	0.72

Table 79. The effect of 3-HAA on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	3-HAA	71.00	0.03	0.07	0.36	0.72
	Age		-0.43	0.12	-3.55	0.00
	Sex		3.62	3.60	1.00	0.32
	Race		-19.14	3.73	-5.14	<.0001
	Smoker		-0.04	2.41	-0.02	0.99

Table 80. The effect of AA on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	AA	71.00	0.02	0.09	0.16	0.87
	Age		-0.43	0.12	-3.56	0.00
	Sex		3.46	3.57	0.97	0.34
	Race		-19.35	3.70	-5.23	<.0001
	Smoker		-0.01	2.43	-0.01	1.00

Table 81. The effect of Neopterin on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	Neopterin	71.00	0.50	0.53	0.94	0.35
	Age		-0.44	0.12	-3.67	0.00
	Sex		3.49	3.54	0.99	0.33
	Race		-19.11	3.68	-5.20	<.0001
	Smoker		-0.09	2.40	-0.04	0.97

Table 82. The effect of Tyrosine on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	Tyr	71.00	0.05	0.07	0.76	0.45
	Age		-0.42	0.12	-3.54	0.00
	Sex		3.48	3.55	0.98	0.33
	Race		-19.33	3.68	-5.26	<.0001
	Smoker		0.27	2.44	0.11	0.91

Table 83. The effect of Phenylalanine on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	Phe	71.00	0.16	0.08	1.97	0.05
	Age		-0.43	0.12	-3.69	0.00
	Sex		3.46	3.47	1.00	0.32
	Race		-19.39	3.59	-5.40	<.0001
	Smoker		0.14	2.35	0.06	0.95

Table 84. The effect of Phenylalanine-Tyrosine ratio on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	Phe-Tyr ratio	71.00	8.32	6.01	1.38	0.17
	Age		-0.44	0.12	-3.69	0.00
	Sex		3.37	3.52	0.96	0.34
	Race		-19.70	3.65	-5.40	<.0001
	Smoker		-0.71	2.43	-0.29	0.77

Table 85. The effect of Kynurenine-Tryptophan ratio on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	KYN-Tryp ratio	71.00	-4.21	51.36	-0.08	0.94
	Age		-0.43	0.12	-3.52	0.00
	Sex		3.42	3.57	0.96	0.34
	Race		-19.33	3.69	-5.23	<.0001
	Smoker		-0.04	2.42	-0.02	0.99

Table 86. The effect of OHAA-AA ratio on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
RIST Index	OHAA-AA ratio	71.00	0.72	0.90	0.80	0.43
	Age		-0.43	0.12	-3.58	0.00
	Sex		3.55	3.55	1.00	0.32
	Race		-18.75	3.75	-5.01	<.0001
	Smoker		-0.17	2.41	-0.07	0.95

Table 87. The effect of Tryptophan on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	Tryp	71.00	0.05	0.02	1.99	0.05
	Age		-0.08	0.04	-2.13	0.04
	Sex		-0.90	1.09	-0.82	0.41
	Race		-2.91	1.14	-2.56	0.01
	smoker		0.40	0.74	0.55	0.58

Table 88. The effect of Kynurenine on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	KYN	71.00	0.13	0.39	0.32	0.75
	Age		-0.09	0.04	-2.45	0.02
	Sex		-0.99	1.13	-0.88	0.38
	Race		-3.14	1.17	-2.68	0.01
	Smoker		0.36	0.76	0.47	0.64

Table 89. The effect of Kynurenic Acid on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	KYNA	71.00	0.00	0.01	-0.07	0.95
	Age		-0.09	0.04	-2.43	0.02
	Sex		-1.02	1.13	-0.91	0.37
	Race		-3.21	1.17	-2.75	0.01
	Smoker		0.37	0.78	0.48	0.64

Table 90. The effect of 3-HAA on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	3-HAA	71.00	0.01	0.02	0.52	0.60
	Age		-0.09	0.04	-2.40	0.02
	Sex		-0.94	1.13	-0.83	0.41
	Race		-3.12	1.17	-2.67	0.01
	Smoker		0.39	0.76	0.52	0.61

Table 91. The effect of AA on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	AA	71.00	-0.03	0.03	-0.89	0.38
	Age		-0.09	0.04	-2.50	0.01
	Sex		-1.08	1.12	-0.97	0.34
	Race		-3.16	1.15	-2.74	0.01
	Smoker		0.31	0.76	0.41	0.68

Table 92. The effect of Neopterin on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	Neopterin	71.00	-0.24	0.17	-1.47	0.15
	Age		-0.09	0.04	-2.34	0.02
	Sex		-1.06	1.10	-0.96	0.34
	Race		-3.31	1.14	-2.89	0.01
	Smoker		0.40	0.75	0.54	0.59

Table 93. The effect of Tyrosine on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	Tyr	71.00	-0.01	0.02	-0.43	0.67
	Age		-0.09	0.04	-2.46	0.02
	Sex		-1.04	1.12	-0.92	0.36
	Race		-3.20	1.16	-2.76	0.01
	Smoker		0.33	0.77	0.42	0.67

Table 94. The effect of Phenylalanine on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	Phe	71.00	0.00	0.03	0.06	0.95
	Age		-0.09	0.04	-2.43	0.02
	Sex		-1.03	1.12	-0.91	0.36
	Race		-3.20	1.16	-2.76	0.01
	Smoker		0.39	0.76	0.51	0.61

Table 95. The effect of Kynurenine-Tryptophan ratio on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
WMS	KYN-Tryp ratio	71.00	-25.46	15.83	-1.61	0.11
	Age		-0.08	0.04	-2.20	0.03
	Sex		-1.05	1.10	-0.96	0.34
	Race		-3.23	1.14	-2.84	0.01
	Smoker		0.47	0.75	0.62	0.53

Table 96. The effect of OHAA-AA ratio on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
WMS	OHAA-AA ratio	71.00	0.06	0.28	0.21	0.83
	Age		-0.09	0.04	-2.43	0.02
	Sex		-1.02	1.12	-0.91	0.37
	Race		-3.16	1.18	-2.67	0.01
	Smoker		0.38	0.76	0.49	0.62

Table 97. The effect of Tryptophan on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	Tryp	71.00	0.00	0.00	-1.53	0.13
	Age		0.01	0.00	2.98	0.00
	Sex		0.26	0.13	1.94	0.06
	Race		0.36	0.14	2.59	0.01
	smoker		-0.01	0.09	-0.09	0.92

Table 98. The effect of Kynurenine on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	KYN	71.00	-0.04	0.05	-0.91	0.37
	Age		0.02	0.00	3.29	0.00
	Sex		0.26	0.14	1.90	0.06
	Race		0.37	0.14	2.61	0.01
	Smoker		0.00	0.09	0.03	0.98

Table 99. The effect of Kynurenic Acid on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	KYNA	71.00	0.00	0.00	-1.69	0.10
	Age		0.01	0.00	3.30	0.00
	Sex		0.29	0.13	2.17	0.03
	Race		0.37	0.14	2.66	0.01
	Smoker		-0.04	0.09	-0.47	0.64

Table 100. The effect of 3-HAA on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	3-HAA	71.00	0.00	0.00	-0.79	0.43
	Age		0.01	0.00	3.19	0.00
	Sex		0.26	0.14	1.87	0.07
	Race		0.38	0.14	2.64	0.01
	Smoker		-0.01	0.09	-0.08	0.93

Table 101. The effect of AA on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	AA	71.00	0.00	0.00	0.23	0.82
	Age		0.01	0.00	3.24	0.00
	Sex		0.28	0.14	2.00	0.05
	Race		0.39	0.14	2.75	0.01
	Smoker		0.00	0.09	-0.05	0.96

Table 102. The effect of Neopterin on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	Neopterin	71.00	0.01	0.02	0.44	0.66
	Age		0.01	0.00	3.19	0.00
	Sex		0.27	0.14	2.01	0.05
	Race		0.40	0.14	2.79	0.01
	Smoker		-0.01	0.09	-0.08	0.94

Table 103. The effect of Tyrosine on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	Tyr	71.00	0.00	0.00	-0.55	0.58
	Age		0.01	0.00	3.21	0.00
	Sex		0.27	0.14	1.99	0.05
	Race		0.39	0.14	2.77	0.01
	Smoker		-0.02	0.09	-0.17	0.87

Table 104. The effect of Phenylalanine on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	Phe	71.00	0.00	0.00	-0.29	0.77
	Age		0.01	0.00	3.24	0.00
	Sex		0.27	0.14	1.99	0.05
	Race		0.39	0.14	2.77	0.01
	Smoker		-0.01	0.09	-0.08	0.93

Table 105. The effect of Phenylalanine-Tyrosine ratio on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	Phe-Tyr ratio	71.00	0.04	0.23	0.16	0.87
	Age		0.01	0.00	3.22	0.00
	Sex		0.27	0.14	1.99	0.05
	Race		0.39	0.14	2.75	0.01
	Smoker		-0.01	0.09	-0.10	0.92

Table 106. The effect of Kynurenine-Tryptophan ratio on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	KYN-Tryp ratio	71.00	0.18	1.97	0.09	0.93
	Age		0.01	0.00	3.18	0.00
	Sex		0.27	0.14	2.00	0.05
	Race		0.39	0.14	2.77	0.01
	Smoker		-0.01	0.09	-0.08	0.94

Table 107. The effect of OHAA-AA ratio on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
logTMT	OHAA-AA ratio	71.00	-0.07	0.03	-1.94	0.06
	Age		0.01	0.00	3.30	0.00
	Sex		0.26	0.13	1.96	0.05
	Race		0.34	0.14	2.42	0.02
	Smoker		0.00	0.09	0.04	0.97

Table 108. The effect of Tryptophan on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
LNS	Tryp	71.00	0.05	0.02	2.18	0.03
	Age		-0.16	0.04	-4.17	<.0001
	Sex		-0.84	1.10	-0.76	0.45
	Race		-2.88	1.15	-2.50	0.02
	smoker		-0.98	0.75	-1.31	0.20

Table 109. The effect of Kynurenine on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	KYN	71.00	0.48	0.40	1.21	0.23
	Age		-0.17	0.04	-4.55	<.0001
	Sex		-0.84	1.14	-0.74	0.46
	Race		-2.98	1.18	-2.52	0.01
	Smoker		-1.10	0.77	-1.43	0.16

Table 110. The effect of Kynurenic Acid on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	KYNA	71.00	0.03	0.01	2.08	0.04
	Age		-0.17	0.04	-4.59	<.0001
	Sex		-1.18	1.11	-1.06	0.29
	Race		-2.98	1.15	-2.59	0.01
	Smoker		-0.62	0.77	-0.80	0.43

Table 111. The effect of 3-HAA on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	3-HAA	71.00	0.05	0.02	2.05	0.04
	Age		-0.17	0.04	-4.45	<.0001
	Sex		-0.64	1.12	-0.58	0.57
	Race		-2.87	1.16	-2.48	0.02
	Smoker		-0.97	0.75	-1.30	0.20

Table 112. The effect of AA on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	AA	71.00	0.01	0.03	0.50	0.62
	Age		-0.17	0.04	-4.42	<.0001
	Sex		-0.95	1.14	-0.83	0.41
	Race		-3.22	1.18	-2.73	0.01
	Smoker		-0.96	0.78	-1.23	0.22

Table 113. The effect of Neopterin on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	Neopterin	71.00	-0.16	0.17	-0.93	0.35
	Age		-0.17	0.04	-4.38	<.0001
	Sex		-1.00	1.14	-0.88	0.38
	Race		-3.27	1.18	-2.78	0.01
	Smoker		-0.99	0.77	-1.29	0.20

Table 114. The effect of Tyrosine on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	Tyr	71.00	0.03	0.02	1.29	0.20
	Age		-0.17	0.04	-4.43	<.0001
	Sex		-0.95	1.13	-0.85	0.40
	Race		-3.20	1.17	-2.74	0.01
	Smoker		-0.82	0.78	-1.06	0.29

Table 115. The effect of Phenylalanine on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	Phe	71.00	0.05	0.03	1.75	0.08
	Age		-0.17	0.04	-4.56	<.0001
	Sex		-0.97	1.12	-0.87	0.39
	Race		-3.22	1.16	-2.78	0.01
	Smoker		-0.94	0.76	-1.25	0.22

Table 116. The effect of Phenylalanine-Tyrosine ratio on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	Phe-Tyr ratio	71.00	0.34	1.95	0.18	0.86
	Age		-0.17	0.04	-4.45	<.0001
	Sex		-0.99	1.14	-0.86	0.39
	Race		-3.21	1.19	-2.71	0.01
	Smoker		-1.03	0.79	-1.30	0.20

Table 117. The effect of Kynurenine-Tryptophan ratio on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	KYN-Tryp ratio	71.00	-19.65	16.26	-1.21	0.23
	Age		-0.16	0.04	-4.26	<.0001
	Sex		-1.00	1.13	-0.89	0.38
	Race		-3.22	1.17	-2.75	0.01
	Smoker		-0.94	0.77	-1.22	0.23

Table 118. The effect of OHAA-AA ratio on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
LNS	OHAA-AA ratio	71.00	0.38	0.29	1.32	0.19
	Age		-0.17	0.04	-4.49	<.0001
	Sex		-0.92	1.13	-0.81	0.42
	Race		-2.90	1.19	-2.44	0.02
	Smoker		-1.06	0.76	-1.38	0.17

Table 119. The effect of Tryptophan on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	Tryp	71.00	0.00	0.03	-0.05	0.96
	Age		-0.23	0.06	-4.07	0.00
	Sex		-0.88	1.64	-0.54	0.59
	Race		-3.51	1.71	-2.06	0.04
	smoker		-0.67	1.11	-0.61	0.54

Table 120. The effect of Kynurenine on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	KYN	71.00	0.47	0.57	0.83	0.41
	Age		-0.23	0.05	-4.18	<.0001
	Sex		-0.73	1.64	-0.45	0.65
	Race		-3.28	1.70	-1.93	0.06
	Smoker		-0.78	1.11	-0.70	0.49

Table 121. The effect of Kynurenic Acid on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	KYNA	71.00	0.03	0.02	1.38	0.17
	Age		-0.23	0.05	-4.18	<.0001
	Sex		-1.07	1.62	-0.66	0.51
	Race		-3.28	1.68	-1.96	0.05
	Smoker		-0.31	1.12	-0.27	0.79

Table 122. The effect of 3-HAA on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	3-HAA	71.00	0.02	0.03	0.66	0.51
	Age		-0.22	0.05	-4.09	0.00
	Sex		-0.72	1.65	-0.44	0.66
	Race		-3.34	1.70	-1.96	0.05
	Smoker		-0.66	1.10	-0.60	0.55

Table 123. The effect of AA on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	AA	71.00	0.03	0.04	0.59	0.56
	Age		-0.22	0.05	-4.09	0.00
	Sex		-0.82	1.63	-0.51	0.62
	Race		-3.54	1.69	-2.10	0.04
	Smoker		-0.60	1.11	-0.54	0.59

Table 124. The effect of Neopterin on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	Neopterin	71.00	0.00	0.25	-0.02	0.99
	Age		-0.23	0.06	-4.11	0.00
	Sex		-0.88	1.63	-0.54	0.59
	Race		-3.50	1.70	-2.06	0.04
	Smoker		-0.67	1.11	-0.61	0.55

Table 125. The effect of Tyrosine on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	Tyr	71.00	0.01	0.03	0.27	0.79
	Age		-0.23	0.06	-4.11	0.00
	Sex		-0.87	1.63	-0.53	0.60
	Race		-3.50	1.69	-2.07	0.04
	Smoker		-0.62	1.12	-0.55	0.58

Table 126. The effect of Phenylalanine on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	Phe	71.00	0.04	0.04	1.09	0.28
	Age		-0.23	0.05	-4.17	<.0001
	Sex		-0.87	1.62	-0.54	0.59
	Race		-3.52	1.68	-2.10	0.04
	Smoker		-0.62	1.10	-0.57	0.57

Table 27. The effect of Phenylalanine-Tyrosine ratio on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	Phe-Tyr ratio	71.00	2.13	2.78	0.77	0.45
	Age		-0.23	0.05	-4.18	<.0001
	Sex		-0.90	1.63	-0.55	0.58
	Race		-3.59	1.69	-2.13	0.04
	Smoker		-0.84	1.12	-0.75	0.46

Table 128. The effect of Kynurenine-Tryptophan ratio on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	KYN-Tryp ratio	71.00	8.98	23.50	0.38	0.70
	Age		-0.23	0.06	-4.14	0.00
	Sex		-0.87	1.63	-0.53	0.60
	Race		-3.49	1.69	-2.06	0.04
	Smoker		-0.70	1.11	-0.63	0.53

Table 129. The effect of OHAA-AA ratio on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
HVLT-R	OHAA-AA ratio	71.00	0.02	0.42	0.05	0.96
	Age		-0.23	0.05	-4.12	0.00
	Sex		-0.88	1.64	-0.54	0.59
	Race		-3.48	1.72	-2.02	0.05
	Smoker		-0.68	1.11	-0.61	0.54

Table 130. The effect of Tryptophan on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	Tryp	71.00	-0.02	0.04	-0.51	0.62
	Age		-0.27	0.07	-4.03	0.00
	Sex		-0.89	1.93	-0.46	0.65
	Race		-5.94	2.01	-2.95	0.00
	smoker		1.94	1.31	1.48	0.14

Table 131. The effect of Kynurenine on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	KYN	71.00	0.06	0.68	0.09	0.93
	Age		-0.26	0.07	-3.99	0.00
	Sex		-0.81	1.94	-0.42	0.68
	Race		-5.78	2.03	-2.85	0.01
	Smoker		1.93	1.32	1.47	0.14

Table 132. The effect of Kynurenic Acid on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	KYNA	71.00	0.04	0.02	2.06	0.04
	Age		-0.26	0.06	-4.12	0.00
	Sex		-1.16	1.88	-0.62	0.54
	Race		-5.44	1.95	-2.79	0.01
	Smoker		2.58	1.31	1.98	0.05

Table 133. The effect of 3-HAA on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	3-HAA	71.00	0.05	0.04	1.14	0.26
	Age		-0.25	0.06	-3.95	0.00
	Sex		-0.50	1.94	-0.26	0.80
	Race		-5.49	2.00	-2.75	0.01
	Smoker		1.97	1.30	1.52	0.13

Table 134. The effect of AA on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	AA	71.00	0.05	0.05	1.09	0.28
	Age		-0.25	0.06	-3.95	0.00
	Sex		-0.71	1.92	-0.37	0.71
	Race		-5.90	1.98	-2.97	0.00
	Smoker		2.10	1.30	1.61	0.11

Table 135. The effect of Neopterin on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	Neopterin	71.00	-0.04	0.29	-0.14	0.89
	Age		-0.26	0.07	-3.97	0.00
	Sex		-0.83	1.93	-0.43	0.67
	Race		-5.82	2.00	-2.91	0.01
	Smoker		1.95	1.31	1.49	0.14

Table 136. The effect of Tyrosine on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	Tyr	71.00	0.01	0.04	0.26	0.80
	Age		-0.26	0.07	-3.97	0.00
	Sex		-0.82	1.93	-0.42	0.67
	Race		-5.81	2.00	-2.90	0.01
	Smoker		2.01	1.33	1.51	0.14

Table 137. The effect of Phenylalanine on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	Phe	71.00	-0.02	0.04	-0.47	0.64
	Age		-0.26	0.06	-4.00	0.00
	Sex		-0.83	1.93	-0.43	0.67
	Race		-5.80	2.00	-2.90	0.01
	Smoker		1.92	1.31	1.47	0.15

Table 138. The effect of Phenylalanine-Tyrosine ratio on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	Phe-Tyr ratio	71.00	-1.66	3.30	-0.50	0.62
	Age		-0.26	0.06	-3.97	0.00
	Sex		-0.82	1.93	-0.42	0.67
	Race		-5.73	2.00	-2.86	0.01
	Smoker		2.08	1.33	1.56	0.12

Table 139. The effect of Kynurenine-Tryptophan ratio on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	KYN-Tryp ratio	71.00	18.19	27.74	0.66	0.51
	Age		-0.27	0.07	-4.06	0.00
	Sex		-0.81	1.93	-0.42	0.68
	Race		-5.79	1.99	-2.90	0.01
	Smoker		1.89	1.31	1.44	0.15

Table 140. The effect of OHAA-AA ratio on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
Fluency	OHAA-AA ratio	71.00	0.77	0.48	1.60	0.11
	Age		-0.26	0.06	-4.05	0.00
	Sex		-0.69	1.90	-0.36	0.72
	Race		-5.19	2.00	-2.59	0.01
	Smoker		1.83	1.29	1.42	0.16

Table 141. The effect of Tryptophan on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	Tryp	71.00	0.01	0.08	0.09	0.93
	Age		-0.69	0.13	-5.10	<.0001
	Sex		-8.10	3.96	-2.05	0.04
	Race		-13.24	4.13	-3.21	0.00
	smoker		-2.22	2.68	-0.83	0.41

Table 142. The effect of Kynurenine on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	KYN	71.00	2.50	1.35	1.85	0.07
	Age		-0.70	0.13	-5.41	<.0001
	Sex		-7.36	3.88	-1.90	0.06
	Race		-12.14	4.04	-3.01	0.00
	Smoker		-2.76	2.62	-1.05	0.30

Table 143. The effect of Kynurenic Acid on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	KYNA	71.00	0.11	0.04	2.47	0.02
	Age		-0.69	0.13	-5.43	<.0001
	Sex		-8.93	3.79	-2.35	0.02
	Race		-12.40	3.93	-3.15	0.00
	Smoker		-0.68	2.63	-0.26	0.80

Table 144. The effect of 3-HAA on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	3-HAA	71.00	0.02	0.08	0.20	0.84
	Age		-0.69	0.13	-5.17	<.0001
	Sex		-8.00	4.00	-2.00	0.05
	Race		-13.18	4.13	-3.19	0.00
	Smoker		-2.21	2.68	-0.83	0.41

Table 145. The effect of AA on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	AA	71.00	0.16	0.10	1.59	0.12
	Age		-0.68	0.13	-5.17	<.0001
	Sex		-7.77	3.89	-2.00	0.05
	Race		-13.57	4.02	-3.38	0.00
	Smoker		-1.78	2.64	-0.67	0.50

Table 146. The effect of Neopterin on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	Neopterin	71.00	-0.38	0.59	-0.64	0.52
	Age		-0.68	0.13	-5.13	<.0001
	Sex		-8.17	3.94	-2.07	0.04
	Race		-13.46	4.09	-3.29	0.00
	Smoker		-2.20	2.67	-0.82	0.41

Table 147. The effect of Tyrosine on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	Tyr	71.00	-0.02	0.08	-0.23	0.82
	Age		-0.69	0.13	-5.20	<.0001
	Sex		-8.14	3.95	-2.06	0.04
	Race		-13.29	4.09	-3.25	0.00
	Smoker		-2.33	2.72	-0.86	0.39

Table 148. The effect of Phenylalanine on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	Phe	71.00	-0.11	0.09	-1.25	0.22
	Age		-0.69	0.13	-5.25	<.0001
	Sex		-8.15	3.91	-2.08	0.04
	Race		-13.24	4.04	-3.27	0.00
	Smoker		-2.36	2.65	-0.89	0.38

Table 149. The effect of Phenylalanine-Tyrosine ratio on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	Phe-Tyr ratio	71.00	-5.77	6.72	-0.86	0.39
	Age		-0.68	0.13	-5.17	<.0001
	Sex		-8.08	3.93	-2.05	0.04
	Race		-13.03	4.08	-3.19	0.00
	Smoker		-1.77	2.71	-0.65	0.52

Table 150. The effect of Kynurenine-Tryptophan ratio on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	KYN-Tryp ratio	71.00	79.72	56.05	1.42	0.16
	Age		-0.72	0.13	-5.43	<.0001
	Sex		-8.05	3.89	-2.07	0.04
	Race		-13.21	4.03	-3.28	0.00
	Smoker		-2.48	2.64	-0.94	0.35

Table 151. The effect of OHAA-AA ratio on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	t	p-value
BACS-SC	OHAA-AA ratio	71.00	0.32	1.00	0.31	0.75
	Age		-0.69	0.13	-5.19	<.0001
	Sex		-8.06	3.95	-2.04	0.05
	Race		-13.04	4.17	-3.13	0.00
	Smoker		-2.27	2.68	-0.85	0.40

CHAPTER 3. PUBLIC HEALTH IMPLICATIONS, FUTURE DIRECTIONS AND SUMMARY

Better understanding of the mechanism of cognitive impairments in schizophrenia could help with the development of better drugs to help with these impairments. In this study, we explore the recently discovered GPR35 receptor and its role in *T.gondii* infection and cognition. GPR35 is a known receptor for KYNA which in turn is neuroprotective. Higher levels of KYNA in the periphery may correspond to better cognition as evidenced in our study.

These findings can serve as a basis for future experiments with GPR35 and KYNA. One of the possible direction would be exploring the levels of KYNA in the cerebrospinal fluid of schizophrenia patients and controls and studying the association of these levels with the performance on cognitive tests. Another metabolite that can be explored in relation to cognition is quinolinic acid, which is neuroexcitatory. The levels of quinolinic acid can be studied in relation to the levels of KYNA and the effect on cognition.

Appendices

Effect of all predictors on FTT dominant hand

Dependent	Independent	B	SE	t	p-value	Variance Inflation Factor
FTT dominant hand	TRYP	0.49	0.64	0.76	0.45	2.25
	KYN	-3.98	9.42	-0.42	0.67	1.82
	KYNA	0.68	0.52	1.32	0.19	5.29
	3OHAA	0.85	0.58	1.46	0.15	1.96
	AA	-1.24	1.02	-1.21	0.23	3.80
	Neopterin	2.41	3.65	0.66	0.51	1.42
	Tyr	-0.70	0.68	-1.03	0.31	3.07
	Phe	-0.48	0.71	-0.67	0.51	2.26
	Toxo	-41.62	18.83	-2.21	0.03	1.42
	Diagnosis	-26.44	16.27	-1.63	0.11	1.47
	age	-0.26	0.73	-0.35	0.72	1.20
	Sex_01	-2.91	22.79	-0.13	0.90	1.32
	Race_01	-7.56	22.48	-0.34	0.74	1.16
	smoker	-2.70	15.36	-0.18	0.86	1.35

The effect of all biomarkers on logWCST pers while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
	TRYP	71	-0.00265	0.00658	-0.4	0.6884
	KYN		0.14708	0.097	1.52	0.1351
	KYNA		-0.00448	0.00533	-0.84	0.4044
	_OHAA		-0.01083	0.00601	-1.8	0.077
	AA		-0.00354	0.01053	-0.34	0.7381
	Neopterin		-0.03368	0.03761	-0.9	0.3744
	Tyr		0.01531	0.007	2.19	0.0329
	Phe		-0.00615	0.00735	-0.84	0.4067
	Toxo		0.46822	0.19378	2.42	0.019
	Diagnosis		0.11463	0.16746	0.68	0.4965
	age		0.00794	0.00752	1.06	0.2956
	Sex_01		-0.08249	0.23454	-0.35	0.7264

Race_01	0.46536	0.23139	2.01	0.0491
smoker	0.22941	0.15811	1.45	0.1524

The effect of all biomarkers on logWCST nonpers while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
	TRYP	71	-0.01017	0.00655	-1.55	0.1265
	KYN		-0.16412	0.09658	-1.7	0.0948
	KYNA		-0.00134	0.00531	-0.25	0.8019
	_OHAA		0.01573	0.00599	2.63	0.0111
	AA		-0.00504	0.01048	-0.48	0.6322
	Neopterin		0.05067	0.03745	1.35	0.1814
	Tyr		-0.00062	0.00697	-0.09	0.9294
	Phe		-0.0073	0.00732	-1	0.3228
	Toxo		-0.15166	0.19293	-0.79	0.4351
	Diagnosis		-0.05446	0.16673	-0.33	0.7452
	age		0.00113	0.00749	0.15	0.8801
	Sex_01		0.10631	0.23352	0.46	0.6507
	Race_01		0.08548	0.23038	0.37	0.712
	smoker		0.06895	0.15742	0.44	0.6631

The effect of all biomarkers on RIST Index while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
RIST Index	Tryp	71	0.02371	0.10737	0.22	0.826
	KYN		-2.21335	1.58219	-1.4	0.1674
	KYNA		0.18162	0.08697	2.09	0.0413
	OHAA		-0.03234	0.0981	-0.33	0.7429
	AA		-0.26567	0.17172	-1.55	0.1275
	Neopterin		0.5127	0.61352	0.84	0.4069
	Tyr		-0.11046	0.11418	-0.97	0.3375
	Phe		0.18453	0.11992	1.54	0.1295
	Toxo		-1.01807	3.16079	-0.32	0.7486
	Diagnosis		-2.34201	2.73145	-0.86	0.3949
	Age		-0.45966	0.12266	-3.75	0.0004
	Sex		0.82143	3.82571	0.21	0.8308
	Race		-17.3853	3.77425	-4.61	<.0001
	smoker		2.02225	2.57894	0.78	0.4363

The effect of all biomarkers on WMS while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
WMS	Tryp	71	0.05835	0.0354	1.65	0.1049
	KYN		-0.0008	0.52164	0	0.9988
	KYNA		0.01783	0.02867	0.62	0.5365
	OHAA		0.00102	0.03234	0.03	0.9749
	AA		-0.03246	0.05662	-0.57	0.5687
	Neopterin		-0.14749	0.20227	-0.73	0.4689
	Tyr		-0.05148	0.03765	-1.37	0.1769
	Phe		0.0159	0.03954	0.4	0.6891
	Toxo		-0.05129	1.04209	-0.05	0.9609
	Diagnosis		0.04385	0.90054	0.05	0.9613
	Age		-0.08021	0.04044	-1.98	0.0522
	Sex		-1.14824	1.26131	-0.91	0.3665
	Race		-2.70714	1.24435	-2.18	0.0338
	smoker		0.29004	0.85026	0.34	0.7343

The effect of all biomarkers on logTMT while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
	TRYP	71	-0.00044	0.00399	-0.11	0.9134
	KYN		-0.02285	0.05884	-0.39	0.6993
	KYNA		-0.00617	0.00323	-1.91	0.0615
	_OHAA		0.000503	0.00365	0.14	0.8909
	AA		0.01254	0.00639	1.96	0.0546
	Neopterin		0.01062	0.02282	0.47	0.6435
	Tyr		0.000501	0.00425	0.12	0.9065
	Phe		0.00125	0.00446	0.28	0.7798
	Toxo		0.02573	0.11756	0.22	0.8276
	Diagnosis		0.24201	0.10159	2.38	0.0206
	age		0.01637	0.00456	3.59	0.0007
	Sex_01		0.30965	0.14229	2.18	0.0338
	Race_01		0.22175	0.14037	1.58	0.1198
	smoker		-0.06331	0.09592	-0.66	0.5119

The effect of all biomarkers on LNS while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
LNS	Tryp	71	0.0554	0.0334	1.66	0.1028
	KYN		-0.15811	0.49212	-0.32	0.7492
	KYNA		0.05245	0.02705	1.94	0.0575
	OHAA		0.01528	0.03051	0.5	0.6185
	AA		-0.05956	0.05341	-1.12	0.2695
	Neopterin		-0.08911	0.19083	-0.47	0.6423
	Tyr		-0.06137	0.03552	-1.73	0.0895
	Phe		0.06142	0.0373	1.65	0.1052
	Toxo		-2.26843	0.98313	-2.31	0.0248
	Diagnosis		0.46133	0.84959	0.54	0.5893
	Age		-0.14765	0.03815	-3.87	0.0003
	Sex		-1.86743	1.18995	-1.57	0.1222
	Race		-2.46647	1.17394	-2.1	0.0402
	smoker		-0.32409	0.80215	-0.4	0.6877

The effect of all biomarkers on HVLT-R while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
HVLT-R	Tryp	71	-0.06202	0.05195	-1.19	0.2375
	KYN		0.48034	0.76548	0.63	0.5329
	KYNA		0.02975	0.04208	0.71	0.4824
	OHAA		0.00618	0.04746	0.13	0.8968
	AA		-0.02467	0.08308	-0.3	0.7676
	Neopterin		-0.29735	0.29683	-1	0.3208
	Tyr		-0.01848	0.05524	-0.33	0.7392
	Phe		0.04712	0.05802	0.81	0.4201
	Toxo		1.68662	1.52923	1.1	0.2748
	Diagnosis		-1.66712	1.32151	-1.26	0.2123
	Age		-0.25892	0.05934	-4.36	<.0001
	Sex		-0.58415	1.85093	-0.32	0.7535
	Race		-2.88378	1.82603	-1.58	0.1199
	smoker		-0.67527	1.24773	-0.54	0.5905

The effect of all biomarkers on Fluency while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
Fluency	Tryp	71	-0.13525	0.05517	-2.45	0.0174
	KYN		-0.3704	0.81307	-0.46	0.6505
	KYNA		0.06967	0.04469	1.56	0.1247
	OHAA		0.08722	0.05041	1.73	0.0891
	AA		-0.08794	0.08825	-1	0.3233
	Neopterin		-0.29692	0.31528	-0.94	0.3504
	Tyr		0.04079	0.05868	0.7	0.4898
	Phe		-0.09436	0.06163	-1.53	0.1314
	Toxo		2.40045	1.62429	1.48	0.1451
	Diagnosis		-3.79786	1.40366	-2.71	0.009
	Age		-0.30884	0.06303	-4.9	<.0001
	Sex		-0.33767	1.96599	-0.17	0.8642
	Race		-4.19729	1.93954	-2.16	0.0347
	smoker		2.69775	1.32529	2.04	0.0465

The effect of all biomarkers on BACS-SC while adjusting for demographics

Dependent	Independent	N	β	SE	F	p-value
BACS-SC	Tryp	71	-0.14587	0.11072	-1.32	0.1931
	KYN		3.24277	1.63157	1.99	0.0518
	KYNA		0.08894	0.08968	0.99	0.3256
	OHAA		-0.02542	0.10116	-0.25	0.8026
	AA		-0.04052	0.17708	-0.23	0.8199
	Neopterin		-1.12838	0.63267	-1.78	0.0799
	Tyr		0.03418	0.11775	0.29	0.7727
	Phe		-0.14156	0.12367	-1.14	0.2572
	Toxo		1.336	3.25944	0.41	0.6835
	Diagnosis		-8.46464	2.8167	-3.01	0.004
	Age		-0.75716	0.12648	-5.99	<.0001
	Sex		-6.95773	3.94512	-1.76	0.0832
	Race		-9.35416	3.89205	-2.4	0.0196
	smoker		-1.64776	2.65943	-0.62	0.538

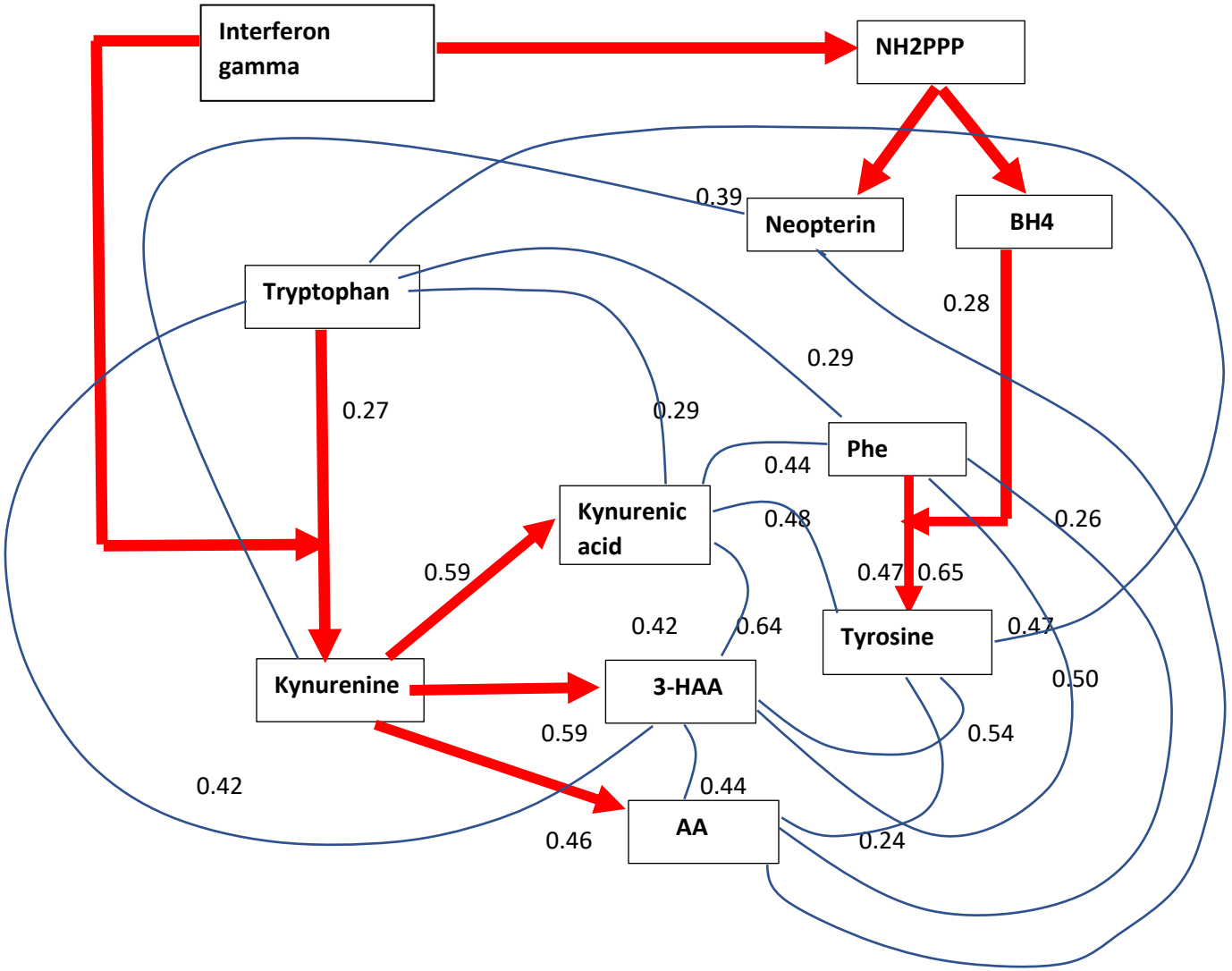


Diagram showing correlations between various KP metabolites and Neopterin, Tyrosine and phenylalanine