Psychoneuroendocrinology 101 (2019) 72–79

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Cross-sectional relationship between kynurenine pathway metabolites and cognitive function in major depressive disorder

Yanling Zhou[a,b], Wei Zheng[a,b], Weijian Liu[a,b], Chengyu Wang[a,b], Yanni Zhan[a,b], Hanqiu Li[a,b], Lijian Chen[a,b], Yuping Ning[a,b,*]

[a] The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[b] Guangdong Engineering Technology Research Center for Translational Medicine of Metal Disorders, Guangzhou, China

ARTICLE INFO

Keywords:
Depression
Kynurenine
Cognition
Tryptophan

ABSTRACT

Objective: Cognitive impairment is common among patients with major depressive disorder (MDD), but its pathological mechanism is complex and not fully understood. Evidence suggests that the kynurenine (KYN) pathway may be implicated in the pathophysiology of depression, but few studies have explored the association between the KYN pathway and cognitive impairment in MDD. Our aim was to examine the relationship between cognitive impairment and KYN pathway metabolites in patients with MDD.

Methods: A total of 146 patients with MDD according to DSM-V and 72 healthy controls (HCs) were enrolled, and the severity of depressive symptoms using the 17-item Hamilton Depression Rating Scale (HAMD-17) and cognitive performance including speed of processing, working memory, visual learning and verbal learning were assessed. Blood samples were collected, and serum concentrations of tryptophan (TRP), kynurenine (KYN) and kynurenic acid (KYNA) were measured by liquid chromatography-tandem mass spectrometry.

Results: In females with MDD, there was a significant negative association between the KYN level and verbal learning (B = -0.039, adjusted $p = 0.018$), and the KYN/TRP ratio was negatively correlated with speed of processing (B = -470.086, adjusted $p = 0.029$), verbal learning (B = -544.251, adjusted $p = 0.002$) and visual learning (B = -513.777, adjusted $p = 0.004$). Those associations were not present in male individuals with MDD or in HCs, except for a significant negative correlation between the KYNA/KYN ratio and category fluency (B = −0.373, adjusted $p = 0.039$) in female HCs.

Conclusion: Our results suggest that learning function and speed of processing in female MDD were associated with KYN serum level and the KYN/TRP ratio, potentially implicating the KYN pathway in the pathological mechanism of cognitive function in female MDD.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent and disabling psychiatric illness, with a high lifetime prevalence ranging from 10 to 15% (Kessler et al., 2005, 2013a). Cognitive dysfunction is a core diagnostic feature of MDD and is likely to cause considerable interference and functional impairment in patients' daily life function (Mcintyre et al., 2013), but effective alleviation of the cognitive deficits is difficult to achieve with current antidepressant therapies (Amado-Boccara et al., 1995).

The factors associated with cognitive impairment vary and include the severity of depression symptoms, duration of illness and number of episodes. In subgroups of patients with MDD, cognitive deficits constitute an independent dimension of depressive symptoms that is dissociable from depressive symptomatology (Naismith et al., 2003; Iverson et al., 2011). The underlying pathological mechanism of cognitive dysfunction in depression is complex and not fully understood but seems to involve neural circuitry, multiple neurotransmitter systems, immune activation, oxidative stress and changes in neurotrophins (Millan et al., 2012; Femenia et al., 2012).

Tryptophan (TRP), an essential amino acid critical for protein synthesis, is degraded into several neuroactive compounds including serotonin (5-hydroxytryptamine, 5-HT), an important neurotransmitter involved in the control of adaptive responses in the central nervous system and linked to alterations in mood and cognition. Under normal conditions, more than 90% of TRP is metabolized via the kynurenine

* Corresponding author at: The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, Mingxin Road #36, Liwan District, 510370, China.
E-mail address: ningjeny@126.com (Y. Ning).

https://doi.org/10.1016/j.psyneuen.2018.11.001
Received 21 August 2018; Received in revised form 7 October 2018; Accepted 1 November 2018

(KYN) pathway rather than the 5-HT pathway. Pro-inflammatory cytokines, such as interferon gamma (IFN-γ), are considered the critical inducers of tryptophan 2,3-dioxygenase (TDO) and indolamine 2,3-dioxygenase (IDO), the rate-limiting enzymes of the KYN pathway (Dantzer et al., 2011). KYN is further metabolized into several main downstream metabolites: neurotoxic 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN), as well as kynurenic acid (KYNA), a blocker of N-methyl-D-aspartate (NMDA) receptors that has neuroprotective effects (Schwarcz et al., 2012). In addition, KYNA is an Alpha 7 Nicotinic Receptor (a7nAChR) antagonist (Anderson and Maes, 2017), with a7nAChR agonists being trialled as cognitive enhancers.

Increasing evidence has shown that KYN metabolism may be involved in the pathological mechanism of depression based on the inflammatory hypothesis of depression (Krishnadas and Harrison, 2016). Experimental animal models have shown that genetic or pharmacological inhibition of KYN pathway activation inhibits the induction of depression-like behaviour by lipopolysaccharide (LPS) administration (O'Connor et al., 2009). Evidence from patients with inflammatory diseases or patients treated with interferon-α also demonstrated a strong associated between depressive symptoms and the production of neurotoxic kynurenine metabolites (Raison et al., 2009; Georgin-Lavialle et al., 2016). A meta-analysis compared KYN pathway metabolite concentrations between depressed patients and healthy controls (HCs) and found a significant reduction in circulating concentrations of KYNA and KYN and the ratio of KYNA/QUIN in depressed patients relative to those in control subjects (Ogyu et al., 2018). This imbalance in the KYN pathway not only emerged in depressed phases but also persisted in patients with major depression who were in long-term remission (Savitz et al., 2015a).

Abnormalities of the KYN pathway may contribute to the pathogenesis of cognitive deficits as TRP exhaustion within the periphery increases the rate of TRP degradation and an imbalance between the neurotoxic metabolite QUIN and the neuroprotective metabolite KYNA. Few studies have explored the direct correlation between the levels of KYN metabolites and cognitive function in patients with MDD; however, there is evidence for this relationship in other mood disorders, such as bipolar disorder (Platzer et al., 2017), and other cognitive disorders including schizophrenia (Wonodi et al., 2014), dementia (Ting et al., 2009) and Huntington's disease (Schwarcz et al., 2010). Furthermore, imaging studies have also demonstrated that abnormal KYN metabolites in MDD and other psychiatric disorders are correlated with volume loss in the hippocampus and reduced grey matter density in the prefrontal lobe, both critical areas for learning and memory function (Savitz et al., 2015b, 2015c; Meier et al., 2016).

Although most studies support the hypothesis that abnormal KYN metabolites are linked to depression, few existing studies have been able to identify an association between the KYN pathway and cognitive impairment in MDD. Given the existing evidence showing the involvement of distinct KYN pathway intermediates in cognitive function, we hypothesized that deficits in cognitive performance in MDD are associated with abnormal levels of KYN metabolites. Our aim was to examine the relationship between KYN pathway metabolism and cognitive performance in individuals with MDD in order to explore a novel target and a valuable pharmacological strategy for the prevention and treatment of depression and for improving cognitive performance associated with depression.

2. Material and methods

Patient data were from baseline information acquired in a 9-month follow-up study aimed to examine the molecular targets to predict the antidepressant efficacy of antidepressants. We enrolled subjects from the Affiliated Brain Hospital of Guangzhou Medical University between September 2016 and December 2017. In the beginning of the study, the experimental protocol was approved by the Clinical Research Ethics Committees of the Affiliated Brain Hospital of Guangzhou Medical University. All participants confirmed their understanding of the study procedures and signed a consent form prior to entering this study.

2.1. Participants

Patients meeting the following criteria were enrolled: (1) male or female, aged 18–65; (2) diagnosed with MDD based on the structured clinical interview for DSM-V (SCID) criteria; (3) a total score on the 17-item Hamilton Depression Rating Scale (HAMD-17) ≥ 17; (4) the ability to understand the study procedures and assessment; and (5) written informed consent provided before entering into the study. The exclusion criteria included the following: (1) a comorbidity of current or previous substance abuse or dependence; (2) a serious and unstable medical or concomitant medications likely to influence central nervous system or immunological function including respiratory, cardiovascular, endocrine and neurological diseases; (3) a current or previous moderate/severe traumatic brain injury; (4) a current or past diagnosis of any other serious mental disorder, such as schizophrenia, according to SCID or a comorbidity of an Axis I anxiety disorder, obsessive-compulsive disorder, phobia, or panic disorder that was the primary cause of illness within the previous year; and (5) pregnancy or lactation. A total of 163 patients were enrolled, but 146 patients completed the cognitive assessment, and their data were included in the final analyses.

Seventy healthy controls (HCs) were recruited through the Affiliated Brain Hospital of Guangzhou Medical University between 2015 and 2017, and they were conveniently selected from community in Guangzhou by online recruitment. The controls were in a healthy state without any previous or current psychiatric illness or substance abuse or dependence. They were examined for personal or family history of psychiatric disorder using the SCID and were free of medication.

2.2. Assessments

The severity of depressive symptoms was measured by the 17-item Hamilton Depression Rating Scale (HAMD-17). Cognitive performance was assessed using four domains of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) (Nuechterlein, et al., 2008), including speed of processing, working memory, visual learning and verbal learning. Speed of processing was measured using the Category Fluency test, Trail Making A test, and Brief Assessment of Cognition in Schizophrenia (BACS). Working memory, visual learning and verbal learning were measured using a verbal (WAIS-III, letter-number sequencing (LNS) subtest) and nonverbal (WMS-III, Spatial Span) test, the Hopkins Verbal Learning Test-Revised, and the Brief Visuospatial Memory Test-Revised, respectively. Each domain score was standardized to a T score with a mean of 50 and a standard deviation of 10. For the domain with more than one test, a composite T score was calculated by standardizing the average of each T score. Although the MCCB is a commonly used tool for the assessment of neurocognitive function in patients with schizophrenia, it has been increasingly applied for patients with mood disorders in recent years (Kessler et al., 2013b, 2014). These four domains of the MCCB were selected because impairment in processing speed, learning and memory is common in MDD and is often associated with severity of depressive symptom (Halvorsen et al., 2011; Marianne et al., 2012).

2.3. Biochemical analysis

All participants fasted overnight and blood was sampled between 8 a.m. and 10 a.m. when they were recruited in the study. Blood samples were collected in vacutainers without further additives, then were centrifuged (3000 rpm/min, at + 4 °C) for 10 min within 1 h, and the supernatant was aliquoted into Eppendorf tubes (Eppendorf, Hamburg, Germany) and immediately frozen at −80 °C until assay.

Serum concentrations of tryptophan (TRP), kynurenine (KYN) and

kynurenic acid (KYNA) were examined using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) as previously described in detail (Hu, et al., 2017). HPLC and mass spectrometry were conducted by an Agilent 1200 series HPLC system (Agilent Technologies, Inc., Santa Clara, CA, USA) and an Agilent 6410 triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source, respectively. L-TRP, L-KYN and KYNA were obtained from Sigma-Aldrich. The Lowest level of quantification concentration of TRP, KYN and KYNA were 1 μg/mL, 100 ng/mL and 1 ng/mL, respectively. Coefficient of variation (CV%) were obtained for intra- and inter-assay precision of all three analytes; TRP intra-day CVs were 0.55–1.88% and inter-day CVs were 2.80–7.06%, KYN intra-day CVs were 0.92–4.33% and inter-day CVs were 5.37–9.85%, KYNA intra-day CVs were 1.37–4.08% and inter-day CVs were 5.34–10.73%.

2.4. Statistical analysis

Differences in demographics and HAMD-17 scores between groups (males and females, MDD and HCs) were calculated using Student's t-test, Mann–Whitney U test and chi-square test, as appropriate. Covariance analysis was used to compare the differences in cognitive test scores and serum KYN pathway metabolite levels between genders considering demographics variables which were different between genders as covariates. Similarly, covariance analysis also was used to compare the differences in MCCB score and metabolites between MDD and HCs controlling age, smoking and drinking as covariates.

Association between serum KYN pathway metabolite concentrations and cognitive test scores were examined using linear regression analysis, with cognitive test scores as dependent variable and KYN pathway metabolite concentration as independent variable. Covariates for multivariable linear regression included body mass index (BMI), age, education, smoking (yes/no), drinking (yes/no), combined use of antidepressant/mood stabilizer/benzodiazepine/antipsychotic (yes/no, only in patients with MDD), HAMD total score.

All the above analyses were performed separately for gender as significant differences in depressed severity, cognitive function and serum KYN pathway metabolite concentrations were found between females and males in this patient sample.

All statistical analyses were performed using IBM SPSS Statistics version 22, and p-values < 0.05 were considered statistically significant. P-values were adjusted for multiple comparisons using False Discovery Rate (FDR) correction.

3. Results

3.1. Sample characteristics

In MDD sample, there was no significant difference in age, education, duration of illness, number of previous depressive episodes or current pharmacotherapies between male and female patients ($p > 0.05$). Female patients showed less smoking and drinking, a lower body mass index and more serious depressive symptoms than male patients ($p < 0.05$). Male controls were significantly younger and smoked and drank more than female controls ($p < 0.05$) (Table 1).

Patients with MDD showed less employed and married and more depressed symptom than HCs both in female and male cases ($p < 0.05$). Male patients had higher numbers of smokers ($p = 0.001$) and drinkers ($p = 0.007$) compared to male HCs. Male MDD were elder ($p = 0.037$) than male HCs, but no significant difference between female MDD and HCs (Supplementary Table 1).

In MDD subjects, after considering BMI, depressed symptom, current smoking and drinking as covariates, males had significantly higher speed of processing ($F = 2.338$, adjusted $p = 0.027$) (Trail Making: $F = 2.679$, adjusted $p = 0.008$) and visual learning ($F = 2.474$, adjusted $p = 0.018$) scores than females, as well as higher levels of TRP ($F = 2.517$, adjusted $p = 0.015$) and KYN ($F = 2.614$, adjusted $p = 0.011$) (Tables 2 and 3). In the control group, after considering current smoking and drinking as covariates, males and females did not perform differently in any cognitive tasks, but males had higher levels of TRP ($F = 2.950$, adjusted $p = 0.004$) and KYN ($F = 2.308$, adjusted $p = 0.032$) than females (Tables 2 and 3).

After controlling age, smoking and drinking as covariates, female MDD showed worse performance in all domains of cognition than female HCs ($F = 3.918 \sim 5.222$, all adjusted $p < 0.001$), and male MDD performed worse in speed of processing ($F = 2.741$, adjusted $p = 0.014$) and verbal learning ($F = 3.802$, adjusted $p < 0.001$) compared male HCs (Supplementary Table 2). Patients with MDD had lower levels of KYNA (female: $F = 2.612$, adjusted $p = 0.027$; male: $F = 2.895$, adjusted $p = 0.009$) and KYNA/KYN ratio (female: $F = 3.744$, adjusted $p < 0.001$; male: $F = 2.939$, adjusted $p = 0.007$), higher KYN/TRP ratio (female: $F = -2.705$, adjusted $p = 0.019$, male: $F = -2.761$, adjusted $p = 0.015$) than HCs both in female and male subjects, and male MDD had lower TRP levels compared to male HCs ($F = 4.647$, adjusted $p < 0.001$) (Supplementary Table 3).

3.2. Association between neurocognitive function and levels of KYN pathway metabolites

In HCs, a significant negative association was found between the KYNA/KYN ratio and the category fluency score ($B = -0.373$, adjusted $p = 0.039$) only in females (Supplementary Tables 4 and 5).

In individuals with MDD, a significant negative correlation was found between KYN levels and verbal learning in females ($B = -0.039$, adjusted $p = 0.018$). The KYN/TRP ratio was negatively correlated with speed of processing ($B = -470.086$, adjusted $p = 0.029$), verbal learning ($B = -544.251$, adjusted $p = 0.002$) and visual learning ($B = -513.777$, adjusted $p = 0.004$) (Table 4). No significant association was found between any cognitive function domain and any KYN pathway metabolite in male patients (adjusted $p > 0.05$) (Table 5). For a graphical depiction of correlations between cognitive performances between KYN/TRP ratios as well as KYN level see Fig. 1.

4. Discussion

To the best of our knowledge, this is the first study to explore the relationship between cognitive performance and levels of KYN pathway metabolites in individuals with MDD. We demonstrated a significant but modest association between cognitive impairment and an elevated serum KYN level and the KYN/TRP ratio in female individuals with MDD. This association remained significant after covarying for the effects of depressive symptoms. However, no relationship was found in male individuals with MDD or in HCs.

Cognitive deficits in individuals with MDD have been demonstrated to not only occur during depressive episodes but also persist after remission of a depressive episode (Reppermund et al., 2009; Savitz et al., 2015a). To a large extent, cognitive deficits have been regarded as a part of depressive symptomatology or a clinical phenomenon driven by depressive symptomatology (Iverson et al., 2011; Naismith et al., 2003). However, growing evidence suggests that cognitive deficits are independent of depressive symptoms and may even be more severe than depressive symptoms, and these deficits are unable to completely recover with remission of depressive symptoms (Mcdermott and Ebmeier, 2009; Mcclintock, et al., 2010). Therefore, additional studies are required to further elucidate the mechanisms underlying cognitive impairment and identify targets for its clinical prevention and treatment.

In the present study, KYN/TRP, a measure of IDO activity, was significantly negatively corrected with speed of processing, verbal learning and visual learning. IDO, the rate-limiting enzyme of the KYN pathway, can be activated by pro-inflammatory cytokines such as IFN-γ (Dantzer et al., 2011). Although few studies have examined the relationship between KYN metabolites and cognition in MDD, evidence has shown that activation of IDO plays a critical role in cognitive

Table 1
Demographic and clinical characteristics of participants.

Variables	Major Depressive Disorder						Healthy Controls					
	Male(N = 76)		Female(N = 70)		Statistics		Male(N = 41)		Female(N = 31)		Statistics	
	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
Employed	30	39.5	19	27.1	2.485	0.115	39	90.2	24	77.4	2.243	0.134
Married	20	26.3	19	27.1	0.013	0.910	23	56.1	22	71.0	1.665	0.197
Current smoking	14	18.4	2	2.9	9.046a	**0.003**	19	46.3	1	3.2	16.357[a]	< **0.001**
Current drinkingc	17	22.4	4	5.7	8.207a	**0.004**	19	46.3	3	9.7	11.183[a]	**0.001**
Number of previous episodes	–	–	–	–	2.097	0.351	–	–	–	–	–	–
0	35	46.1	24	34.3	–	–	–	–	–	–	–	–
1	23	30.3	26	37.1	–	–	–	–	–	–	–	–
≥2	18	23.7	20	28.6	–	–	–	–	–	–	–	–
Psychiatric comorbidity (yes)	9	11.8	6	8.6	0.423	0.516	–	–	–	–	–	–
Previous hospitalization(yes)	16	21.1	16	22.9	0.069	0.792	–	–	–	–	–	–
Positive psychiatric family history	25	32.9	17	24.3	1.318	0.251	–	–	–	–	–	–
Free-medication	28	36.8	22	31.4	0.474	0.491	–	–	–	–	–	–
On one antidepressant	43	56.6	44	62.9	0.596	0.440	–	–	–	–	–	–
On two antidepressants	5	6.6	4	5.7	0.047a	0.828	–	–	–	–	–	–
On benzodiazepine	29	38.2	27	38.6	0.003	0.959	–	–	–	–	–	–
On antipsychotic	18	23.7	22	31.4	1.099	0.295	–	–	–	–	–	–
	Mean	SD	Mean	SD	t/z	*p*	Mean	SD	Mean	SD	t/z	*p*
Age (years)	33.3	11.7	35.0	12.4	−0.846	0.399	28.8	9.7	36.3	11.9	−2.959	**0.004**
Education (years)	12.4	3.4	12.4	3.3	−0.029	0.977	12.0	2.0	11.8	3.2	0.370	0.712
BMI (kg/m2)	22.8	3.2	21.1	3.3	3.119	**0.002**	23.1	5.6	21.8	3.0	1.129	0.263
Duration of illness (months)	65.2	69.1	58.5	61.6	0.624b	0.533	–	–	–	–	–	–
Dose of antidepressant (mg/day)d	28.7	17.9	30.4	21.0	−0.435b	0.665	–	–	–	–	–	–
HAMD-17	21.6	3.8	23.4	5.2	−2.344	**0.020**	0.4	0.7	0.2	0.5	1.341	0.184

BMI = body mass index; HAMD-17 = the 17-item Hamilton Rating Scale for Depression.
aFisher's exact test.
bMann-Whitney U test.
cCurrent drinking but not meet diagnostic criteria for alcohol abuse or dependence.
dFluoxetine equivalents equals in participants receiving antidepressant.

Table 2
Comparison of cognitive performance between male and female.

Variables	Major Depressive Disorder							Healthy Controls						
	Male(N = 76)		Female(N = 70)		Statistics[a]			Male(N = 41)		Female(N = 31)		Statistics[b]		
	Mean	SD	Mean	SD	F	*p*	Adjusted *p*	Mean	SD	Mean	SD	F	*p*	Adjusted *p*
Speed of processing	41.9	13.5	37.0	11.9	2.338	0.021	**0.027**	48.6	10.8	49.5	8.8	−0.359	0.721	1.000
Trail Making	44.9	13.5	39.3	11.6	2.679	0.008	**0.008**	50.8	11.4	48.6	9.3	0.879	0.383	0.919
BACS	41.8	12.7	38.3	10.6	1.748	0.083	0.133	45.8	8.8	50.2	10.2	−1.937	0.057	0.080
Category Fluency	45.1	10.8	42.9	12.1	1.125	0.262	0.484	50.4	10.8	50.1	9.5	0.117	0.907	1.000
Working memory	42.4	11.7	39.1	10.3	1.763	0.080	0.120	41.8	10.3	43.0	11.2	−0.492	0.624	1.000
Verbal learning	41.2	12.5	39.3	10.0	1.023	0.308	0.616	49.5	8.7	49.1	10.4	0.209	0.835	1.000
Visual learning	42.6	11.0	38.2	10.6	2.474	0.015	**0.018**	46.8	11.6	47.7	7.8	−0.364	0.717	1.000

BACS = Brief Assessment of Cognition in Schizophrenia. P-values were adjusted using False Discovery Rate (FDR) correction.
[a] considering body mass index, depressed symptom, current smoking and drinking as covariates.
[b] considering current smoking and drinking as covariates.

Table 3
Serum KYN pathway metabolites of participants.

Variables	Major Depressive Disorder							Healthy Controls						
	Male(N = 76)		Female(N = 70)		Statistics[a]			Male(N = 41)		Female(N = 31)		Statistics[b]		
	Mean	SD	Mean	SD	F	*p*	Adjusted *p*	Mean	SD	Mean	SD	F	*p*	Adjusted *p*
TRP (ng/ml)	10,857.1	2281.2	9849.8	2554.1	2.517	0.013	**0.015**	12561.1	2032.5	11220.4	1732.0	2.950	0.004	**0.004**
KYN (ng/ml)	285.3	75.2	253.1	73.6	2.614	0.010	**0.011**	286.0	76.9	245.5	69.1	2.308	0.024	**0.032**
KYNA (ng/ml)	5.6	2.3	5.3	2.4	0.842	0.401	1.000	7.1	3.1	6.8	3.0	0.457	0.649	1.000
KYN/TRP	0.027	0.007	0.026	0.007	0.878	0.382	0.833	0.023	0.007	0.022	0.005	0.839	0.404	1.000
KYNA/KYN	0.020	0.007	0.021	0.008	−0.453	0.651	1.000	0.025	0.008	0.028	0.009	−1.660	0.101	0.173

TRP = Tryptophan; KYN = Kynurenine; KYNA = Kynurenic Acid. P-values were adjusted using False Discovery Rate (FDR) correction.
[a] considering body mass index, depressed symptom, current smoking and drinking as covariates.
[b] considering current smoking and drinking as covariates.

Table 4
Association of cognitive function and levels of KYN pathway metabolites in female with MDD.

Variables	Speed of processing				Working memory				Verbal learning				Visual learning			
	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*
TRP	0.000	0.772	0.443	0.886	0.000	0.148	0.883	1.000	0.000	0.852	0.397	0.756	0.001	1.921	0.059	0.067
KYN	−0.012	−0.596	0.553	1.000	−0.022	−1.294	0.200	0.267	−0.039	−2.447	0.017	**0.018**	−0.008	−0.465	0.643	1.000
KYNA	−0.240	−0.381	0.704	1.000	−0.160	−0.290	0.773	1.000	−0.647	−1.238	0.220	0.314	0.018	0.034	0.973	1.000
KYN/TRP	−470.086	−2.265	0.027	**0.029**	−182.841	−0.979	0.331	0.602	−544.251	−3.310	0.002	**0.002**	−513.777	−2.978	0.004	**0.004**
KYNA/KYN	62.164	0.351	0.727	1.000	106.169	0.687	0.494	1.000	74.757	0.503	0.617	1.000	94.177	0.622	0.536	1.000

MDD = Major Depressive Disorder; TRP = Tryptophan; KYN = Kynurenine; KYNA = Kynurenic Acid. Covariates included body mass index, age, education, smoking, drinking, combined use of antidepressant/mood stabilizer/benzodiazepine/antipsychotic, HAMD total score. P-values were adjusted using False Discovery Rate (FDR) correction.

Table 5
Association of cognitive function and levels of KYN pathway metabolites in male with MDD.

Variables	Speed of processing				Working memory				Verbal learning				Visual learning			
	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*	B	t	*p*	Adjusted *p*
TRP	0.001	1.265	0.210	0.290	0.000	−0.248	0.805	1.000	0.001	1.199	0.235	0.362	0.001	1.644	0.105	0.124
KYN	0.011	0.527	0.600	1.000	0.005	0.283	0.778	1.000	0.006	0.295	0.769	1.000	0.033	2.026	0.046	0.051
KYNA	−0.368	−0.540	0.591	1.000	−0.676	−1.124	0.265	0.424	−0.660	−1.038	0.303	0.505	0.720	1.306	0.196	0.253
KYN/TRP	−26.363	−0.110	0.913	1.000	−15.805	−0.074	0.941	1.000	−268.739	−1.204	0.233	0.345	128.779	0.654	0.515	1.000
KYNA/KYN	−224.678	−1.022	0.310	0.539	−300.474	−1.555	0.124	0.150	−272.605	−1.331	0.188	0.235	−29.999	−0.166	0.868	1.000

MDD = Major Depressive Disorder; TRP = Tryptophan; KYN = Kynurenine; KYNA = Kynurenic Acid. Covariates included body mass index, age, education, smoking, drinking, combined use of antidepressant/mood stabilizer/benzodiazepine/antipsychotic, HAMD total score. P-values were adjusted using False Discovery Rate (FDR) correction.

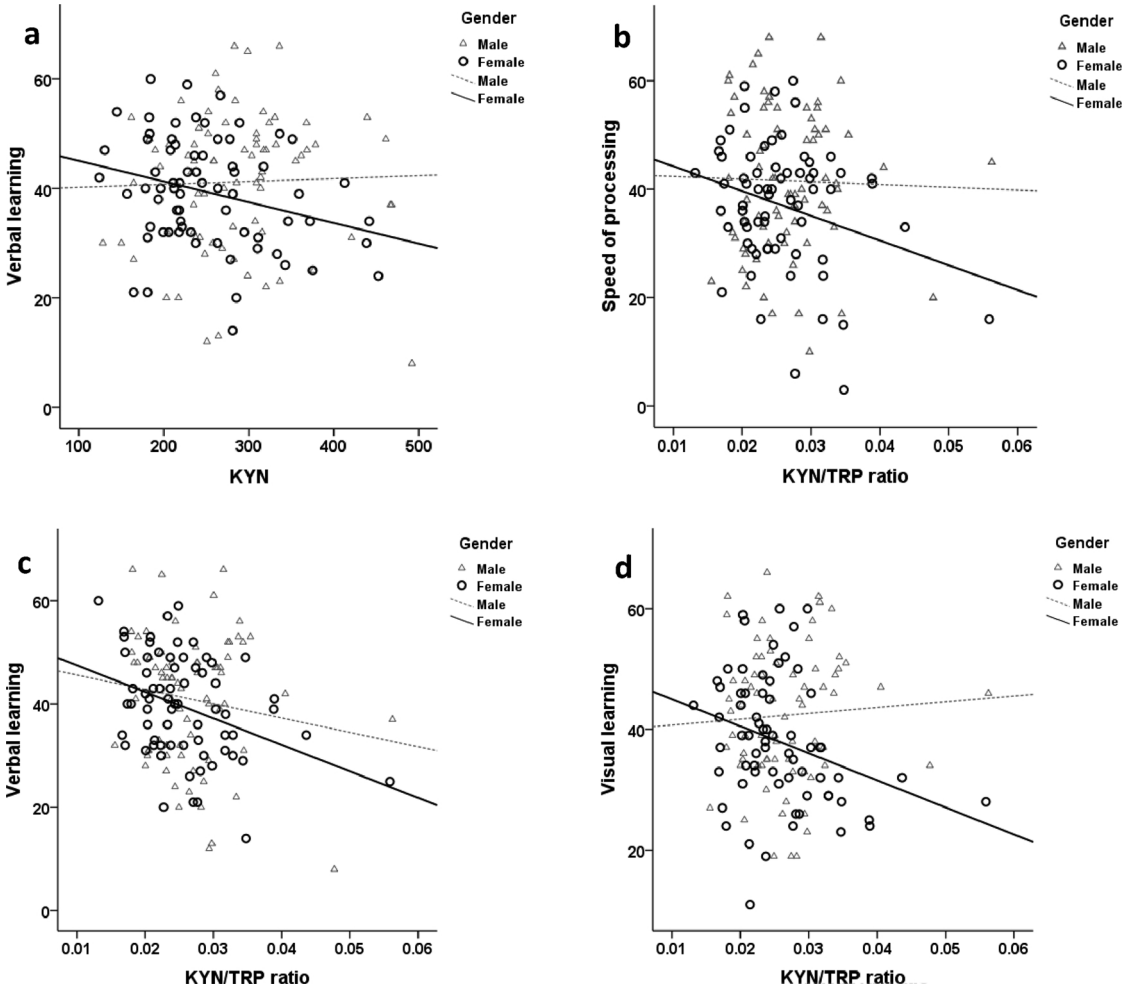

Fig. 1. Associations between cognitive performances between KYN pathway metabolite concentration in patients using linear regression analysis. TRP = Tryptophan; KYN = Kynurenine; KYNA = Kynurenic Acid. (a) Associations between KYN and verbal learning in male (B = 0.006, adjusted p = 1.000) and female (B = -0.039, adjusted p = 0.018); (b) Associations between KYN/TRP ratio and speed of processing in male (B = -26.363, adjusted p = 1.000) and female (B = -470.086, adjusted p = 0.029); (c) Associations between KYN/TRP ratio and verbal learning in male (B = -268.739, adjusted p = 0.345) and female (B = -544.251, adjusted p = 0.002); (d) Associations between KYN/TRP ratio and visual learning in male (B = 128.779, adjusted p = 1.000) and female (B = -513.777, adjusted p = 0.004).

deficits. Preclinical work has demonstrated that many LPS-induced depressive-like behaviours and cognitive deficits in laboratory rodents are mediated by activation of brain IDO (O'Connor et al., 2009, 2012). In addition, an animal model elicited by the long-lasting effects of inescapable-predator stress showed activation of IDO leads to cognitive deficits (Miura, et al., 2011). Furthermore, Jillian and colleagues demonstrated that a decline in cognitive performance induced by peripheral immune challenge was mediated by IDO and downstream neurotoxic KYN metabolism, and animals with pharmacological or genetic inhibition of IDO activity were protected from cognitive impairment induced by inflammation (Heisler and O'Connor, 2015). In addition, the KYN/TRP ratio in peripheral blood was elevated in patients with Alzheimer's disease and in patients after stroke and was associated with reduced cognitive function (Widner et al., 2000; Gold et al., 2011). The administration of etanercept, a tumour necrosis factor (TNF)-α antagonist, has been shown to improve cognition in patients with Alzheimer's disease over a six-month administration period as well as acutely following a single dose (Tobinick and Gross, 2008).

Evidence from other psychiatric disorders supports the role of the KYN pathway in cognitive function. Patients with bipolar disorder during the euthymic phase showed a significant negative correlation between the 3-HK/KYNA ratio and verbal learning and memory measured using the California Verbal Learning Test. Additionally, the KYN/3-HK ratio was correlated with performance on the sub-score of the California Verbal Learning Test (Platzer et al., 2017). Increasing evidence has shown that abnormal levels of KYN pathway metabolites are linked to cognitive impairment in neurodegenerative disorders, including schizophrenia (Wonodi et al., 2014), dementia (Ting et al., 2009) and Huntington's disease (Schwarcz et al., 2010).

In a human study, a smaller hippocampal volume and prefrontal cortex abnormalities were found in depression along with a decline in learning function and memory (Drevets et al., 2008). Imaging studies have also found that KYN pathway metabolites are correlated with the hippocampus or prefrontal cortex in MDD and other psychiatric disorders. Savitz and colleagues reported reductions in the serum KYNA/QUIN ratio in 29 unmedicated MDD patients along with positive correlations between the KYNA/QUIN ratio and grey matter volumes of the hippocampus (Savitz et al., 2015b). These authors also found a positive correlation between KYNA/3 H K and hippocampal volume in depressed patients with bipolar disorder (Savitz et al., 2015c). In another study, patients with MDD showed a reduction in cortical thickness of medial prefrontal cortex (mPFC) regions, as well as the KYNA/3 H K ratio and log KYNA/QUIN, and the reductions in KYNA/3 H K and log KYNA/QUIN mediated the reductions in the cortical thickness of mPFC regions in MDD patients (Meier et al., 2016). The results above presented a possibility that structural abnormalities in these parts of the

brain were strongly linked to an imbalance of KYN pathway metabolism, especially excessive neurotoxic kynurenine metabolites. Although the current study did not quantify neurotoxic kynurenine metabolites (e.g., 3 H K and QUIN), KYN levels and the KYN/TRP ratio were negatively correlated with verbal learning, visual learning and speed of processing, thereby suggesting a role of the KYN pathway in cognitive impairment to some degree.

KYNA, an NMDAR and a7nAChR antagonist, is associated with cognitive function. The correlation of KYNA with cognition in MDD may be linked to alterations in a7nAChR activities, which as well as regulating cognition can also negatively modulate immune inflammatory processes and mitochondrial functioning (Anderson, 2017). Gut microbiota, a hot issue in recent years, is important mediators of pro-inflammatory processes occuring in MDD. Mounting evidence over the past five years suggest that microbiota play a key role at the gut–brain interphase, an imbalanced microbial community can lead dysregulated immune response which modulates several brain processes impacting mood, behavior and cognition (Waclawiková and El Aidy, 2018; Jeon and Kim, 2017). Therefore gut microbiota driving the pro-inflammatory may mediate changes in kyurenine pathway activity in MDD (O'Mahony, et al., 2015). It would behoove future researchers to devote more attention to immune inflammatory, mitochondrial functioning, intestinal barrier and diversity of the gut microbiome in MDD.

In the current study, associations between KYN, the KYN/TRP ratio and learning function and processing speed were observed in female patients with MDD but not in males. This difference may be due to the inherent heterogeneity of the sample groups. The female patients in this sample experienced more serious depressive symptoms and worse cognitive impairment than males in this study. Gender differences in depression have been demonstrated in psychology and physiology. Females are two to three times more likely to develop mental disorders such as depression or anxiety disorders (Kessler et al., 2005). In addition to the sex differences in the incidence of depression, males and females may also experience different symptoms. Furthermore, men are less likely to seek treatment, and the efficacy of certain types of antidepressants is dependent on sex (Martin, et al., 2013; Sramek, et al., 2016). In addition, both clinical observations and experimental findings in humans have provided compelling evidence that inflammatory responses markedly differ across sexes, with women showing a more pronounced pro-inflammatory profile during experimental immune challenge and naturally occurring infections (Klein, et al., 2010; Klein, 2012). BMI is known to increase levels of inflammation, likely increasing KYN and TRP levels, since BMI in male patient was greater than female in this study (de Heredia et al., 2012; Favennec et al., 2016).

5. Limitations

Several limitations should be considered when interpreting these results. First, the ability to interpret the comprehensive causal relationships between cognitive performance and KYN pathway metabolism from the results of this cross-sectional investigation is limited. Second, the study lacked the quantification of several useful biological variables, such as 3-HK and QUIN, other products of KYN metabolism; related rate-limiting enzyme such as IDO; and measurements of their causative factors such as pro-inflammatory factors. Future studies including these biological variables would better illuminate the contribution of KYN pathway metabolites to cognitive performance than the current results. Third, most of the patients were receiving various psychiatric medications and had suffered from illness for a long time when they entered the study, potentially affecting the KYN pathway. Whether similar KYN pathway changes would also occur in first-episode un-medicated patients remains unknown. Fourth, kynurenine metabolites were determined in peripheral blood rather than cerebrospinal fluid (CSF). Since changes in central KYN pathway functioning was considered not identical to changes in peripheral KYN pathway functioning, although high correlations were found between CSF and plasma KYN as well as CSF and plasma QUIN in patients with hepatitis C (Raison et al., 2009).

6. Conclusions

Our results showed that worse learning function and speed of processing in female MDD was associated with increased KYN levels and KYN/TRP ratio, suggesting that the KYN pathway may be involved in the pathological mechanism of neurocognitive function in female MDD. The KYN pathway of TRP metabolism could be considered a novel target and a valuable pharmacological strategy in the prevention and treatment of depression and for improving cognitive performance associated with depression.

Role of funding source

This work was supported by the National Key Research and Development Program of China (grant number 2016YFC0906300), the National Natural Science Foundation of China (grant number 81801343), Science and Technology Department of Guangdong Province major science and technology (grant number 2016B010108003) and Guangzhou Municipal Psychiatric Disease Clinical Transformation Laboratory (grant number 201805010009), Key Laboratory for Innovation platform Plan, Science and Technology Program of Guangzhou, China. The funding source had no role in the study design, analysis or interpretation of data or in the preparation of the report or decision to publish.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgement

We want to acknowledge the patients participating in the trial and contributions of all investigators.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.11.001.

References

Amado-Boccara, I., Gougoulis, N., Poirier Littré, M.F., Galinowski, A., Lôo, H., 1995. Effects of antidepressants on cognitive functions: a review. Neurosci. Biobehav. Rev. 19, 479–493.

Anderson, G., 2017. Linking the biological underpinnings of depression: role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, DNA repair and oxidative and nitrosative stress, with consequences for classification and cognition. Prog. Neuropsychopharmacol. Biol. Psychiatry 20 (80), 255–266 Pt C.

Anderson, G., Maes, M., 2017. Interactions of tryptophan and its catabolites with melatonin and the alpha 7 nicotinic receptor in central nervous system and psychiatric disorders: role of the aryl hydrocarbon receptor and direct mitochondria regulation. Int. J. Tryptophan Res. 10 1178646917691738.

Dantzer, R., O'Connor, J.C., Lawson, M.A., Kelley, K.W., 2011. Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinology 36, 426–436.

de Heredia, F.P., Gómez-Martínez, S., Marcos, A., 2012. Obesity, inflammation and the immune system. Proc. Nutr. Soc. 71, 332–338.

Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.

Favennec, M., Hennart, B., Caiazzo, R., Leloire, A., Yengo, L., Verbanck, M., Arredouani, A., Marre, M., Pigeyre, M., Bessede, A., Guillemin, G.J., Chinetti, G., Staels, B., Pattou, F., Balkau, B., Allorge, D., Froguel, P., Poulain-Godefroy, O., 2016. The kynurenine pathway is activated in human obesity and shifted toward kynurenine

monooxygenase activation. Obesity 24, 2066–2074.
Femenia, T., Gomez-Galan, M., Lindskog, M., Magara, S., 2012. Dysfunctional hippocampal activity affects emotion and cognition in mood disorders. Brain Res. 1476, 58–70.
Georgin-Lavialle, S., Moura, D.S., Salvador, A., Chauvet-Gelinier, J.C., Launay, J.M., Damaj, G., Côté, F., Soucié, E., Chandesris, M.O., Barète, S., Grandpeix-Guyodo, C., Bachmeyer, C., Alyanakian, M.A., Aouba, A., Lortholary, O., Dubreuil, P., Teyssier, J.R., Trojak, B., Haffen, E., Vandel, P., Bonin, B., Hermine, O., Gaillard, R., 2016. Mast cells' involvement in inflammation pathways linked to depression: evidence in mastocytosis. Mol. Psychiat. 21, 1511.
Gold, A.B., Herrmann, N., Swardfager, W., Black, S.E., Aviv, R.I., Tennen, G., Kiss, A., Lanctôt, K.L., 2011. The relationship between indoleamine 2,3-dioxygenase activity and post-stroke cognitive impairment. J. Neuroinflamm. 8 (1), 17.
Halvorsen, M., Waterloo, K., Sundet, K., Eisemann, M., Wang, C.E., 2011. Verbal learning and memory in depression: a 9-year follow-up study. Psychiat. Res. 188, 350.
Heisler, J.M., O'Connor, J.C., 2015. Indoleamine 2,3-dioxygenase-dependent neurotoxic kynurenine metabolism mediates inflammation-induced deficit in recognition memory. Brain Behav. Immun. 50, 115–124.
Hu, L.J., Li, X.F., Hu, J.Q., Ni, X.J., Lu, H.Y., Wang, J.J., Huang, X.N., Lin, C.X., Shang, D.W., Wen, Y.G., 2017. A simple HPLC–MS/MS method for determination of tryptophan, Kynurenine and kynurenic acid in human serum and its potential for monitoring antidepressant therapy. J. Anal. Toxicol. 41.
Iverson, G.L., Brooks, B.L., Langenecker, S.A., Young, A.H., 2011. Identifying a cognitive impairment subgroup in adults with mood disorders. J. Affect. Disord. 132, 360–367.
Jeon, S.W., Kim, Y.K., 2017. Inflammation-induced depression: its pathophysiology and therapeutic implications. J. Neuroimmunol. 313, 92–98.
Kessler, R.C., Bromet, E.J., 2013a. The epidemiology of depression across cultures. Annu. Rev. Public Health 34, 119–138.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. BMC Complement. Altern. Med. 14 422-422.
Kessler, U., Schoeyen, H.K., Andreassen, O.A., Eide, G.E., Hammar, Å., Malt, U.F., Oedegaard, K.J., Morken, G., Sundet, K., Vaaler, A.E., 2013b. Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression. BMC Psychiatr. 13, 105.
Kessler, U., Schoeyen, H.K., Andreassen, O.A., Eide, G.E., Malt, U.F., Oedegaard, K.J., Morken, G., Sundet, K., Vaaler, A.E., 2014. The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. J. Clin. Psychiat. 75, 1306–1313.
Klein, S.L., 2012. Immune cells have sex and so should journal articles. Endocrinology 153, 2544–2550.
Klein, S.L., Jedlicka, A., Pekosz, A., 2010. The Xs and Y of immune responses to viral vaccines. Lancet Infect. Dis. 10 (5), 338–349.
Krishnadas, R., Harrison, N.A., 2016. Depression phenotype, inflammation, and the brain: implications for future research. Psychosom. Med. 78, 384.
Marianne, H., Ragnhild, S.H., Ingvild, N.M., Kjetil, S., Martin, E., Knut, W., 2012. Cognitive function in unipolar major depression: a comparison of currently depressed, previously depressed, and never depressed individuals. J. Clin. Exp. Neuropsyc. 34, 782–790.
Martin, L.A., Neighbors, H.W., Griffith, D.M., 2013. Symptoms of depression in men vs women. JAMA Psychiat. 70, 1100–1106.
Mcclintock, S.M., Husain, M.M., Greer, T.L., Cullum, C.M., 2010. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. Neuropsychology 24, 9–34.
Mcdermott, L.M., Ebmeier, K.P., 2009. A meta-analysis of depression severity and cognitive function. J. Affect. Disord. 119, 1–8.
Mcintyre, R.S., Cha, D.S., Soczynska, J.K., Woldeyohannes, H.O., Gallaugher, L.A., Kudlow, P., Alsuwaidan, M., Baskaran, A., 2013. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress. Anxiety 30, 515–527.
Meier, T.B., Drevets, W.C., Wurfel, B.E., Ford, B.N., Morris, H.M., Victor, T.A., Bodurka, J., Teague, T.K., Dantzer, R., Savitz, J., 2016. Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. Brain Behav. Immun. 53, 39–48.
Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141.
Miura, H., Ando, Y., Noda, Y., Isobe, K., Ozaki, N., 2011. Long-lasting effects of inescapable-predator stress on brain tryptophan metabolism and the behavior of juvenile mice. Stress 14, 262–272.
Naismith, S.L., Hickie, I.B., Turner, K., Little, C.L., Winter, V., Ward, P.B., Wilhelm, K., Mitchell, P., Parker, G., 2003. Neuropsychological performance in patients with depression is associated with clinical, etiological and genetic risk factors. J. Clin. Exp. Neuropsyc. 25, 866.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese 3rd, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiat. 165, 203–213.
O'Connor, J.C., Lawson, M.A., André, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R., 2009. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol. Psychiat. 14, 511–522.
O'Connor, J.C., Salazar, A., Gonzalez-Rivera, B.L., Redus, L., Parrott, J.M., 2012. Indoleamine 2,3-dioxygenase mediates anhedonia and anxiety-like behaviors caused by peripheral lipopolysaccharide immune challenge. Horm. Behav. 26, 202–209.
O'Mahony, S.M., Clarke, G., Borre, Y.E., Dinan, T.G., Cryan, J.F., 2015. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav. Brain Res. 277, 32–48.
Ogyu, K., Kubo, K., Noda, Y., Iwata, Y., Tsugawa, S., Omura, Y., Wada, M., Tarumi, R., Plitman, E., Moriguchi, S., 2018. Kynurenine pathway in depression: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 90.
Platzer, M., Dalkner, N., Fellendorf, F.T., Birner, A., Bengesser, S.A., Queissner, R., Kainzbauer, N., Pilz, R., Herzog-Eberhard, S., Hamm, C., Hörmanseder, C., Maget, A., Rauch, P., Mangge, H., Fuchs, D., Zelzer, S., Schütze, G., Moll, N., Schwarz, M.J., Mansur, R.B., McIntyre, R.S., Reininghaus, E.Z., 2017. Tryptophan breakdown and cognition in bipolar disorder. Psychoneuroendocrinology 81, 144.
Raison, C.L., Dantzer, R., Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., Miller, A.H., 2009. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. Mol. Psychiat. 15, 393–403.
Reppermund, S., Ising, M., Lucae, S., Zihl, J., 2009. Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. Psychol. Med. 39, 603–614.
Savitz, J., Drevets, W.C., Wurfel, B.E., Ford, B.N., Bellgowan, P.S., Victor, T.A., Bodurka, J., Teague, T.K., Dantzer, R., 2015a. Reduction of kynurenic acid to quinolinic acid ratio in both the depressed and remitted phases of major depressive disorder. Brain Behav. Immun. 46, 55–59.
Savitz, J., Drevets, W.C., Smith, C.M., Victor, T.A., Wurfel, B.E., Bellgowan, P.S., Bodurka, J., Teague, T.K., Dantzer, R., 2015b. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. Neuropsychopharmacology 40, 463–471.
Savitz, J., Dantzer, R., Wurfel, B.E., Ford, B.N., Bodurka, J., Bellgowan, P.S., Teague, T.K., Drevets, W.C., 2015c. Neuroprotective kynurenine metabolite indices are abnormally reduced and positively associated with hippocampal and amygdalar volume in bipolar disorder. Psychoneuroendocrinology 52, 200–211.
Schwarcz, R., Guidetti, P., Sathyasaikumar, K.V., Muchowski, P.J., 2010. Of mice, rats and men: revisiting the quinolinic acid hypothesis of Huntington's disease. Prog. Neurobiol. 90, 230–245.
Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci. 13, 465–477.
Sramek, J.J., Murphy, M.F., Cutler, N.R., 2016. Sex differences in the psychopharmacological treatment of depression. Dialogues Clin. Neurosci. 18, 447–457.
Ting, K.K., Brew, B.J., Guillemin, G.J., 2009. Effect of quinolinic acid on human astrocytes morphology and functions: implications in Alzheimer's disease. J. Neuroinflamm. 6, 36.
Tobinick, E.L., Gross, H., 2008. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. J. Neuroinflamm. 5 (2).
Waclawiková, B., El Aidy, S., 2018. Role of microbiota and tryptophan metabolites in the remote effect of intestinal inflammation on brain and depression. Pharmaceuticals (Basel) 25 (3), 11.
Widner, B., Leblhuber, F., Walli, J., Tilz, G.P., Demel, U., Fuchs, D., 2000. Tryptophan degradation and immune activation in Alzheimer's disease. J. Neural. Transm (Vienna) 107, 343–353.
Wonodi, I., Mcmahon, R.P., Krishna, N., Mitchell, B.D., Liu, J., Glassman, M., Hong, L.E., Gold, J.M., 2014. Influence of kynurenine 3-monooxygenase (KMO) gene polymorphism on cognitive function in schizophrenia. Schizophr. Res. 160, 80.