European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-022-01406-8

ORIGINAL PAPER

Disturbance of neurotransmitter metabolism in drug-naïve, first-episode major depressive disorder: a comparative study on adult and adolescent cohorts

Liwei Wang[1,2] · Ping Yang[3] · Chao Yang[4] · Dong Yang[3] · Xiangxin Wu[1,2] · Ting Cao[1,2] · Cuirong Zeng[1,2] · Qian Chen[1,2] · Shuangyang Zhang[1,2] · Zhenyu Zhu[1,2] · Shimeng Jiao[1,2] · Hualin Cai[1,2]

Received: 30 October 2021 / Accepted: 25 March 2022

Abstract

Neurotransmitter metabolism plays a critical role in the pathophysiology of major depressive disorder (MDD). However, whether the neurotransmitter metabolism in adolescent MDD is differentiated from adult MDD is still elusive. In the current study, plasma concentrations of monoamine and amino acid neurotransmitters as well as their metabolites, including tryptophan (TRP), kynurenine (KYN), kynurenic acid (KYNA), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), norepinephrine (NE), vanillylmandelic acid (VMA), 3-methoxy-4-hydroxyphenylglycol (MHPG), glutamine (GLN), glutamate (GLU) and gamma-aminobutyric acid (GABA), were measured and compared in two cohorts of subjects (adult cohort: 31 first-episode MDD vs. 35 healthy controls; adolescent cohort: 33 first-episode MDD vs. 30 healthy controls). To assess the effects of antidepressant treatment, we also analyzed the concentrations of these indexes pre- and post-treatment in adult and adolescent cohorts. At baseline, the deficits of neurotransmitter metabolism in adult MDD were manifested in all the neurotransmitter systems. In contrast, for adolescent MDD, the dysregulation of neurotransmission was mainly indicated in the catecholaminergic systems. After antidepressant treatment, adult MDD showed increased TRP, KYN, KYNA and GLU levels, together with decreased levels of 5-HIAA and DOPAC. Adolescent MDD illustrated an increased level of 5-HT and decreased levels of TRP and GABA. The improvements of Hamilton total scores correlated with the changes in plasma TRP and the turnover of KYN/TRP after treatment in all MDD patients. However, these correlations were only manifested in the adult MDD rather than in adolescent MDD patients. The findings highlight the shared and distinguished neurotransmitter pathways in MDD and emphasize the different antidepressant responses between adults and adolescents. Potentially, the neurotransmitters above could serve as diagnostic biomarkers and provide a novel pharmacological treatment strategy for MDD.

Keywords Major depressive disorder · Adolescent · Neurotransmitter · First episode · Tryptophan

Introduction

Depression, also known as major depressive disorder (MDD) or clinical depression, is a mood disorder causing a persistent feeling of sadness and loss of interest. MDD is a very common psychiatric disorder and is among the leading contributors of disability and social burden worldwide [1, 2]. Despite a plethora of studies exploring neurobiological mechanisms of depression in the last decades, our understanding of its pathophysiology is still rudimentary. Till now, neurotransmitter deficiency, genetic, environmental, immunologic, endocrine factors and neurogenesis have been proposed as mechanisms that explain different perspectives for the pathophysiology of depression [3].

Liwei Wang and Ping Yang contributed equally to this work.

✉ Hualin Cai
hualincai@csu.edu.cn

1 Department of Pharmacy, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China

2 Institute of Clinical Pharmacy, Central South University, Changsha 410011, Hunan, China

3 Department of Psychiatry, The Second People's Hospital of Hunan Province, Changsha 410007, Hunan, China

4 Department of Child Psychology, Xinjiang Mental Health Center and Urumqi Fourth People's Hospital, Urumqi 830000, Xinjiang, China

Published online: 11 April 2022

Currently, growing evidence indicates that disturbed metabolisms of neurotransmitters in the brain are intimately involved in the pathogenesis of depression [4–6]. A previous study reported that serotonin (5-HT), dopamine (DA) and norepinephrine (NE) could influence the brain circuits associated with motivation, mood regulation, cognitive performance and response to psychological stress in depression [4]. Thus, it has been postulated that the etiological origin of depression is a deficit in monoaminergic neurotransmission (serotonergic, dopaminergic and noradrenergic). Moreover, based on the monoaminergic hypothesis of depression, monoamine reuptake inhibitors have been developed as antidepressants [7]. Specifically, ample studies show that a 5-HT deficiency may influence mood in a way that leads to depression and the role of 5-HT in the antidepressant response has been highlighted [5, 8]. In addition, glutamate (GLU) and gamma-aminobutyric acid (GABA) as the major excitatory and inhibitory neurotransmitters, respectively, their changes causing the excitatory/inhibitory (E/I) imbalance during the brain development may result in abnormalities in the GABAergic pathway, which contribute to the recurrences and refractoriness of MDD at a later stage [6]. It is widely believed that these neurotransmitter systems are dynamically linked and play a pivotal role in depression; however, there is no practical way to measure the levels of these neurotransmitters and their metabolites in the living brain [9, 10]. Although with some inconsistencies, accumulating evidence has suggested that peripheral neurotransmitters can reflect corresponding alterations in the central nervous systems (CNS), thus potentially serving as a surrogate source to explore the potential mechanisms underlying MDD [9, 11, 12].

Depression can occur at any age, but often begins in adulthood. Notably, early onset of depression in children and adolescents is increasingly common [13–15]. Depressed adolescents are at high risks of school failure, social isolation, promiscuity, "self-medication", and even suicide, urging us to pay more attention to adolescent depression [16–18]. It is well established that there are symptom profile and treatment response differences between adolescent and adult depression. As to the clinical presentation, findings suggest that vegetative symptoms are a common presentation in adolescent depression, whereas anhedonia/loss of interest and concentration difficulties were more common in adult depression [17]. Moreover, adult and adolescent depression may respond differently to antidepressant drugs, indicating that lower efficacy and more side effects were observed in adolescent MDD than in adult MDD [19]. However, the etiological mechanism of MDD, especially for adolescents, is still poorly understood. Interestingly, with a metabolomic approach, a recent study has revealed that the decreased tryptophan (TRP) in plasma is only observed in first-episode adult depression compared with healthy control, whereas there are no apparent changes of plasma TRP in adolescent depression versus control [12]. As well established, TRP and its metabolites (5-HT; 5-hydroxyindoleacetic acid, 5-HIAA; kynurenine, KYN; kynurenic acid, KYNA) and related neurotransmitters (DA; NE; glutamine, GLN; GABA) play crucial roles in physiological functions, and their imbalances are implicated in the pathology of depression [20, 21]. Therefore, there is an urgent need to explore further the differential roles of neurotransmitter metabolism and discrepant response to antidepressant treatment between adult and adolescent MDD.

Consequently, the present study is considered hypothesis generating and aims to investigate the TRP and related neurotransmitters as well as their metabolites in the circulating blood of first-episode antidepressant-naïve MDD patients. Systematically, the baseline neurotransmitter metabolic profiles and related responses to antidepressant treatment were compared between two independent cohorts of adult and adolescent MDD, with the aim of enriching our understanding of the pathophysiology of depression.

Materials and methods

Participants

A total of 129 participants (31 first-episode adult MDD, 35 healthy adults, 33 first-episode adolescent MDD and 30 healthy adolescents) were recruited in this study. The first-episode MDD patients of adults and adolescents were recruited from the Department of Psychiatry and Child Psychology of the Fourth People's Hospital of Urumqi (Urumqi, China). All healthy controls in the two cohorts were recruited from the physical examination center of the Fourth People's Hospital of Urumqi (Urumqi, China) between May 2019 and May 2020. MDD patients were diagnosed following the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and the severity of symptoms was assessed according to the Hamilton Depression Scale (24-Items) (HAMD-24) by trained psychiatrists [22]. Adult MDD patients were excluded if: (1) patients had a history of physical or other mental disorders; (2) patients had illicit drug or alcohol abuse; (3) patients were actively suicidal or considered a high suicide risk; (4) female patients in pregnancy, nursing, breast-feeding or menstruation. Adolescent MDD patients should be enrolled without comorbid physical, neurological, or psychiatric disorders, drug or alcohol dependence. Healthy controls without pre-existing psychiatric disorders, chronic diseases or mental retardation were recruited in this study. This study was approved by the Ethical Committee of the Fourth People's Hospital of Urumqi. All subjects or their legal guardians were told the corresponding details about the study's procedures and

provided informed consent. The sample collections and pre-treatments were carried out uniformly to avoid any impact from the disparity between the two cohorts by strictly following the protocol.

Antidepressant treatment for adult and adolescent MDD patients

The regimens primarily prescribed were selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and second-generation antipsychotics (SGAs), either in monotherapy or combination treatment for adult and adolescent MDD patients. The detailed information of antidepressants used during hospitalization for adult and adolescent MDD is presented in Supplementary Tables S1 and S2.

Determination of plasma neurotransmitters

Blood samples were collected at 7 a.m. after 12-h fasting at week 0 and week 4 and centrifuged (3000 rpm, 4 °C) for 5 min immediately. Then the plasma samples were separated and stored at − 80 °C for subsequent biochemical analysis. In this study, the concentrations of TRP, KYN, KYNA, 5-HT, 5-HIAA, DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), NE, vanillylmandelic acid (VMA), 3-methoxy-4-hydroxyphenylglycol (MHPG), GLN, GLU and GABA were examined by an LC–MS/MS method previously reported with some modifications [23, 24].

Briefly, 300 µL of plasma was mixed with 900 µL pure acetonitrile (cooled to -20 °C) and the mixture was vortexed for 3 min and then centrifuged (15,000*g*, 4 °C) for 15 min. Then, 1 mL supernatant was added to an Eppendorf tube and placed at -80 °C for 2 h, and later it was evaporated to dryness by using a vacuum freeze dryer. After that, a dansyl derivatization process was applied. After evaporation, the sample residue was mixed with 100 µL of dansyl chloride (4 mg/mL) in a new Eppendorf tube and vortexed for 2 min. Then, 100 µL of buffer solution ($NaHCO_3$:Na_2CO_3, pH = 11.0) was added to the tubes and the mixture was vortexed for 2 min and subsequently incubated at 60 °C for 15 min, avoiding light. After the derivatization, the pH of the mixture was adjusted to approximately 7.0 by adding 5 µL of 15% formic acid–water solution. The mixture was then centrifuged at 4 °C for 3 min at 15,000 g and 5 µL of the resulting supernatant was used for LC–MS/MS analysis.

Statistical analysis

Baseline levels of plasma neurotransmitters and related turnovers, age and BMI were analyzed by Mann–Whitney *U* test and the sex composition was analyzed by Chi-squared test between MDD patients and healthy controls. Wilcoxon matched-pairs signed-ranks test was used to analyze the concentration of each neurotransmitter and the turnover of neurotransmitters in each system between pre-treatment and post-treatment status of MDD. The correlations between neurotransmitters and symptomatology were analyzed by partial correlation analysis, which analyzed the change of Hamilton total score (S_{0w}–S_{4w}) and the change of neurotransmitter level (NT_{0w}–NT_{4w}), with age, fluoxetine-equivalent dose of antidepressants and chlorpromazine-equivalent dose of antipsychotics as the controlling factors. Owing to the abnormal distribution of numerical data and the small sample size, Bonferroni correction was applied for multiple comparisons. P value less than 0.05/14 = 0.0036 was considered significant in neurotransmitter data, while a P value less than 0.05/13 = 0.0038 was statistically significant in turnover comparisons. Statistical analyses were performed using SPSS (version 26.0, IBM, Armonk, NY, USA).

Results

Demographic and clinical characteristics

The demographic characteristics for patients with MDD and healthy controls are summarized in Supplementary Table S3. There were no significant differences in age, sex and BMI between patients and healthy controls in the adult or adolescent MDD cohorts. The fluoxetine-equivalent dosages were 29.71 ± 19.07 for adult MDD patients, and 22.44 ± 21.58 for adolescent MDD patients. The chlorpromazine-equivalent dosages were 129.15 ± 140.60 for adult MDD patients, and 136.44 ± 125.61 for adolescent MDD patients. There was no significant difference in the equivalent dosages of SSRIs ($U = 441.5$, $P = 0.344$) and antipsychotics ($U = 480.0$, $P = 0.673$) between adult and adolescent MDD.

The onset of adult MDD relies on the changes in the TRPergic metabolic pathway

Depressed patients vs. healthy controls

The decreased TRP has been identified as a critical difference between first-episode adult and adolescent MDD, but the alterations in downstream pathways of TRP are unknown [12]. To uncover how the TRP metabolic pathway manifested differently in the early stage of adult and adolescent MDD, TRP, KYN, KYNA, 5-HT and 5-HIAA were examined. The decreased TRP ($U = 210.0$, $P < 0.0001$; Fig. 1A) was only observed in adult instead of adolescent MDD relative to healthy controls. Although 5-HT was not changed in either adult or adolescent MDD compared with controls, its downstream metabolite 5-HIAA ($U = 112.0$,

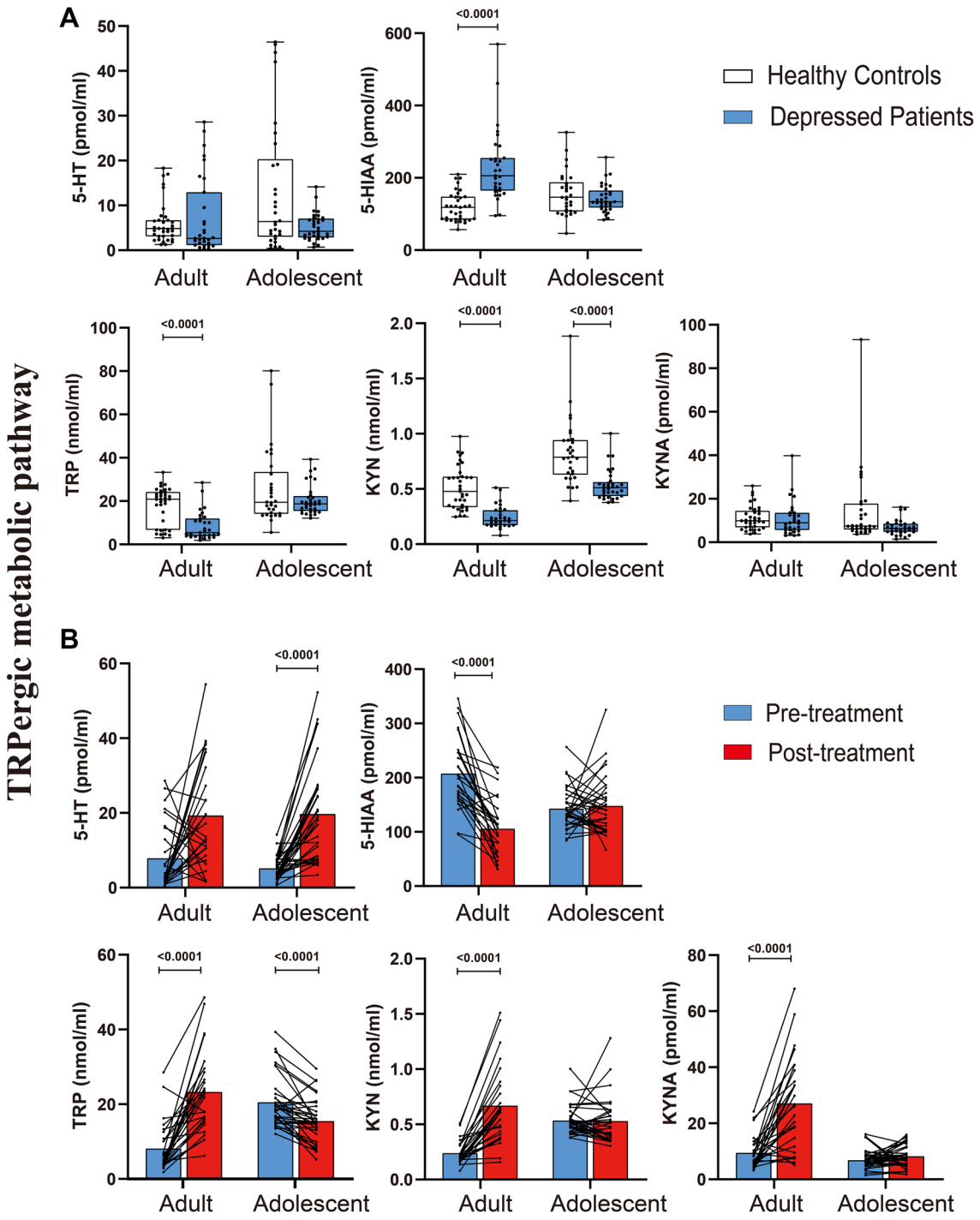

Fig. 1 Identified differential changes of neurotransmitters between first-episode MDD and healthy controls and between post-treatment and pre-treatment in tryptophanergic metabolic pathway. **A** Depressed patients vs. healthy controls in adult and adolescent cohorts. **B** Post-treatment vs. pre-treatment in adult and adolescent cohorts. Mann–Whitney *U* test was applied for comparing depressed patients and healthy controls, Wilcoxon matched-pairs signed-ranks test was applied for comparing post-treatment and pre-treatment levels ($n=31$ for adult MDD, $n=33$ for adolescent MDD, $n=35$ for adult healthy controls, $n=30$ for adolescent healthy controls). P value less than $0.05/14=0.0036$ was considered significant

$P<0.0001$; Fig. 1A) was also elevated in adult MDD patients. In addition, KYN significantly decreased in both adult ($U=91.5$, $P<0.0001$; Fig. 1A) and adolescent MDD ($U=143.5$, $P<0.0001$; Fig. 1A). Furthermore, the analyses of neurotransmitters turnover changes revealed that KYNA/KYN ($U=244.5$, $P<0.0001$; Table 1) and 5-HIAA/5-HT

Table 1 The turnover of neurotransmitters between depressed patients and healthy controls in the tryptophanergic, dopaminergic, noradrenergic and GABAergic systems

	Adult[a]		*U*	p-value[b]	Adolescent[a]		*U*	p-value[b]
	Control	Disease			Control	Disease		
1. Tryptophanergic system								
KYN + 5-HT/TRP	36.85 ± 20.71	43.38 ± 28.88	466.0	0.3311	43.15 ± 27.26	28.26 ± 9.27	308.0	0.0096
KYN/TRP	36.19 ± 19.99	41.89 ± 27.53	473.0	0.3778	42.44 ± 27.06	27.97 ± 9.21	315.0	0.0128
KYNA/KYN	0.02 ± 0.01	0.05 ± 0.04	244.5	**< 0.0001**	0.02 ± 0.03	0.01 ± 0.01	468.0	0.7141
5-HT/TRP	0.65 ± 1.11	1.49 ± 2.51	446.0	0.2178	0.71 ± 0.90	0.29 ± 0.20	419.5	0.3026
5-HIAA/5-HT	30.08 ± 22.45	144.60 ± 199.60	298.0	**0.0014**	44.97 ± 58.55	40.25 ± 35.65	393.0	0.1635
2. Dopaminergic system								
DOPAC + HVA/DA	258.00 ± 104.00	156.30 ± 152.80	283.0	**0.0007**	135.20 ± 72.94	191.30 ± 85.38	283.0	**0.0032**
DOPAC/DA	20.47 ± 13.51	24.23 ± 18.07	454.0	0.2601	26.44 ± 14.01	22.63 ± 14.60	361.0	0.0659
HVA/DA	237.60 ± 97.33	132.10 ± 143.90	244.0	**< 0.0001**	108.70 ± 63.59	168.70 ± 79.61	265.0	**0.0013**
3. Noradrenergic system								
VMA + MHPG/NE	99.11 ± 183.40	71.72 ± 91.40	393.0	0.0522	42.70 ± 56.22	17.91 ± 15.22	228.0	**0.0002**
VMA/NE	85.07 ± 160.4	60.26 ± 75.28	404.0	0.0761	31.61 ± 44.80	22.56 ± 42.73	276.0	**0.0023**
MHPG/NE	14.04 ± 23.72	11.46 ± 16.85	431.0	0.1548	11.08 ± 13.74	5.48 ± 9.54	183.0	**< 0.0001**
4. GABAergic system								
GABA/GLU	46.03 ± 19.73	94.06 ± 87.52	372.0	0.0280	31.95 ± 26.97	28.83 ± 15.56	493.0	0.9836
GLU + GABA/GLN	42.16 ± 21.07	35.86 ± 19.85	442.0	0.2003	77.53 ± 43.05	99.25 ± 46.57	358.0	0.0600

After the Bonferroni correction, significant p-values less than 0.05/13 = 0.0038 are given in bold

[a]The data was showed as mean ± standard deviation (SD)

[b]Analyzed by Mann–Whitney *U* test

($U = 298.0$, $P = 0.0014$; Table 1) were higher in adult MDD versus healthy controls.

Post-treatment vs. pre-treatment

In response to 4-week treatment, the level of TRP was increased in adult MDD ($W = 366.0$, $P < 0.0001$; Fig. 1B), whereas an opposite changing trend is shown in adolescent MDD ($W = -463.0$, $P < 0.0001$; Fig. 1B). Moreover, elevated 5-HT ($W = -372.0$, $P < 0.0001$; Fig. 1B) was found in post-treatment adolescent MDD, while post-treatment adult MDD just exhibited a marked decrease in 5-HIAA ($W = 545.0$, $P < 0.0001$; Fig. 1B). The metabolic difference was also seen for the KYN pathway between the two cohorts of MDD: post-treatment adult MDD showed a significantly increasing trend in KYN ($W = 378.0$, $P < 0.0001$; Fig. 1B) and KYNA ($W = 340.0$, $P < 0.0001$; Fig. 1B), but no alteration was seen in post-treatment adolescent MDD compared to the pre-treatment levels. When analyzing the difference of changes in neurotransmitters turnover across MDD subgroups, both KYN/TRP ($W = 375.0$, $P = 0.0005$; Supplementary Table S4) and KYN + 5-HT/TRP ($W = 411.0$, $P = 0.0001$; Supplementary Table S4) were significantly increased, whereas 5-HT/TRP ($W = 555.0$, $P < 0.001$; Supplementary Table S4) was only decreased in post-treatment adolescent MDD patients. For both adult and adolescent MDD cohorts, significantly lower levels of 5-HIAA/5-HT was observed in post-treatment versus pre-treatment ($W = -300.0$, $P = 0.0001$; $W = -525.0$, $P < 0.0001$; Supplementary Table S4).

Differentially expressed catecholaminergic metabolic pathway between adults and adolescents with MDD

Depressed patients vs. healthy controls

In catecholaminergic metabolic pathway, adult MDD showed significant changes in concentration comparisons. However, the neurotransmitter turnover changes were more common in adolescent depression than in healthy controls. Specifically, baseline levels of NE ($U = 235.5$, $P < 0.0001$; Fig. 2A), VMA ($U = 94.0$, $P < 0.0001$; Fig. 2A), and MHGP ($U = 124.0$, $P < 0.0001$; Fig. 2A) were significantly higher in adult MDD, while adolescent MDD only showed a decreased MHPG level ($U = 251.0$, $P = 0.0006$; Fig. 2A) in the NE metabolic pathway. In the DA metabolic pathway, the level of DOPAC ($U = 274.0$, $P = 0.0004$; Fig. 2A) was higher, whereas the HVA level ($U = 184$, $P < 0.0001$; Fig. 2A) was lower in adult MDD, but with no changes in adolescent MDD compared to healthy controls. In ratio analyses, adolescents with MDD showed lower MHPG/

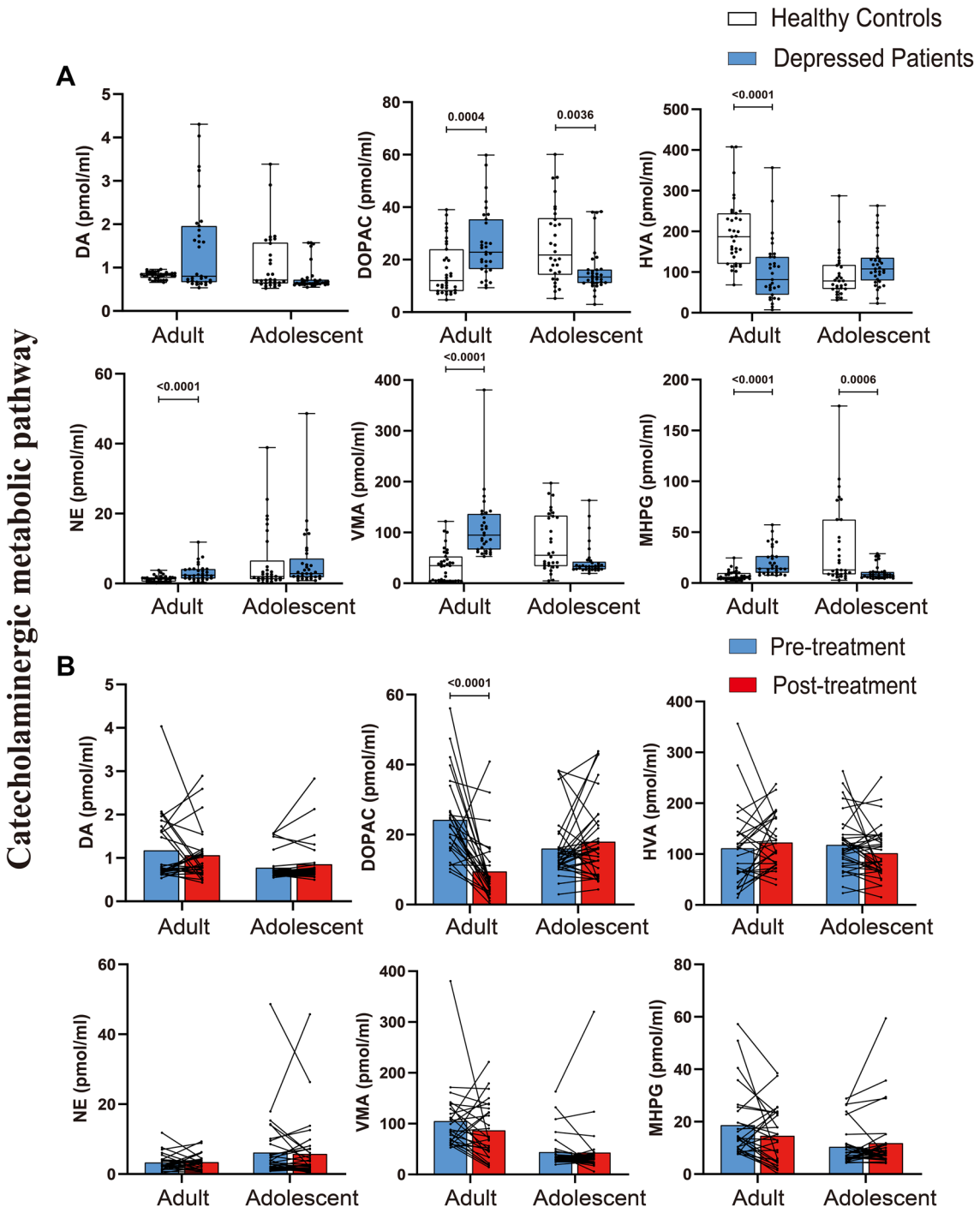

Fig. 2 Identified differential changes of neurotransmitters between first-episode MDD and healthy controls and between post-treatment and pre-treatment in catecholaminergic metabolic pathway. **A** Depressed patients vs. healthy controls in adult and adolescent cohorts. **B** Post-treatment vs. pre-treatment in adult and adolescent cohorts. Mann–Whitney *U* test was applied for comparing depressed patients and healthy controls, Wilcoxon matched-pairs signed-ranks test was applied for comparing post-treatment and pre-treatment levels ($n=31$ for adult MDD, $n=33$ for adolescent MDD, $n=35$ for healthy adults, $n=30$ for healthy adolescents). The significance level was set at $P<0.05/14=0.0036$

NE ($U=183.0$, $P<0.0001$; Table 1) and VMA + MHPG/NE ($U=228.0$, $P=0.0002$; Table 1) than healthy controls. However, all ratio indicators above have not changed in adult MDD compared to healthy controls. Notably, the ratio of HVA/DA and DOPAC + HVA/DA were decreased in adult MDD ($U=244.0$, $P<0.0001$; $U=283.0$, $P=0.0007$;

Table 1), but opposite trends were observed in adolescent MDD ($U = 265.0$, $P = 0013$; $U = 283.0$, $P = 0.0032$; Table 1) when compared with healthy controls.

Post-treatment vs. pre-treatment

The catecholamine metabolic pathway in adolescent MDD was not sensitive to antidepressant treatment, since no significant changes in concentration or neurotransmitters turnover were observed. However, adult MDD presented lower DOPAC ($W = -326.0$, $P < 0.0001$; Fig. 2B) level and DOPAC/DA ($W = -302.0$, $P < 0.0001$; Supplementary Table S4) following the 4-week antidepressant treatment.

Different responses to antidepressant treatment in the GABAergic metabolic pathway

Depressed patients vs. healthy controls

Notably, GLN, GLU and GABA showed no significant changes at baseline of both adult and adolescent MDD compared to healthy controls. Moreover, no significant changes emerged in comparing the related neurotransmitter turnover between MDD and healthy controls in the adult or adolescent cohort (Fig. 3A and Table 1).

Post-treatment vs. pre-treatment

After the 4-week treatment, GLN did not respond to antidepressant treatment either in adult ($W = 115.0$, $P = 0.0901$; Fig. 3B) or adolescent MDD ($W = -47.0$, $P = 0.7656$; Fig. 3B) patients. Interestingly, the antidepressant treatment

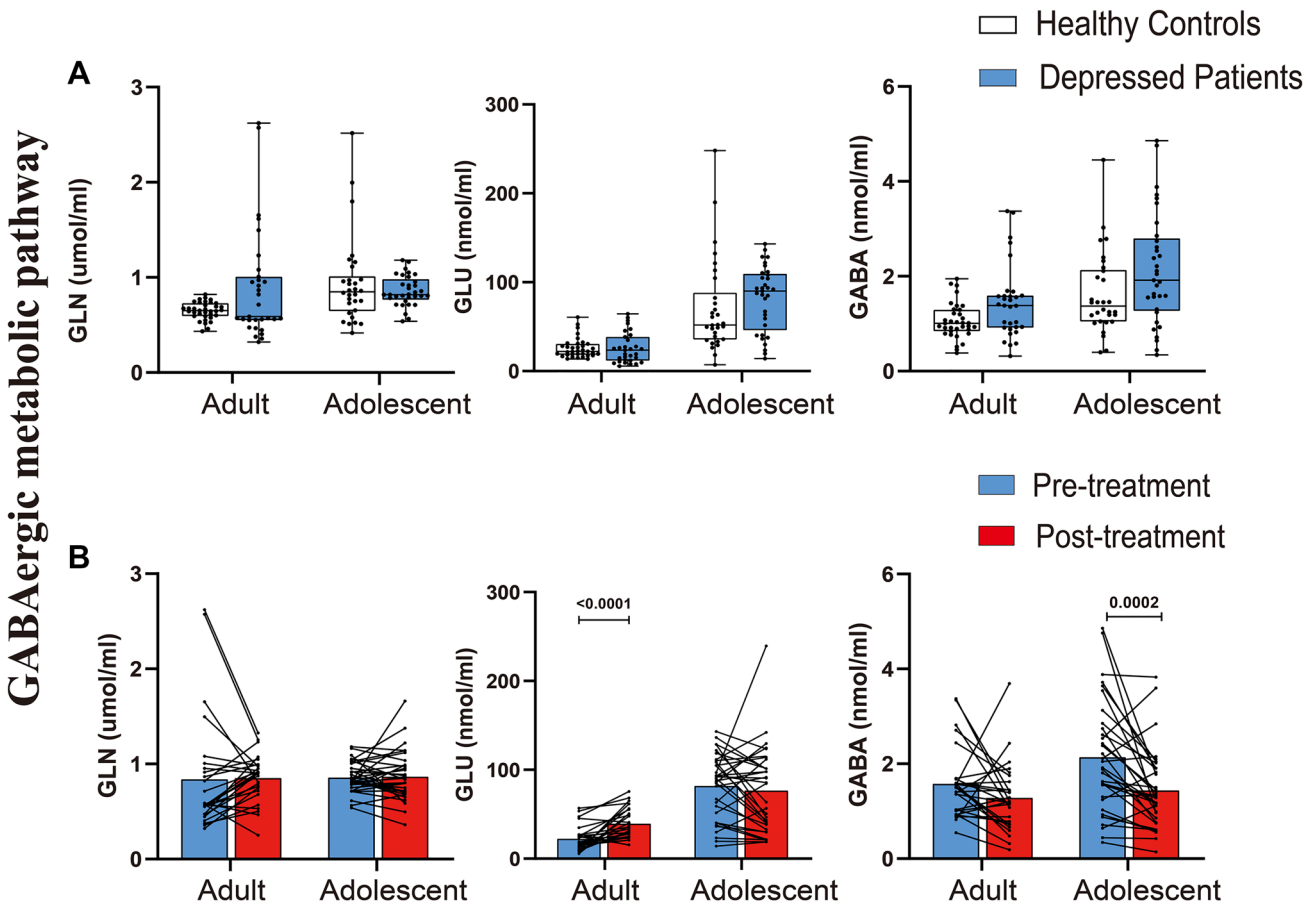

Fig. 3 Identified differential changes of neurotransmitters between first-episode MDD and healthy controls and between post-treatment and pre-treatment in GABAergic metabolic pathway. **A** Depressed patients vs. healthy controls in adult and adolescent cohorts. **B** Post-treatment vs. pre-treatment in adult and adolescent cohorts. Mann–Whitney *U* test was applied for comparing depressed patients and healthy controls, Wilcoxon matched-pairs signed-ranks test was applied for comparing post-treatment and pre-treatment levels ($n = 31$ for adult depression, $n = 33$ for adolescent depression, $n = 35$ for healthy adults, $n = 30$ for healthy adolescents). Significance value was presented when it was less than $P < 0.05/14 = 0.0036$

exerted different effects on the GABAergic system, manifested as elevated GLU levels ($W = 318.0$, $P < 0.0001$, Fig. 3B) in adult MDD and decreased GABA ($W = -401.0$, $P < 0.0001$, Fig. 3B) levels in adolescent MDD, respectively. Moreover, we also found a reduced turnover of GABA/GLU ($W = -316.0$, $P < 0.0001$, Supplementary Table S4) in post-treatment adult MDD.

Hamilton total scores positively correlated with the plasma tryptophan levels and negatively correlated with KYN/TRP in adult MDD

The partial correlation analyses showed that the reduction of Hamilton total scores was positively correlated with increase of plasma TRP levels ($r = 0.347$, $P = 0.006$) after overall treatment in MDD patients. Interestingly, this correlation only manifested in the adult MDD cohort ($r = 0.385$, $P = 0.043$) rather than in adolescent MDD cohort ($r = 0.195$, $P = 0.302$). Moreover, a negative correlation between HAMD total score reduction and KYN/TRP changes was found in total MDD patients ($r = -0.354$, $P = 0.005$) and adult MDD cohort ($r = -0.427$, $P = 0.024$), but not adolescent MDD cohort ($r = -0.200$, $P = 0.290$). No other associations between the changes in neurotransmitter or turnover and the changes in Hamilton total score approached significance (Fig. 4).

All the above-mentioned significant findings are summarized in Supplementary Table S5 for the sake of a better understanding of the results.

Discussion

Our study revealed that the neurotransmitters have different baseline levels and diverse responses to antidepressants in TRP, DA, NE and GABA metabolic pathways between adult and adolescent MDD. In the TRPergic pathway, we confirmed that decreased TRP was only observed in first-episode adult depression compared with healthy controls. Further exploration showed that the correlation between the

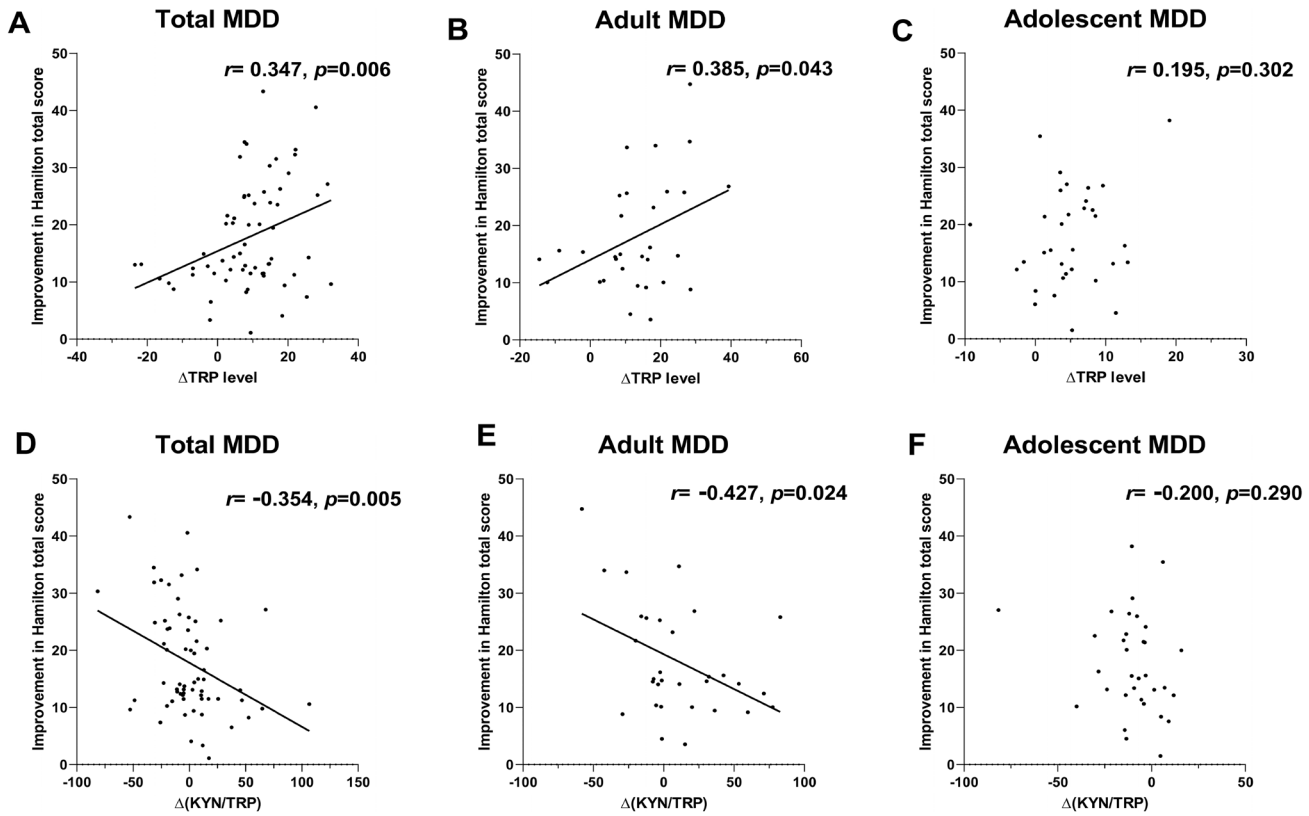

Fig. 4 The correlation between the plasma neurotransmitter level changes and the Hamilton total score changes. **A**–**C** The correlation between the changes of TRP concentration and the improvement in Hamilton total score in total MDD patients, adult MDD patients and adolescent MDD patients. **D**–**F** The correlation between the the changes of KYN/TRP level and the improvement in Hamilton total score in total MDD patients, adult MDD patients and adolescent MDD patients. The improvement in Hamilton total score, ΔTRP and Δ(KYN/TRP) was obtained by calculating their differences between week 0 and week 4. The correlation exploration was performed by partial correlation analysis controlling for age, fluoxetine-equivalent dose of antidepressants and chlorpromazine-equivalent dose of antipsychotics

improvement in Hamilton total scores and changes of TRP or turnover KYN/TRP were significant only in adult MDD after 4-week antidepressant treatment. For the catecholaminergic pathway, we found that the neurotransmitters are closely related to the pathophysiology of both cohorts of MDD, but less relevant to the treatment outcomes as it is almost not changed in response to the antidepressant treatment. In addition, comparisons of the GABAergic pathway revealed an increment of excitatory neurotransmitter GLU in post-treatment adult MDD, whereas a reduction of inhibitory neurotransmitter GABA was found in post-treatment adolescent MDD.

TRP metabolic pathway was considered central in the pathophysiology of MDD [25]. Our findings are consistent with the previous literature, where adults with MDD showed lower TRP than healthy controls [12]. The correlation between the improvement of Hamilton total score and the change of TRP was only found in adult MDD, suggesting that TRP was closely related with both the onset and recovery of MDD in adults rather than in adolescents. In addition, KYN was found to be decreased at baseline of both adult and adolescent MDD, which is in accordance with the previous study [26]. Interestingly, the imbalanced KYN metabolism thus can disturb the compositions of neuroprotective and neurotoxic metabolites, which help to maintain the activity of excitotoxic neuronal cells and the release of GLU via interacting with the N-methyl-D-aspartate (NMDA) receptors [11]. Emerging evidence suggests that NMDA receptor is the target for treating MDD, as its antagonist ketamine showed a rapid antidepressant effect [27]. Quinolinic acid (QA), a neurotoxic metabolite of KYN, could cause excitotoxic neuronal cell loss and convulsions and increase the generation of reactive oxygen species (ROS) via activating the NMDA receptor. KYNA, another metabolite of KYN, functions as NMDA receptor antagonists, which have a therapeutical effect in neurological disorders by reducing free radicals and modulating immune functions [11, 28]. As a downstream metabolite of TRP, 5-HT is lower in the hippocampus [29], serum [30], frontal cortex [31], and prefrontal cortex (PFC) [32], but not in the cingulate cortex [33] of the chronic unpredictable mild stress (CUMS) model. Yet, we only observed a non-significant decreasing trend in first-episode adult or adolescent MDD in our study. Besides, a lower level of 5-HT in plasma has been found in the association with MDD [34, 35] and its metabolite 5-HIAA is connected with suicidal behavior in humans [36–38]. In support, a post-mortem study has found that reduced 5-HIAA concentrations in cerebrospinal fluid (CSF) were closely related to attempted suicidal history in MDD [36]. It is consistent with the study in the periphery that confirmed that lower plasma 5-HIAA and TRP could manifest in suicide attempt patients compared to non-suicidal MDD and healthy controls [37, 38]. Notably, the neurotransmitter turnover analyses illustrated that 5-HIAA/5-HT and KYNA/KYN were elevated in first-episode adult MDD rather than adolescent MDD, suggesting imbalanced metabolisms of 5-HT and KYN are more prominent at a later stage of this disease. These differences indicate that the TRPergic system of first-episode adult MDD is more sensitive and more compromised than first-episode adolescent MDD, which may be attributed to the immaturity of the central serotonin system or the lower serotonin transporter binding in the brain regions during the adolescent period [39].

The brain contains vast numbers of serotonergic, dopaminergic and noradrenergic neurons, and the three neurotransmitter systems mutually interact. Serotonin innervates all brain areas and is the largest cohesive neurotransmitter system in the brain. In contrast, the dopaminergic system modulates reward and motivation functions, working memory and attention. The noradrenergic system plays a role in working memory processing and regulates behavior and attention [3]. As proposed in the monoamine hypothesis of depression, an increase in the levels of 5-HT (and also DA and NE) in the brain of depressed subjects should be accompanied by fewer depressive symptoms. Evidence suggests that SSRI treatment increasing the availability of 5-HT can stimulate 5-HT_{2A} receptors to enhance the release of NE, whereas stimulation of 5-HT_{1A} receptors in the medial prefrontal cortex could enhance the activity of the ventral tegmental area DA neurons, along with meso-cortical DA release [40]. Additionally, 5-HT_{2C} receptors play a role in the tonic regulation of ascending dopaminergic activity, which may also contribute to the effects of antidepressant drugs [41]. In accordance with these findings, our data indicate that the turnovers of serotonergic, dopaminergic and noradrenergic systems were decreased after antidepressant treatment, especially in adult MDD (Supplementary Table S4).

It is supported by a range of studies that DA and NE together play an important role in the mood regulation of MDD [40, 42]. The different symptoms in adult and adolescent MDD may be attributed to the different pathophysiological mechanisms underlying the catecholaminergic system of MDD [17]. In our study, the disturbance of the catecholamine system was evident in adult MDD, revealed by the higher levels of NE, VMA, MHPG and DOPAC, together with a lower HVA level. However, at the onset of adolescent MDD, the neurotransmitter turnover rate of DA showed an opposite situation to adult MDD. Higher ratios of HVA/DA and HVA + DOPAC/DA at the onset of adolescent MDD suggest that the metabolism of the dopaminergic system was hyperactive in adolescent MDD, whereas the dopamine metabolism was downregulated in adult MDD. Given the interactions between serotonergic, dopaminergic and noradrenergic, the serotonergic system may be able to modulate both dopaminergic and noradrenergic systems

via a receptor-mediated mechanism [4], which can partly explain the different catecholamine metabolism between adult and adolescent MDD.

Glutamate and Gaba were, respectively, regarded as the primary excitatory and inhibitory neurotransmitters in the brain. The ratio of GABA/GLU was suggested to reflect the E/I balance of neurotransmission systems and its disturbance may be associated with the pathophysiology of MDD [43]. Recently, a meta-analysis showed lower GABA in plasma and anterior cingulate cortex (ACC) in MDD [44], which was not replicated in our study. Nevertheless, inconsistent results in the GABAergic system have been reported in the CNS. A magnetic resonance spectroscopy (MRS) study used to determine the relevant neurotransmitters in CSF has revealed elevated GABA and decreased GLU availabilities in first-episode MDD patients [6]. Even without significance, an increasing GABA and GABA/GLU trend was only found in adult MDD, suggesting that E/I imbalance is not that obvious in adolescent MDD. This is explainable, since the evidence of previous studies indicated that brain functions, including E/I balance, can show different aspects during brain development [43].

Although the neurotransmitter metabolic profile of adult MDD differs from adolescent MDD, their disturbances of neurotransmitter metabolism may eventually lead to MDD pathophysiology through a shared pathway (Fig. 5). As shown in our study, the enhanced metabolism of the TRP pathway induced by the activated indoleamine-2,3-dioxygenase (IDO) [45] and the hyperactivity of DA metabolism [46] were considered to be responsible for the onset of adult MDD and adolescent MDD, respectively. KYN could be catabolized into two active metabolites: the neuroprotective KYNA and neurotoxicity QA [11]. In our study, the lower KYN and unchanged KYNA were indicated in both adult and adolescent MDD, suggesting that KYN is degraded into 3-hydroxykynurenine (3-HK) to a greater extent and then converted to QA. It has been reported that inflammation and oxidative stress interactions can influence the KYN metabolism [47]. The QA and 3-HK from the activated KYN metabolic pathway could also enforce oxidative stress [48, 49]. Meanwhile, the higher ratios of HVA/DA and DOPAC + HVA/DA in adolescent MDD suggest a higher metabolic turnover rate in this pathway, which results in more free radicals or ROS and promotes oxidative stress [50, 51]. Additionally, the energy and membrane fatty acid metabolism intimately related to neurotransmitter signaling could be modulated by oxidative stress and considered the pivotal components of MDD for a long time [52].

With regard to the antidepressant treatment, there is no significant difference in the equivalent dosages of SSRIs between adult and adolescent MDD (Supplementary Table S3). SSRIs, the kind of drugs that inhibit the reuptake of 5-HT, are recognized as the most common and effective antidepressants [53, 54], and in animal models of MDD, the juvenile rats have shown a different sensitivity to SSRIs in structural plasticity and serotonin synthesis of the brain compared to adult rats [55]. Interestingly, the metabolite 5-HT and its precursor TRP can predict the outcomes of antidepressant treatment, suggesting higher levels of TRP and 5-HT are positively correlated with the efficacy of the antidepressant treatment [56]. Our results showed a higher TRP in post-treatment adult depression, but a lower TRP in post-treatment adolescent depression relative to the pre-treatment level in this study. It may be one of the reasons why adolescents with MDD usually have a worse response when treated with SSRIs or other antidepressant drugs [57]. Meanwhile, the increase of DA and NE modulated by SSRIs could enhance the catecholaminergic transmission to alleviate depressive symptoms [58]. However, we failed to find these changes in the current study, which may be attributed to the confounding influence of the antipsychotics used for the patients. In addition, the decreased GABA in adult depression and the elevated GLU in adolescent depression were found after treatment. The opposite trends of these amino acid neurotransmitters in the two different cohorts may produce a similar excitatory effect on brain activity. Consistently, the increase of GLU and the decrease of GABA/GLU in the brain have reduced depressive symptoms in MDD patients [59].

There are several limitations to this study. Firstly, the small sample size may restrict the generalization of the findings. The results were adjusted for multiple testing by very conservative Bonferroni correction to screen out the most truly significant results, but at the same time may result in missing some meaningful indicators. Secondly, the neurotransmitters were tested in plasma, which may be controversial. Relatively more evidence supports the central–peripheral associations for monoamine neurotransmitters and their metabolites such as DA, DOPAC, HVA, 5-HT, 5-HIAA, KYN, KYNA, NE, VMA and MHPG, whereas conflicting reports indicate that peripheral amino acid neurotransmitter levels of TRP, GLN, GLU and GABA do not necessarily predict central alterations [10, 21]. Thirdly, QA, was not able to be analyzed in this study. This metabolite cannot be derivatized by dansyl chloride, since the dansylation procedure selects the molecules' primary amino, secondary amino, and phenolic hydroxyl groups. QA has none of these groups and thus cannot be determined by our established method. Fourthly, we recruited adult patients aged 19–30 years. However, patients over 30 years of age may have a different metabolic profile than younger patients.

In conclusion, our study has revealed that multiple neurotransmitter systems are involved in the onset of MDD and indicated shared and distinct neurotransmitter pathways in the pathogenesis of MDD between adults and adolescents. Further studies are warranted to elaborate these findings as

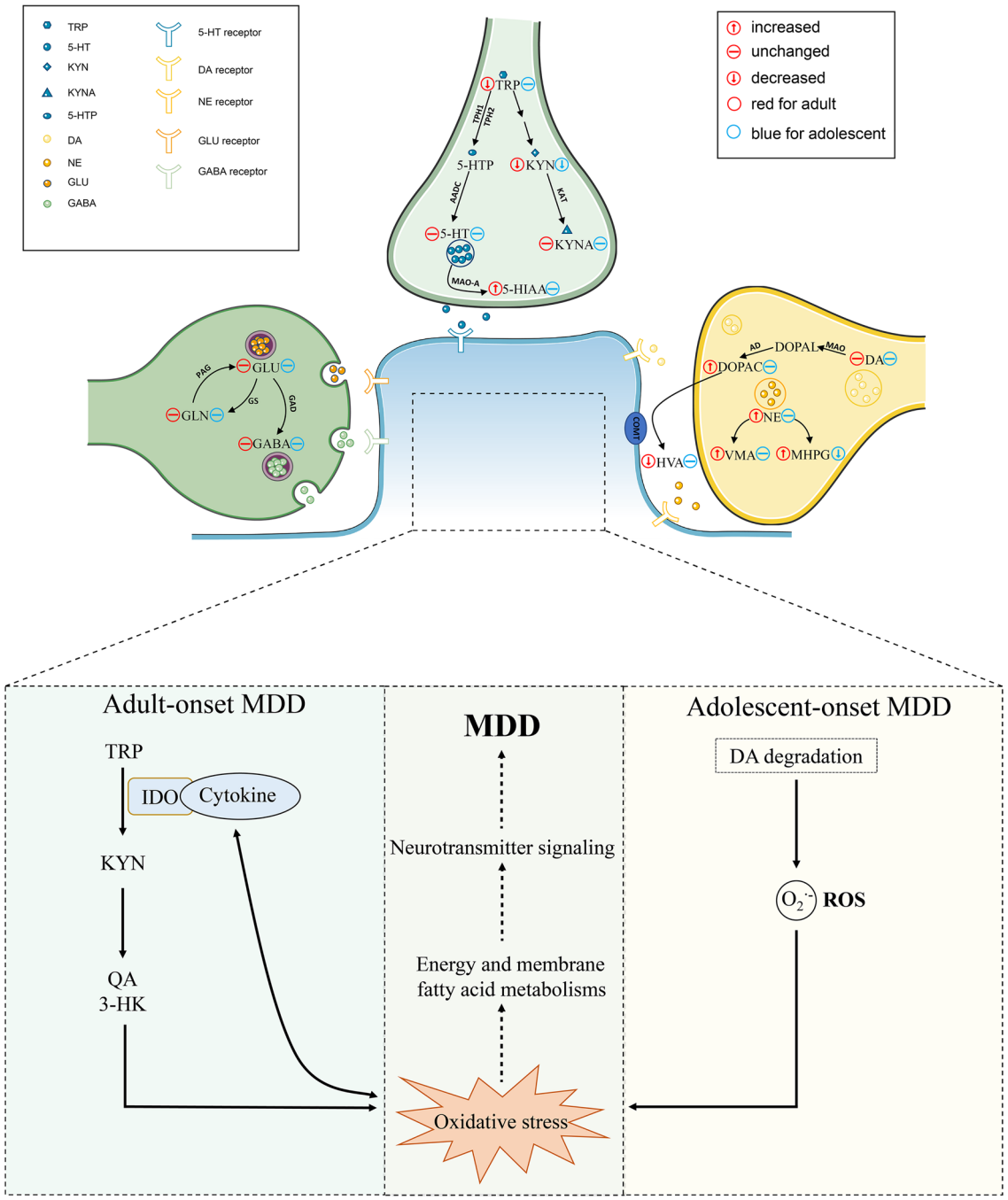

Fig. 5 The different changes of neurotransmitter systems and the possible shared and distinguished mechanisms in first-episode adult MDD and first-episode adolescent MDD. The top half of this figure showed the metabolic pathways of TRP, DA, NE and GLN in adult and adolescent MDD. As compared with matched healthy controls, the change directions of neurotransmitters or related metabolites in adult MDD were shown on left of the index with red color, while the change directions of neurotransmitters in adolescent MDD were shown on right of the parameter with blue color. The bottom half of this figure showed that TRP was metabolized into KYN via IDO which induced by cytokines. The downstream metabolites QA and 3-HK from KYN metabolic pathway and the free radicals and ROS derived from DA degradation could both facilitate oxidative stress, thereby modulating the process of the energy and membrane fatty acids metabolism, which are closely related to the neurotransmitter signaling and the neuroplasticity in specific neural circuits of MDD. *TPH1* tryptophan hydroxylase 1, *TPH2* tryptophan hydroxylase 2, *AADC* aromatic L-amino acid decarboxylase, *KAT* kynurenine aminotransferase, *MAO-A* monoamine oxidase-A, *IDO* indoleamine 2,3-dioxygenase, *PAG* phosphate-activated glutaminase, *GAD* glutamic acid decarboxylase, *GS* Gln synthetase, *MAO* monoamine oxidase, *AD* aldehyde dehydrogenase, *COMT* catechol-O-methyltransferase, *DOPAL* 3,4-dihydroxyphenylacetaldehyde, *QA* quinolinic acid, *3-HK* 3-hydroxykynurenine, *ROS* reactive oxygen species

diagnostic biomarkers and provide a novel pharmacological treatment strategy for MDD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-022-01406-8.

Acknowledgements We express our sincere gratitude to our colleagues and thank all the participants for their cooperation.

Funding This article was funded by Natural Science Foundation of Hunan Province (2021JJ30922), Natural Science Foundation of Xinjiang Uygur Autonomous Region (2019D01A13), Hunan Provincial Health Commission Research Project (202113010595), Wu Jieping Medical Foundation Funded Special Clinical Research Project (320.6750.2020-04-2), Changsha Municipal Natural Science Foundation (kq2007045), Science and Technology Major Project of Hunan Provincial Science and Technology Department (2020SK2123), Fundamental Research Funds for the Central Universities of Central South University (2019zzts1049, 2020zzts884, 2021zzts1073) and New Clinical Medical Technology Project of the Second Xiangya Hospital of Central South University (No. [2021] 94).

Declarations

Conflict of interest There is no conflict of interest.

Ethical approval The procedures of this study were reviewed and approved by the Ethical Committee of the Fourth People's Hospital of Urumqi (No. 2019-018-01). The corresponding details about the study's procedures were told to all subjects and the informed consent was obtained from participants or their legal guardians. This study was conducted according to the principles of the Helsinki Declaration and registered on the Chinese Clinical Trial Registry with the registered number ChiCTR2000040573.

References

1. James SL, Abate D, Abate KH et al (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 392(10159):1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7
2. World Health Organization (2008) The global burden of disease (2004) update. WHO, Geneva
3. Jesulola E, Micalos P, Baguley IJ (2018) Understanding the pathophysiology of depression: from monoamines to the neurogenesis hypothesis model—are we there yet? Behav Brain Res 341:79–90. https://doi.org/10.1016/j.bbr.2017.12.025
4. Hamon M, Blier P (2013) Monoamine neurocircuitry in depression and strategies for new treatments. Prog Neuropsychopharmacol Biol Psychiatry 45:54–63. https://doi.org/10.1016/j.pnpbp.2013.04.009
5. Fakhoury M (2016) Revisiting the serotonin hypothesis: implications for major depressive disorders. Mol Neurobiol 53(5):2778–2786. https://doi.org/10.1007/s12035-015-9152-z
6. Draganov M, Vives-Gilabert Y, de Diego-Adeliño J, Vicent-Gil M, Puigdemont D, Portella MJ (2020) Glutamatergic and GABAergic abnormalities in First-episode depression. A 1-year follow-up 1H-MR spectroscopic study. J Affect Disord 266:572–577. https://doi.org/10.1016/j.jad.2020.01.138
7. Perez-Caballero L, Torres-Sanchez S, Romero-López-Alberca C, González-Saiz F, Mico JA, Berrocoso E (2019) Monoaminergic system and depression. Cell Tissue Res 377(1):107–113. https://doi.org/10.1007/s00441-018-2978-8
8. Yim J (2016) Therapeutic benefits of laughter in mental health: a theoretical review. Tohoku J Exp Med 239(3):243–249. https://doi.org/10.1620/tjem.239.243
9. Pan J-X, Xia J-J, Deng F-L, Liang W-W, Wu J, Yin B-M, Dong M-X, Chen J-J, Ye F, Wang H-Y, Zheng P, Xie P (2018) Diagnosis of major depressive disorder based on changes in multiple plasma neurotransmitters: a targeted metabolomics study. Transl Psychiatry 8(1):130. https://doi.org/10.1038/s41398-018-0183-x
10. Cao T, Li N, Cai H (2020) Candidate metabolic biomarkers for schizophrenia in CNS and periphery: Do any possible associations exist? Schizophr Res 226:95–110. https://doi.org/10.1016/j.schres.2019.03.009
11. Németh H, Toldi J, Vécsei L (2005) Role of kynurenines in the central and peripheral nervous systems. Curr Neurovasc Res 2(3):249–260. https://doi.org/10.2174/1567202054368326
12. Zhou X, Liu L, Lan X, Cohen D, Zhang Y, Ravindran AV, Yuan S, Zheng P, Coghill D, Yang L, Hetrick SE, Jiang X, Benoliel J-J, Cipriani A, Xie P (2019) Polyunsaturated fatty acids metabolism, purine metabolism and inosine as potential independent diagnostic biomarkers for major depressive disorder in children and adolescents. Mol Psychiatry 24(10):1478–1488. https://doi.org/10.1038/s41380-018-0047-z
13. Kessler RC, Avenevoli S, Ries Merikangas K (2001) Mood disorders in children and adolescents: an epidemiologic perspective. Biol Psychiat 49(12):1002–1014. https://doi.org/10.1016/s0006-3223(01)01129-5
14. Thapar A, Collishaw S, Pine DS, Thapar AK (2012) Depression in adolescence. The Lancet 379(9820):1056–1067. https://doi.org/10.1016/S0140-6736(11)60871-4
15. Mohammadi MR, Alavi SS, Ahmadi N, Khaleghi A, Kamali K, Ahmadi A, Hooshyari Z, Mohamadian F, Jaberghaderi N, Nazaribadie M, Sajedi Z, Farshidfar Z, Kaviani N, Davasazirani R, Shahbakhsh AJ, Rad MR, Shahbazi K, Khodaverdloo RR, Tehrani LN, Nasiri M, Naderi F, Kiani A, Chegeni M, Hashemi Nasab SM, Ghaneian M, Parsamehr H, Nilforoushan N, Amiri S, Fooladi MF, Mohammadzadeh S, Ahmadipour A, Sarraf N, Hojjat SK, Nadermohammadi M, Mostafavi S-A, Zarafshan H, Salmanian M, Shakiba A, Ashoori S (2019) The prevalence, comorbidity and socio-demographic factors of depressive disorder among Iranian children and adolescents: to identify the main predictors of depression. J Affect Disord 247:1–10. https://doi.org/10.1016/j.jad.2019.01.005
16. Shain B (2016) Suicide and suicide attempts in adolescents. Pediatrics 138(1). https://doi.org/10.1542/peds.2016-1420
17. Rice F, Riglin L, Lomax T, Souter E, Potter R, Smith DJ, Thapar AK, Thapar A (2019) Adolescent and adult differences in major depression symptom profiles. J Affect Disord 243:175–181. https://doi.org/10.1016/j.jad.2018.09.015
18. Zhang J, Liu X, Fang Le (2019) Combined effects of depression and anxiety on suicide: a case-control psychological autopsy study in rural China. Psychiatry Res 271:370–373. https://doi.org/10.1016/j.psychres.2018.11.010
19. Bylund DB, Reed AL (2007) Childhood and adolescent depression: why do children and adults respond differently to antidepressant drugs? Neurochem Int 51(5):246–253. https://doi.org/10.1016/j.neuint.2007.06.025
20. Zheng X, Zhang X, Wang G, Hao H (2015) Treat the brain and treat the periphery: toward a holistic approach to major depressive disorder. Drug Discovery Today 20(5):562–568. https://doi.org/10.1016/j.drudis.2015.03.015
21. Wang L-S, Zhang M-D, Tao X, Zhou Y-F, Liu X-M, Pan R-L, Liao Y-H, Chang Q (2019) LC-MS/MS-based quantification of

tryptophan metabolites and neurotransmitters in the serum and brain of mice. J Chromatogr B Anal Technol Biomed Life Sci 1112:24–32. https://doi.org/10.1016/j.jchromb.2019.02.021
22. HAMILTON M, (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23(1):56–62. https://doi.org/10.1136/jnnp.23.1.56
23. Cai H-L, Zhu R-H, Li H-D (2010) Determination of dansylated monoamine and amino acid neurotransmitters and their metabolites in human plasma by liquid chromatography-electrospray ionization tandem mass spectrometry. Anal Biochem 396(1):103–111. https://doi.org/10.1016/j.ab.2009.09.015
24. Zhang L-H, Cai H-L, Jiang P, Li H-D, Cao L-J, Dang R-L, Zhu W-Y, Deng Y (2015) Simultaneous determination of multiple neurotransmitters and their metabolites in rat brain homogenates and microdialysates by LC-MS/MS. Anal Methods 7(9):3929–3938. https://doi.org/10.1039/C5AY00308C
25. Miura H, Ozaki N, Sawada M, Isobe K, Ohta T, Nagatsu T (2008) A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. Stress (Amsterdam, Netherlands) 11(3):198–209. https://doi.org/10.1080/10253890701754068
26. Ogyu K, Kubo K, Noda Y, Iwata Y, Tsugawa S, Omura Y, Wada M, Tarumi R, Plitman E, Moriguchi S, Miyazaki T, Uchida H, Graff-Guerrero A, Mimura M, Nakajima S (2018) Kynurenine pathway in depression: a systematic review and meta-analysis. Neurosci Biobehav Rev 90:16–25. https://doi.org/10.1016/j.neubiorev.2018.03.023
27. Hashimoto K (2009) Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 61(2):105–123. https://doi.org/10.1016/j.brainresrev.2009.05.005
28. Zádori D, Veres G, Szalárdy L, Klivényi P, Vécsei L (2018) Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines. J Alzheimer's Dis JAD 62(2):523–547. https://doi.org/10.3233/JAD-170929
29. Xing H, Zhang X, Xing N, Qu H, Zhang K (2019) Uncovering pharmacological mechanisms of Zhi-Zi-Hou-Po decoction in chronic unpredictable mild stress induced rats through pharmacokinetics, monoamine neurotransmitter and neurogenesis. J Ethnopharmacol 243:112079. https://doi.org/10.1016/j.jep.2019.112079
30. Li Y, Wu L, Chen C, Wang L, Guo C, Zhao X, Zhao T, Wang X, an Liu, Yan Z, (2020) Serum metabolic profiling reveals the antidepressive effects of the total iridoids of valeriana jatamansi jones on chronic unpredictable mild stress mice. Front Pharmacol 11:338. https://doi.org/10.3389/fphar.2020.00338
31. Ahmad A, Rasheed N, Banu N, Palit G (2010) Alterations in monoamine levels and oxidative systems in frontal cortex, striatum, and hippocampus of the rat brain during chronic unpredictable stress. Stress (Amsterdam, Netherlands) 13(4):355–364. https://doi.org/10.3109/10253891003667862
32. Li J, Hou L, Wang C, Jia X, Qin X, Wu C (2018) Short term intrarectal administration of sodium propionate induces antidepressant-like effects in rats exposed to chronic unpredictable mild stress. Front Psych 9:454. https://doi.org/10.3389/fpsyt.2018.00454
33. Laugeray A, Launay J-M, Callebert J, Surget A, Belzung C, Barone PR (2010) Peripheral and cerebral metabolic abnormalities of the tryptophan-kynurenine pathway in a murine model of major depression. Behav Brain Res 210(1):84–91. https://doi.org/10.1016/j.bbr.2010.02.014
34. Paul-Savoie E, Potvin S, Daigle K, Normand E, Corbin J-F, Gagnon R, Marchand S (2011) A deficit in peripheral serotonin levels in major depressive disorder but not in chronic widespread pain. Clin J Pain 27(6):529–534. https://doi.org/10.1097/AJP.0b013e31820dfede
35. Keegan MR, Chittiprol S, Letendre SL, Winston A, Fuchs D, Boasso A, Iudicello J, Ellis RJ (2016) Tryptophan metabolism and its relationship with depression and cognitive impairment among HIV-infected individuals. Int J Tryptophan Res IJTR 9:79–88. https://doi.org/10.4137/IJTR.S36464
36. Jones JS, Stanley B, Mann JJ, Frances AJ, Guido JR, Traskman-Bendz L, Winchel R, Brown RP, Stanley M (1990) CSF 5-HIAA and HVA concentrations in elderly depressed patients who attempted suicide. Am J Psychiatry 147(9):1225–1227. https://doi.org/10.1176/ajp.147.9.1225
37. Spreux-Varoquaux O, Alvarez JC, Berlin I, Batista G, Despierre PG, Gilton A, Cremniter D (2001) Differential abnormalities in plasma 5-HIAA and platelet serotonin concentrations in violent suicide attempters: relationships with impulsivity and depression. Life Sci 69(6):647–657. https://doi.org/10.1016/s0024-3205(01)01158-4
38. Messaoud A, Mensi R, Douki W, Neffati F, Najjar MF, Gobbi G, Valtorta F, Gaha L, Comai S (2019) Reduced peripheral availability of tryptophan and increased activation of the kynurenine pathway and cortisol correlate with major depression and suicide. World J Biol Psychiatry 20(9):703–711. https://doi.org/10.1080/15622975.2018.1468031
39. Arrant AE, Jemal H, Kuhn CM (2013) Adolescent male rats are less sensitive than adults to the anxiogenic and serotonin-releasing effects of fenfluramine. Neuropharmacology 65:213–222. https://doi.org/10.1016/j.neuropharm.2012.10.010
40. Liu Y, Zhao J, Guo W (2018) Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Front Psychol 9:2201. https://doi.org/10.3389/fpsyg.2018.02201
41. Demireva EY, Suri D, Morelli E, Mahadevia D, Chuhma N, Teixeira CM, Ziolkowski A, Hersh M, Fifer J, Bagchi S, Chemiakine A, Moore H, Gingrich JA, Balsam P, Rayport S, Ansorge MS (2020) 5-HT2C receptor blockade reverses SSRI-associated basal ganglia dysfunction and potentiates therapeutic efficacy. Mol Psychiatry 25(12):3304–3321. https://doi.org/10.1038/s41380-018-0227-x
42. Ruhé HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 12(4):331–359. https://doi.org/10.1038/sj.mp.4001949
43. Cai H-L, Zhu R-H, Li H-D, Zhang X-H, Hu L, Yang W, Ye H-S (2010) Elevated plasma γ-aminobutyrate/glutamate ratio and responses to risperidone antipsychotic treatment in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 34(7):1273–1278. https://doi.org/10.1016/j.pnpbp.2010.07.006
44. Godfrey KEM, Gardner AC, Kwon S, Chea W, Muthukumaraswamy SD (2018) Differences in excitatory and inhibitory neurotransmitter levels between depressed patients and healthy controls: a systematic review and meta-analysis. J Psychiatr Res 105:33–44. https://doi.org/10.1016/j.jpsychires.2018.08.015
45. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C, Camus V (2021) Neuroinflammation and depression: a review. Eur J Neurosci 53(1):151–171. https://doi.org/10.1111/ejn.14720
46. Felger JC (2017) The role of dopamine in inflammation-associated depression: mechanisms and therapeutic implications. Curr Top Behav Neurosci 31:199–219. https://doi.org/10.1007/7854_2016_13
47. Lopresti AL, Maker GL, Hood SD, Drummond PD (2014) A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Prog Neuropsychopharmacol Biol Psychiatry 48:102–111. https://doi.org/10.1016/j.pnpbp.2013.09.017

48. Duitama M, Vargas-López V, Casas Z, Albarracin SL, Sutachan J-J, Torres YP (2020) TRP channels role in pain associated with neurodegenerative diseases. Front Neurosci 14:782. https://doi.org/10.3389/fnins.2020.00782
49. Parasram K (2018) Phytochemical treatments target kynurenine pathway induced oxidative stress. Redox Rep Commun Free Rad Res 23(1):25–28. https://doi.org/10.1080/13510002.2017.1343223
50. Marino BLB, de Souza LR, Sousa KPA, Ferreira JV, Padilha EC, da Silva CHTP, Taft CA, Hage-Melim LIS (2020) Parkinson's disease: a review from pathophysiology to treatment. Mini Rev Med Chem 20(9):754–767. https://doi.org/10.2174/1389557519666191104110908
51. Zhou ZD, Xie SP, Saw WT, Ho PGH, Wang H, Lei Z, Yi Z, Tan EK (2019) The therapeutic implications of tea polyphenols against dopamine (DA) neuron degeneration in Parkinson's Disease (PD). Cells 8(8). https://doi.org/10.3390/cells8080911
52. Du J, Zhu M, Bao H, Li B, Dong Y, Xiao C, Zhang GY, Henter I, Rudorfer M, Vitiello B (2016) The role of nutrients in protecting mitochondrial function and neurotransmitter signaling: Implications for the treatment of depression, PTSD, and suicidal behaviors. Crit Rev Food Sci Nutr 56(15):2560–2578. https://doi.org/10.1080/10408398.2013.876960
53. Lochmann D, Richardson T (2019) Selective serotonin reuptake inhibitors. Handb Exp Pharmacol 250:135–144. https://doi.org/10.1007/164_2018_172
54. Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M (2007) Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst Rev 3:CD004851. https://doi.org/10.1002/14651858.CD004851.pub2
55. Klomp A, Václavů L, Meerhoff GF, Reneman L, Lucassen PJ (2014) Effects of chronic fluoxetine treatment on neurogenesis and tryptophan hydroxylase expression in adolescent and adult rats. PLoS ONE 9(5):e97603. https://doi.org/10.1371/journal.pone.0097603
56. van der Stelt HM, Broersen LM, Olivier B, Westenberg HGM (2004) Effects of dietary tryptophan variations on extracellular serotonin in the dorsal hippocampus of rats. Psychopharmacology 172(2):137–144. https://doi.org/10.1007/s00213-003-1632-6
57. Karanges EA, Kashem MA, Sarker R, Ahmed EU, Ahmed S, van Nieuwenhuijzen PS, Kemp AH, McGregor IS (2013) Hippocampal protein expression is differentially affected by chronic paroxetine treatment in adolescent and adult rats: a possible mechanism of "paradoxical" antidepressant responses in young persons. Front Pharmacol 4:86. https://doi.org/10.3389/fphar.2013.00086
58. Umene-Nakano W, Yoshimura R, Ueda N, Suzuki A, Ikenouchi-Sugita A, Hori H, Otani K, Nakamura J (2010) Predictive factors for responding to sertraline treatment: views from plasma catecholamine metabolites and serotonin transporter polymorphism. J Psychopharmacol (Oxford, England) 24(12):1764–1771. https://doi.org/10.1177/0269881109106899
59. McNamara RK, Jandacek R, Rider T, Tso P, Chu W-J, Weber WA, Welge JA, Strawn JR, Adler CM, DelBello MP (2016) Effects of fish oil supplementation on prefrontal metabolite concentrations in adolescents with major depressive disorder: a preliminary 1H MRS study. Nutr Neurosci 19(4):145–155. https://doi.org/10.1179/1476830514Y.0000000135