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Research paper

The association between the hypothalamic pituitary adrenal axis and tryptophan metabolism in persons with recurrent major depressive disorder and healthy controls

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ABSTRACT

Objectives: Persistent changes in serotonergic and hypothalamic pituitary adrenal (HPA) axis functioning are implicated in recurrent types of major depressive disorder (MDD). Systemic tryptophan levels, which influence the rate of serotonin synthesis, are regulated by glucocorticoids produced along the HPA axis. We investigated tryptophan metabolism and its association with HPA axis functioning in single episode MDD, recurrent MDD and non-depressed individuals.

Methods: We included depressed individuals (n = 1320) and controls (n = 406) from the Netherlands Study of Depression and Anxiety (NESDA). The kynurenine to tryptophan ratio (kyn/trp ratio) was established using serum kynurenine and tryptophan levels. Several HPA axis parameters were calculated using salivary cortisol samples. We adjusted the regression analyses for a wide range of potential confounders and differentiated between single episode MDD, recurrent MDD and control.

Results: Tryptophan, kynurenine and the kyn/trp ratio did not differ between controls and depressed individuals. Increased evening cortisol levels were associated with a decreased kyn/trp ratio in the total sample (Crude: $\beta = -.102$, $p < .001$; Adjusted: $\beta = -.083$, $p < .001$). This association was found to be restricted to recurrently depressed individuals (Crude: $\beta = -.196$, $p < .001$; Adjusted: $\beta = -.145$, $p = .001$). Antidepressant treatment did not affect this association.

Conclusions: Our results suggest that an imbalance between HPA axis function and tryptophan metabolism could be involved in recurrent depression.

1. Introduction

Major depressive disorder (MDD) is predicted to be the leading cause of disease burden worldwide by the year of 2030 (World Health Organization, 2008). This is largely attributed to the chronic and recurrent nature of the disease. Persistent neurobiological changes in (i) the regulation of cortisol secretion through the hypothalamic pituitary adrenal axis (HPA axis) and (ii) serotonergic functioning have been suggested to be involved (Bhagwagar and Cowen, 2008; Cowen, 2010; Pariante and Lightman, 2008). Tryptophan metabolism, being regulated by cortisol and being crucial in serotonin synthesis, might bridge the gap between these features (Cowen, 2002).

Disturbances of the HPA axis are a common finding in MDD. Several meta-analyses indicated that patients suffering from MDD show increased levels of cortisol throughout the day when compared to healthy controls (Belvederi Murri Martino et al., 2014; Burke et al., 2005; Knorr

Abbreviations: AUCg, Area under the curve with respect to the ground; BMI, Body mass index; CAR, Cortisol awakening response; CIDI, Composite international diagnostic interview; DSM-IV, Diagnostic and statistical manual of mental disorders, fourth edition; DST, Dexamethasone suppression test; HPA axis, Hypothalamic pituitary adrenal axis; hsCRP, High-sensitivity C-reactive protein; IDO, Indoleamine 2,3-dioxygenase; IDS, Inventory of depressive symptoms; IFN-y, Interferon gamma; IL-6, Interleukin-6; Kyn/trp ratio, Kynurenine to tryptophan ratio; MDD, Major depressive disorder; NESDA, Netherlands study of depression and anxiety; SNRI, Serotonin-norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant; TDO, Tryptophan 2,3-dioxygenase; TeCA, Tetracyclic antidepressant; TNF-alpha, Tumour necrosis factor alpha; XLC-MS/MS, Extraction-liquid chromatographic-tandem mass spectrometric

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et al., 2010; Lopez-Duran et al., 2009; Stetler and Miller, 2011). These findings were reproduced in patients in remission of recurrent MDD (Bhagwagar et al., 2003; Lok et al., 2012). Others showed these disturbances to be independent of remission status (Vreeburg et al., 2009). Focusing on recurrence, reports showed that both decreased and increased morning cortisol levels predict the recurrence of depression (Bockting et al., 2012; Hardeveld et al., 2010; Vreeburg et al., 2013; Vrshek-Schallhorn et al., 2012). These inconsistent findings are explained by methodological differences. Nonetheless, all these findings support the believe that disturbances of the HPA axis resemble a trait marker for depression rather than a state-dependent effect of the disease. In recurrent MDD, this trait-dependency suggests biological scarring due to previous episodes of depression.

Serotonergic dysfunction is a central concept in both the pathophysiology and the treatment of MDD (Belmaker and Agam, 2008; Kaufman et al., 2016). Studies indirectly linked serotonergic dysfunction to MDD by showing that acute tryptophan depletion induced depressive symptoms in both remitted MDD patients and non-depressed individuals with a family history of depression (Ruhé et al., 2007). Using neuroimaging technologies, several studies showed increased serotonin 1A receptor binding throughout the brain of currently depressed patients and remitted, unmedicated MDD patients (Miller, et al., 2009b, 2013; Parsey et al., 2010). These results suggest that central serotonergic dysfunction could persist in recurrent types of depression, regardless of the depressive state.

In the central nervous system, serotonin is synthesized de novo from the essential amino acid tryptophan. In order to cross the blood-brain barrier, tryptophan competes with other large neutral amino acids (Fernstrom, 2013). A meta-analysis showed that serum tryptophan levels were decreased in depressed individuals compared to healthy controls (Ogawa et al., 2014). Tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) are the two inducible enzymes that oxidize tryptophan to form kynurenine. The kynurenine to tryptophan (kyn/trp) ratio is often used as an indicator of tryptophan degradation through the kynurenine pathway (Corm et al., 2009; de Jong et al., 2011; Quak et al., 2014; Suzuki et al., 2010). Beside reduced availability of tryptophan for serotonin synthesis, activation of these pathways has been implicated in depression as it results in formation of downstream kynurenine metabolites with neuroactive properties (Schwarcz et al., 2012). Both in vitro and in vivo models showed that glucocorticoids, both endogenous and synthetic, induced expression and activity of TDO resulting in reduced levels of tryptophan (Danesch et al., 1983; Maes et al., 1990b; Young, 1981). IDO activity is induced by inflammatory cytokines including interferon gamma (INF-y), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Campbell et al., 2014). Patients with depression have been found to display increased levels of these cytokines (Miller et al., 2009a). A previous study within the same cohort as the current study, showed that increased levels of high-sensitivity C-reactive protein (hsCRP) and IL-6 were associated with an increased kyn/trp ratio (Quak et al., 2014).

We hypothesize that in patients suffering from recurrent episodes of depression, chronic cortisol hypersecretion causes depletion of tryptophan through activation of tryptophan degrading enzymes including TDO. We believe that the resulting disturbances of serotonergic functioning and central levels of kynurenine metabolites could play a role in the recurrent course of the disease. We first compared tryptophan metabolism and HPA axis functioning across a large cohort of non-depressed, single episode depressed and recurrently depressed individuals. We next assessed the association between HPA axis functioning and the kynurenine to tryptophan ratio while taking into account a wide range of confounding variables including inflammatory parameters and antidepressant treatment. Finally, we investigated whether this association differed between non-recurrent (single episode MDD) and recurrent types of depression.

2. Material and methods

2.1. Subjects

Data were obtained from the longitudinal cohort of the Netherlands Study of Depression and Anxiety (NESDA). Detailed rationale, objectives and methods are described elsewhere (Penninx et al., 2008). In brief, the cohort (n = 2981) consists of subjects (aged 18–65) recruited from the general population, general healthcare institutes and specialized mental healthcare institutes. Besides healthy controls, individuals with a depressive disorder and a prior history of a depressive disorder were included. Patients were excluded when they suffered from a primary clinical diagnosis other than a depressive or anxiety disorder (psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder). Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnoses (American Psychiatric Association, 2000) for anxiety disorders and depressive disorders were assigned on the basis of responses to the Composite International Diagnostic Interview (CIDI) 2.1 lifetime version (Wittchen, 1994) that was administered by trained interviewers. In addition, severity of depression was established in all participants using the 28-item self-report Inventory of Depressive Symptoms (IDS) (Rush et al., 1996). The study protocol was approved by the Ethical Review Board of the VU University Medical Center Amsterdam and subsequently by the local review boards of each participating institute. All subjects provided informed consent.

From the total NESDA sample, we excluded subjects with missing or failed tryptophan and/or kynurenine measurements (n = 32) (see 'Tryptophan, kynurenine and kynurenine to tryptophan ratio'). Next, we excluded individuals who did not return any salivary sample (n = 834) and from which no marker of HPA axis functioning could be obtained (n = 71) (see 'Section 2.3'). We then selected two groups based on the recurrence status of the depression: persons who suffered from a single episode of depression (n = 625) and persons with recurrent depressions (n = 695). Recurrence was defined as a either a history of a single MDD episode ('Single episode MDD') or a history of more than one episodes of depression ('Recurrent MDD'). Recency of MDD diagnosis was defined as either an ongoing MDD episode at the time of data gathering ('Current MDD') or no MDD episode at the time of data gathering but with a lifetime history of MDD ('Remitted MDD'). Both the groups 'Single episode MDD' and 'Recurrent MDD' consisted of currently depressed individuals and individuals in remission of depression. Individuals included in the 'Control' group had no lifetime depression or anxiety disorder (assessed using CIDI) and an IDS score below 15 (n = 406). None of the included participants used corticosteroid derivates. Our final sample thus consisted of 1726 individuals. A flowchart showing sample size and exclusion is provided (Fig. S1A).

2.2. Tryptophan, kynurenine and kynurenine to tryptophan ratio

At baseline, fasting blood samples were drawn and stored at −70 °C. Serum kynurenine and tryptophan concentrations were measured at the department of Laboratory Medicine of the University Medical Center Groningen using a validated automated online solid-phase extraction-liquid chromatographic-tandem mass spectrometric (XLC-MS/MS) method with deuterated internal standards (de Jong et al., 2009). The reliable detection range was established for both tryptophan (range, 30–110 nmol/l) and kynurenine (range, 1–50 nmol/l) (Salter et al., 1995). Values outside these thresholds were assigned missing (n = 20). A kyn/trp ratio was constructed for all included participants by dividing the level of kynurenine by the level of tryptophan and multiplying this value by 1*10^3.

2.3. Salivary cortisol

HPA axis function is reflected by cortisol production. Cortisol output

shows a diurnal pattern and reacts to a variety of stimuli such as stress and meals. Typical is a peak in the morning, the cortisol awakening response (CAR), followed by a logarithmical decline leading to a nadir around midnight. We used three indicators of HPA axis function: the CAR, the evening cortisol level and the DST.

A detailed description of the cortisol collection and measurement in NESDA is given elsewhere (Vreeburg et al., 2009). In short, participants were asked to collect salivary cortisol on a regular working day at seven time points: directly at awakening (T1) and 30, 45 and 60 min after awakening (T2, T3 and T4), at 10:00 p.m. (T5) and at 11:00 p.m. (T6). After this measurement, participants were instructed to ingest .5 mg of dexamethasone. Dexamethasone suppression was measured using cortisol sampling the next morning upon awakening (T7). Cortisol analyses were performed by competitive electrochemiluminescence immunoassay (E170; Roche, Basel, Switzerland). Samples were reported missing when either not returned (n = 663) or when the time of sampling was unknown (n = 1406) (Fig. S1B). During data cleaning, positive and negative outliers (mean plus or minus 2 SDs) were reported missing (n = 129 out of 14227 returned samples). To obtain comparable values, samples T2, T3 and T4 were reported missing when taken outside a five minute margin of the protocol time (n = 72, n = 76 and n = 77 respectively), T5 was reported missing when obtained outside a two-hour margin of the protocol time (n = 92), T6 was reported missing when not taken within 30–90 min of T5 (n = 49) and T7 was reported missing when taken outside a two-hour margin of T1 (n = 118).

2.3.1. Cortisol awakening response

As an indicator of the cortisol awakening response (CAR), the area under the curve with respect to the ground (AUCg) was calculated using a trapezoid formula and cortisol measurements T1, T2, T3 and T4 (Pruessner et al., 2003). The AUCg was only calculated when all samples were available.

2.3.2. Evening cortisol

The evening cortisol level, a measurement of the basal HPA axis activity, was calculated by averaging measurements T5 and T6.

2.3.3. Dexamethasone suppression test

The dexamethasone suppression test (DST) provides information on the negative feedback system of the HPA axis and was calculated by dividing the cortisol value at T1 by the value at T7 the following morning.

2.4. Covariates

Demographics (gender and age), lifestyle factors (alcohol consumption, smoking status and body mass index (BMI)) and inflammatory markers (high-sensitivity C-reactive protein (hsCRP) and interleukine-6 (IL-6)) have been shown to be associated with the kyn/trp ratio (Quak et al., 2014; Theofylaktopoulou et al., 2013). Alcohol consumption (number of glasses of alcohol typically per day for the last 12 months) and smoking status (current smoking (y/n)) were assessed using questionnaires. The BMI was calculated based on the body weight and length of the participants (weight/length^2). Both plasma hsCRP and IL-6 levels were measured in duplicate using ELISA at the Department of Clinical Chemistry of the VU University (Amsterdam, the Netherlands). A more detailed description is given elsewhere (Vogelzangs et al., 2012).

2.5. Antidepressant medication

Antidepressants possibly influence TDO functioning (Ara and Bano, 2012). A dichotomous variable was created for antidepressant use (yes/no). Antidepressant medication use was assessed by inspection of the drug container. All drugs used within the past month were categorized and classified according to the World Health Organization Anatomical Therapeutic Chemical classification. Antidepressant medication included selective serotonin reuptake inhibitors (SSRI) (N06AB), serotonin norepinephrine reuptake inhibitors (SNRI; N06AX16 and N06AX21), tricyclic antidepressants (TCA) (N06AA) and tetracyclic antidepressants (TeCA) (N06AX03, N06AX05, N06AX11).

2.6. Statistical analyses

We used IBM SPSS statistics 23. To improve normality of the error distribution, the kyn/trp ratio was log-transformed. Back-transformed data are reported. Mean and standard deviation (SD) are presented for baseline characteristics. To compare these characteristics, we used Chi-square tests for dichotomous variables and one-way analysis of variance (one-way ANOVA) in combination with Fisher's least significant difference (Fisher's LSD) for continuous variables.

To investigate the association between HPA axis function and tryptophan metabolism, multiple regression analyses were conducted using the kyn/trp ratio as dependent variable and one of the HPA axis indices (AUCg, evening cortisol or DST) separately as continuous predictor variable (Crude). We corrected for demographics, lifestyle and inflammation (Adjusted model). We then used interaction models to investigate differences in the association between HPA axis and tryptophan metabolism between controls and depressed persons. We differentiated based on recurrence of depression. As our group variable contained three groups (No MDD, single episode MDD and recurrent MDD), our interaction analyses were performed by including two dummy variables (Single episode MDD MDD (y/n) and Recurrent MDD (y/n)) and two interaction terms (e.g. AUCg × Single episode MDD and AUCg × Recurrent MDD) to the fully adjusted model. Similarly, we differentiated based on recency of depression (No MDD, current MDD, remitted MDD). Analyses were performed stratified in case of statistically significant interaction. Finally, we wanted to investigate whether antidepressant treatment would affect the association between the HPA axis and the kyn/trp ratio. As most individuals were using SSRI's, we limited these analyses to SSRI use only. These analyses were performed in a sample consisting of all included depressed individuals (n = 1320). In accordance with the above described, we now added one dummy variable (Antidepressant treatment (y/n)) and one interaction term (e.g. AUCg × SSRI use) to the fully adjusted model.

Standardized coefficients (β) and their respective p values are reported as a measure of association and interaction. We considered $p < .05$ statistically significant.

3. Results

3.1. Participant characteristics

The characteristics of the study sample for non-depressed controls (n = 406), single episode MDD (n = 625) and recurrent MDD (n = 695) are shown in Table 1. When compared to depressed persons, individuals in the control group were more often male, less often smokers and had a lower BMI (when compared to single episode MDD). In addition, controls showed lower hsCRP levels (compared to single episode MDD). With regard to psychopathology, individuals in the single episode MDD group more often suffered from a current anxiety disorder and less often had a remitted anxiety disorder. No individuals in the control group used antidepressants. Antidepressant use in general did not differ between single episode MDD and recurrent MDD. Individuals in the group of single episode MDD did use SSRI's more frequently compared to persons with recurrent MDD episodes. Recency of MDD did not differ significantly between the two groups of depressed individuals.

Table 1
Sample characteristics.

	Control (n = 406)	Single episode MDD (n = 625)	Recurrent MDD (n = 695)	p
Demographics				
Female, %	59.9%	67.7%	69.1%	.005
Age, mean in years (SD)	42.9 (14.7)	42.7 (12.8)	44.3 (11.7)	.054
Lifestyle				
Smoker, current, %	22.4%	36.6%	35.9%	< .001
Daily alcohol consumption, mean in number of units (SD)	2.1 (2.7)	2.0 (2.9)	1.9 (2.3)	.368
BMI, kg/m^2, mean (SD)	25.1 (4.6)	26.1 (5.1)	25.7 (5.2)	.007
Inflammation, mean (SD)				
hs-CRP (mg/l)	2.1 (3.0)	3.1 (5.7)	2.7 (5.0)	.014
IL-6 (pg/l)	1.2 (2.8)	1.5 (5.4)	1.1 (1.2)	.043
Psychopathology				
MDD recency[a], current/remitted, %	–	53/47%	57.6/42.4%	.096
Number of MDD episodes[a], mean (SD)	–	1.0 (.0)	8.5 (12.7)	–
IDS, mean (SD)	5.6 (3.8)	25.6 (13.9)	25.4 (12.6)	< .001
Anxiety disorder recency[a], none/current/remitted, %	–	31.5/53.1/15.4%	29.6/49.2/21.1%	.025
Medication use, %				
Antidepressants[a]	0%	36.2%	31.5%	.080
TCA	0%	3.7%	3.0%	.542
SSRI	0%	25.8%	20.1%	< .015
Other antidepressant	0%	6.9%	8.4%	.351

Showing mean and standard deviation (SD) or percentages for all variables used in the current study. The p value is reported for total between-group differences.
Abbreviations: MDD, major depressive disorder; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukine-6; AUCg, area under the curve with respect to the ground; DST, dexamethasone suppression test. TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
[a] Control persons were excluded for statistical analysis.

3.2. Tryptophan metabolism in controls, single episode MDD and recurrent MDD

Levels of tryptophan and kynurenine and the kyn/trp ratio are shown in Table 2. The analyses indicated no differences in tryptophan, kynurenine or the kyn/trp ratio between controls, single episode MDD and recurrent MDD.

3.3. HPA axis functioning in controls, single episode MDD and recurrent MDD

Table 3 displays markers of HPA axis function across the different groups. Compared to controls, recurrently depressed showed higher AUCg and evening cortisol values.

3.4. Association between HPA axis and kyn/trp ratio in total sample

Table 4 shows the associations between markers of HPA axis function (AUCg, evening cortisol or DST) and the kyn/trp ratio. In the total sample of included participants, higher evening cortisol levels were associated with a decreased kyn/trp ratio. Additional adjustment did not change this association to a great extent. No significant associations were found between other HPA axis indices and the kyn/trp ratio.

Table 2
Tryptophan metabolism in non-depressed and depressed individuals.

	Control (n = 406)	Single episode MDD (n = 625)	Recurrent MDD (n = 695)	p
Kynurenine pathway, mean (SD)				
Tryptophan (μmol/l)	63.3 (11.9)	64.2 (12.2)	63.7 (13.1)	.538
Kynurenine (μmol/l)	2.3 (.6)	2.3 (.6)	2.2 (.7)	.625
Kynurenine to tryptophan ratio	3.6 (.8)	3.6 (.8)	3.5 (.9)	.690

Showing mean and standard deviation (SD) for tryptophan, kynurenine and the kyn/trp ratio. The p value is reported for total between-group differences. Abbreviations as in Table 1.

Table 3
HPA axis function in non-depressed and depressed individuals.

	Control (n = 406)	Single episode MDD (n = 625)	Recurrent MDD (n = 695)	p
Cortisol, mean (SD)				
AUCg (nmol/l/h)	18.1 (6.7)	19.1 (7.0)	19.7 (7.5)	.006
Evening cortisol (nmol/l)	5.0 (3.2)	5.2 (2.9)	5.5 (3.0)	.001
DST	2.8 (1.8)	2.7 (1.7)	2.6 (1.6)	.097

Showing mean and standard deviation (SD) for several parameters of HPA axis function. The p value is reported for total between-group differences. Abbreviations as in Table 1.

Table 4
Association between HPA axis and kyn/trp ratio in total sample.

	β	p
AUCg		
Crude	−.042	.088
Adjusted[a]	−.018	.441
Evening cortisol		
Crude	−.102	< .001
Adjusted[a]	−.083	< .001
DST		
Crude	−.033	.201
Adjusted[a]	−.039	.105

Showing standardized coefficient (β) and p value for the association between HPA axis parameters and the kyn/trp ratio in the total sample.
[a] Adjusted for demographics (gender, age), lifestyle (smoking and alcohol consumption) and inflammation (hs-CRP and IL-6). Abbreviations as in Table 1.

In all adjusted models, higher age and increased BMI, were associated with an increased kyn/trp ratio. Current smoking was associated with a reduced kyn/trp ratio. Increased levels of hsCRP were found to be associated with increased kyn/trp ratio in all models. Increased IL-6 associated with an elevated kyn/trp ratio in the model with DST.

Table 5
Interaction effect of MDD recurrence on association between HPA axis and kyn/trp ratio.

		β	*p*
AUCg			
Interaction model[a]	AUCg × Single episode MDD	−.024	.809
	AUCg × Recurrent MDD	−.037	.713
Evening cortisol			
Interaction model[a]	Evening cortisol × Single episode MDD	−.024	.688
	Evening cortisol × Recurrent MDD	−.138	.039
DST			
Interaction model[a]	DST × Single episode MDD	.087	.179
	DST × Recurrent MDD	−.059	.378

Showing standardized coefficient (β) and *p* value for three models investigating the interaction of MDD recurrence (no MDD, single episode MDD or recurrent MDD) on the association between HPA axis and the kyn/trp ratio.

[a] Adjusted model (see Table 4) + two dummy variables (Single episode MDD and Recurrent MDD) and two interaction terms (AUCg, Evening cortisol or DST × Single episode MDD and AUCg, Evening cortisol or DST × Recurrent MDD). Abbreviations as in Table 1.

3.5. Interaction effect of MDD recurrence and MDD recency on association between HPA axis and kyn/trp ratio

To investigate whether recurrence of MDD affected the association between the HPA axis and the kyn/trp ratio, interaction analyses were conducted. Table 5 shows the results of these analyses. Our analyses showed a significant interaction effect for MDD recurrency in the fully adjusted evening cortisol model.

We then performed stratified analyses in control persons, individuals with single episode MDD and persons with recurrent MDD. As shown in Table 6, our results indicated that in recurrently depressed individuals an increased evening cortisol was associated with a decreased kyn/trp ratio. This association remained significant after adjustment. No significant association was found in controls and single episode depressed individuals.

In our adjusted models, higher age was found to be associated with an increased kyn/trp ratio in all groups. In both single episode depressed and recurrently depressed individuals increased BMI was associated with an increased kyn/trp ratio. Current smoking was associated with an increased kyn/trp ratio. In recurrent MDD increased levels of hsCRP were also found to be associated with an increased ratio. In controls, low alcohol consumption and increased IL-6 were associated with an increased kyn/trp ratio. Results of these analyses are not shown.

3.6. Interaction effect of MDD recency on association between HPA axis and kyn/trp ratio

Similarly as to described above, we investigated whether recency of MDD influenced the association between the HPA axis and the kyn/trp ratio. These analyses showed no significant interaction effect in the fully adjusted models (Table S1).

Table 6
Association between evening cortisol and kyn/trp ratio in controls, single episode MDD and recurrent MDD.

	Control		Single episode MDD		Recurrent MDD	
	β	*p*	β	*p*	β	*p*
Evening cortisol						
Crude	.029	.607	−.069	.123	−.196	< .001
Adjusted[a]	−.017	.754	−.028	.513	−.145	.001

Showing standardized coefficient (β) and *p* value for the association between evening cortisol and the kyn/trp ratio in controls, single episode MDD and recurrent MDD.

[a] Adjusted for demographics (gender, age), lifestyle (smoking and alcohol consumption) and inflammation (hs-CRP and IL-6). Abbreviations as in Table 1.

Table 7
Interaction effect of SSRI use on association between HPA axis and kyn/trp ratio.

		β	*p*
AUCg			
Interaction model[a]	AUCg × SSRI use	−.002	.974
Evening cortisol			
Interaction model[a]	Evening cortisol × SSRI use	.032	.501
DST			
Interaction model[a]	DST × SSRI use	−.041	.355

Showing standardized coefficient (β) and *p* value for the interaction of SSRI use (y/n) on the association between HPA axis and the kyn/trp ratio.

[a] Adjusted model (see Table 4) + one dummy variable (SSRI use) and one interaction term (AUCg, Evening cortisol or DST × SSRI use). Abbreviations as in Table 1.

3.7. Interaction effect of antidepressant treatment on association between HPA axis and kyn/trp ratio in depressed individuals

Finally, we tested whether treatment with an SSRI affected the association between HPA axis parameters and the kyn/trp ratio in all individuals with a history of depression (current or remitted). Our results indicated no significant interaction effect of SSRI treatment on the association between any of the HPA axis parameters and the kyn/trp ratio (Table 7).

4. Discussion

We investigated tryptophan metabolism along the kynurenine pathway and its association with HPA axis function (AUCg, evening cortisol and DST) within a large cohort of controls, single episode depressed persons and recurrently depressed persons. Firstly, our results showed no differences in tryptophan metabolism between controls, single episode depressed individuals and recurrently depressed individuals. Secondly, our results indicated that increased levels of evening cortisol were associated with a decreased kyn/trp ratio while taking into account various confounding variables. This association was found to be limited to recurrently depressed individuals. Antidepressant treatment had no effect on this association. Recency of MDD (ongoing/current MDD versus remitted MDD), did not affect the association between the HPA axis and the kyn/trp ratio. To the best of our knowledge, this is the first study to demonstrate an association between HPA axis function and tryptophan degradation in recurrent depression.

Opposing our hypothesis, our results showed (i) no differences in tryptophan metabolism between depressed individuals and non-depressed individuals and (ii) an inverse association between high evening cortisol levels and the kyn/trp ratio. Dysregulation of tryptophan metabolism has been implicated in several neuropsychiatric diseases including MDD and schizophrenia (Myint, 2012). A previous study investigating the NESDA showed a decreased kyn/trp ratio in currently depressed individuals compared to non-currently depressed (either no lifetime history of depression or remitted MDD) (Quak et al., 2014). Moreover, a meta-analysis showed reduced levels of tryptophan in depressed individuals compared to non-depressed persons (Ogawa et al., 2014). In a large sample consisting of 625 single episode depressed persons, 695 recurrently depressed individuals and 406 controls we found no differences in terms of serum levels of tryptophan and kynurenine or the kyn/trp ratio. Compared to other cohorts, the NESDA cohort consists of a heterogeneous population with regard to depression diagnosis. Participants were recruited from the general population, general healthcare institutes and specialized mental healthcare institutes. This leads to a representable but varying cohort of depressed and non-depressed individuals. More importantly, all of these studies - including one using the same cohort - compared tryptophan levels of non-depressed controls and currently depressed individuals. Our study compares recurrent and single episode MDD to control. This suggests that state of depression (currently versus non-currently depressed)

rather than recurrence of depression (single episode versus recurrently depressed) is associated with disturbances in tryptophan metabolism.

Our data are contradictory to previous work on the relationship between glucocorticoids and tryptophan metabolism activity. In vitro models showed marked increases of TDO activity in hepatocytes after administration of dexamethasone (Danesch et al., 1987; Nakamura et al., 1987). In both depressed and non-depressed individuals, administration of dexamethasone lowered the availability of tryptophan (Maes et al., 1990a). Rodent models showed that both physiological stress and administration of glucocorticoids could induce a flux of tryptophan through the kynurenine pathway and thus an increased kyn/trp ratio (Curzon and Green, 1969; Miura et al., 2008; Young, 1981). However, none of these studies directly investigated the relationship between levels of endogenous glucocorticoids and tryptophan degradation. To our knowledge, this is the first study to investigate the relationship between the HPA axis and tryptophan metabolism. When additionally bearing in mind the adaptable nature of the HPA axis, it remains difficult to compare our findings with the above mentioned studies.

Out of several markers for HPA axis function, we found evening cortisol to be associated with tryptophan metabolism. Elevated evening cortisol levels are a consistent finding in patients suffering from chronic forms of depression (Martino et al., 2014; Knorr et al., 2010). Low levels of cortisol during the night are thought to facilitate metabolic and immune recovery. Elevated levels evening cortisol have been associated with several metabolic and cognitive dysfunctions including insulin resistance and memory impairment (Gilpin et al., 2008; Johar et al., 2015; Mocking et al., 2013; Plat et al., 1999). A state in which evening cortisol levels are chronically elevated might cause reduced tryptophan metabolism through reduced activity of TDO. This might prove relevant in chronic and recurrent types of depression as TDO has been proposed to modulate behaviour and cognitive functioning (Gibney et al., 2014; Kanai et al., 2009; Too et al., 2016). Due to the observational nature of this study we can only hypothesize about mechanisms underlying the association between evening cortisol levels and tryptophan metabolism. These mechanism could depend on glucocorticoid resistance (Cohen et al., 2012). We hypothesize that under the constant pressure of high basal cortisol levels, glucocorticoid receptor activity is down-regulated. Diminished glucocorticoid receptor activity in TDO expressing cell types, could reduce transcriptional activation of the TDO gene and results in low enzyme activity. This down-regulation of TDO activity by glucocorticoids has already been shown in glioblastoma cells (Ott et al., 2015). Additionally, polymorphisms that already have been identified in other neuropsychiatric disorders (Comings, 2001; Nabi et al., 2004; Soichot et al., 2013) could exist on tryptophan degrading genes. Experimentally controlled in vivo models investigating the role of endogenously produced levels of glucocorticoids are needed to identify biological pathways involved in the regulation of tryptophan metabolism in depression.

IDO and TDO both have an important role in regulating tryptophan levels. IDO seems mainly active in acute settings of inflammation. Most studies using the kyn/trp ratio as a readout for IDO activity induced inflammation by injecting interferons or interferon-inducers (Campbell et al., 2014). Cytokines levels are often increased in depressed individuals during an episode of depression (Dowlati et al., 2010). IDO-mediated depletion of tryptophan could therefore play an important role in these acute settings. However, we believe that under normal circumstances peripheral levels of tryptophan are regulated in a TDO-dependent manner. This believe is supported by the finding that TDO null mice show increased levels of tryptophan whereas in IDO null mice differences in tryptophan levels only become apparent upon inflammatory stress (Kanai et al., 2009; Larkin et al., 2016). In addition, adjusting for the confounding effect of IDO activity by the addition of IL-6 and hsCRP to our models did not affect the association between evening cortisol and the kyn/trp ratio to a great extent. Taken together, this suggests that a TDO-dependent mechanism would be dominant in the association between increased levels of evening cortisol and a decreased kyn/trp ratio in recurrent depression.

Evidence suggests that antidepressant medication affects TDO activity (Ara and Bano, 2012). In our analyses, use of SSRI's was not found to influence the association between evening cortisol and the kyn/trp ratio. Due to low number of patients using TCA's or other antidepressants, we were unable to investigate their effect on the association between evening cortisol and the kyn/trp ratio. A different study design (e.g. specifically including patients based on antidepressant use and responsiveness) is needed in order to better investigate this.

Several limitations of this study should be addressed. First, due to its cross-sectional design, we cannot make statements about a causative relationship between HPA axis function and tryptophan degradation. Instead, our results show an associative relationship, requiring different ways interpretation. Secondly, our models are shown to predict a moderate proportion of the variance within the kyn/trp ratio. This suggest that other unknown parameters could still play an important role in the activity of both IDO and TDO. Thirdly, we report a substantial loss in sample size compared to the initial sample. These losses were mainly caused by non-returned salivary samples and salivary samples obtained outside protocol times. As interaction analyses are influenced to a great extent by outlying variables, we excluded the most extreme outliers (mean +/− 2 SD). Most of these outliers showed either unphysiologically high cortisol levels or seemed to have been registered under the wrong timepoint. Still, some potentially valuable information has been lost. Finally, we did (i) not include an assessment of branched chain amino acids (BCAA), which compete with central uptake of tryptophan (Fernstrom, 2013), (ii) did not discriminate between free and albumin-bound tryptophan and did not correct for multiple testing. These assessments, together with a more extensive measurement of the kynurenine and serotonergic pathway could be insightful in future research.

5. Conclusion

To conclude, this is the first study to demonstrate that HPA axis activity is associated with tryptophan degradation. Opposing our hypothesis, our results show no differences in tryptophan metabolism between non-depressed, single episode depressed and recurrently depressed individuals and show that elevated evening cortisol levels are associated with a decreased kyn/trp ratio in recurrently depressed individuals. No effect of antidepressant treatment is found. These results indicate that in recurrent depression, disturbances of the HPA axis could cause for the establishment of a new equilibrium between endogenous levels of cortisol and metabolism of tryptophan possibly in a TDO-dependent manner. Replication of these results in other epidemiological samples including analyses in specific subgroups (e.g. antidepressant treated versus non-treated patients or melancholic versus atypical depression) and more fundamental research is needed to unravel the mechanism by which cortisol and tryptophan metabolism interact in health and depression.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.06.052.

References

Ara, I., Bano, S., 2012. Citalopram decreases tryptophan 2,3-dioxygenase activity and brain 5-HT turnover in swim stressed rats. Pharmacol. Rep. 64, 558–566.

Association, A.P., 2000. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association Text Revision.

Belmaker, R.H., Agam, G., 2008. Major depressive disorder. N. Engl. J. Med. 358, 55–68.

Martino, Pariante Belvederi Murri, Mondelli, C., Masotti, V., Atti, M., Mellacqua, A.R., Antonioli, Z., Ghio, M., Menchetti, L., Zanetidou, M., Innamorati, S., Amore, M., 2014. HPA axis and aging in depression: systematic review and meta-analysis. Psychoneuroendocrinology 41C, 46–62.

Bhagwagar, Z., Cowen, P.J., 2008. 'It's not over when it's over': persistent neurobiological abnormalities in recovered depressed patients. Psychol. Med. 38, 307–313.

Bhagwagar, Z., Hafizi, S., Cowen, P.J., 2003. Increase in concentration of waking salivary cortisol in recovered patients with depression. Am. J. Psychiatry 160, 1890–1891.

Bockting, C.L.H., Lok, A., Visser, I., Assies, J., Koeter, M.W., Schene, A.H., 2012. Lower cortisol levels predict recurrence in remitted patients with recurrent depression: a 5.5 year prospective study. Psychiatry Res. 200, 281–287.

Burke, H.M., Davis, M.C., Otte, C., Mohr, D.C., 2005. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 30, 846–856.

Campbell, B.M., Charych, E., Lee, A.W., Möller, T., 2014. Kynurenines in CNS disease: regulation by inflammatory cytokines. Front Neurosci. 6, 12.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad.

Comings, D.E., 2001. Clinical and molecular genetics of ADHD and Tourette syndrome: two related polygenic disorders. Ann. N. Y. Acad. Sci. 931, 50–83.

Corm, S., Berthon, C., Imbenotte, M., Biggio, V., Lhermitte, M., Dupont, C., Briche, I., Quesnel, B., 2009. Indoleamine 2,3-dioxygenase activity of acute myeloid leukemia cells can be measured from patients' sera by HPLC and is inducible by IFN-gamma. Leuk. Res. 33, 490–494.

Cowen, P.J., 2002. Cortisol, serotonin and depression: all stressed out? Br. J. Psychiatry 180, 99–100.

Cowen, P.J., 2010. Not fade away: the HPA axis and depression. Psychol. Med. 40, 1–4.

Curzon, G., Green, R., 1969. Effects of immobilization on rat liver tryptophan pyrrolase and brain 5-hydroxytryptamine metabolism. Br. J. Pharmacol. 37, 689–697.

Danesch, U., Hashimoto, S., Renkawitz, R., Schütz, G., 1983. Transcriptional regulation of the tryptophan oxygenase gene in rat liver by glucocorticoids. J. Biol. Chem. 258, 4750–4753.

Danesch, U., Gloss, B., Schmid, W., Schutz, G., Schule, R., Renkawitz, R., 1987. Glucocorticoid induction of the rat tryptophan oxygenase gene is mediated by two widely separated glucocorticoid-responsive elements. EMBO J. 6, 625–630.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.

Fernstrom, J.D., 2013. Large neutral amino acids: dietary effects on brain neurochemistry and function. Amino Acids 45, 419–430.

Gibney, S.M., Fagan, E.M., Waldron, A., O'Byrne, J., Connor, T.J., Harkin, A., 2014. Inhibition of stress-induced hepatic tryptophan 2,3-dioxygenase exhibits antidepressant activity in an animal model of depressive behaviour. Int. J. Neuropsychopharmacol. 17, 917–928.

Gilpin, H., Whitcomb, D., Cho, K., 2008. Atypical evening cortisol profile induces visual recognition memory deficit in healthy human subjects. Mol. Brain 1, 4.

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T.F., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr. Scand. 122, 184–191.

Johar, H., Emeny, R.T., Bidlingmaier, M., Lacruz, M.E., Reincke, M., Peters, A., Heier, M., Ladwig, K.H., 2015. Lower morning to evening cortisol ratio is associated with cognitive impairment in men but not women: an analysis of 733 older subjects of the cross-sectional KORA-Age study. Psychoneuroendocrinology 51, 296–306.

de Jong, Ra, Nijman, H.W., Boezen, H.M., Volmer, M., Ten Hoor Klaske, A., Krijnen, J., van der, Zee, Ate, G.J., Hollema, H., Kema, I.P., 2011. Serum tryptophan and kynurenine concentrations as parameters for indoleamine 2,3-dioxygenase activity in patients with endometrial, ovarian, and vulvar cancer. Int. J. Gynecol. Cancer.: Off. J. Int. Gynecol. Cancer 21, 1320–1327.

de Jong, W.H.A., Smit, R., Bakker, S.J.L., de Vries, E., G.E., Kema, I.P., 2009. Plasma tryptophan, kynurenine and 3-hydroxykynurenine measurement using automated online solid-phase extraction HPLC-tandem mass spectrometry. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 877, 603–609.

Kanai, M., Funakoshi, H., Takahashi, H., Hayakawa, T., Mizuno, S., Matsumoto, K., Nakamura, T., 2009. Tryptophan 2,3-dioxygenase is a key modulator of physiological neurogenesis and anxiety-related behavior in mice. Mol. Brain 2, 8.

Kaufman, J., DeLorenzo, C., Choudhury, S., Parsey, R.V., 2016. The 5-HT1A receptor in Major Depressive Disorder. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 26, 397–410.

Knorr, U., Vinberg, M., Kessing, L.V., Wetterslev, J., 2010. Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. Psychoneuroendocrinology 35, 1275–1286.

Larkin, P.B., Sathyasaikumar, K.V., Notarangelo, F.M., Funakoshi, H., Nakamura, T., Schwarcz, R., Muchowski, P.J., 2016. Tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase 1 make separate, tissue-specific contributions to basal and inflammation-induced kynurenine pathway metabolism in mice. Biochim. Biophys. Acta – Gen. Subj. 1860, 2345–2354.

Lok, A., Mocking, R.J.T., Ruhé Henricus, G., Visser, I., Koeter, M.W.J., Assies, J., Bockting, C.L.H., Olff, M., Schene, A.H., 2012. Longitudinal hypothalamic-pituitary-adrenal axis trait and state effects in recurrent depression. Psychoneuroendocrinology 37, 892–902.

Lopez-Duran, N.L., Kovacs, M., George, C.J., 2009. Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. Psychoneuroendocrinology 34, 1272–1283.

Maes, M., Jacobs, M.P., Suy, E., Minner, B., Leclercq, C., Christiaens, F., Raus, J., 1990a. Suppressant effects of dexamethasone on the availability of plasma L-tryptophan and tyrosine in healthy controls and in depressed patients. Acta Psychiatr. Scand. 81, 19–23.

Maes, M., Jacobs, M.P., Suy, E., Vandewoude, M., Minner, B., Raus, J., 1990b. Effects of dexamethasone on the availability of L-tryptophan and on the insulin and FFA concentrations in unipolar depressed patients. Biol. Psychiatry 27, 854–862.

Miller, A.H., Maletic, V., Raison, C.L., 2009a. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.

Miller, J.M., Brennan, K.G., Ogden, T.R., Oquendo, M.A., Sullivan, G.M., Mann, J.J., Parsey, R.V., 2009b. Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 34, 2275–2284.

Miller, J.M., Hesselgrave, N., Ogden, R.T., Zanderigo, F., Oquendo, M.A., Mann, J.J., Parsey, R.V., 2013. Brain serotonin 1A receptor binding as a predictor of treatment outcome in major depressive disorder. Biol. Psychiatry 74, 760–767.

Miura, H., Ozaki, N., Shirokawa, T., Isobe, K., 2008. Changes in brain tryptophan metabolism elicited by ageing, social environment, and psychological stress in mice. Stress 11, 160–169.

Mocking, R.J.T., Ruhé Henricus, G., Assies, J., Lok, A., Koeter, M.W.J., Visser, I., Bockting, C.L.H., Schene, A.H., 2013. Relationship between the hypothalamic-pituitary-adrenal-axis and fatty acid metabolism in recurrent depression. Psychoneuroendocrinology 38, 1607–1617.

Myint, A.M., 2012. Kynurenines: from the perspective of major psychiatric disorders. FEBS J. 279, 1375–1385.

Nabi, R., Serajee, F.J., Chugani, D.C., Zhong, H., Huq, aH.M.M., 2004. Association of tryptophan 2,3 dioxygenase gene polymorphism with autism. Am. J. Med. Genet. Part B Neuropsychiatr. Genet.: Off. Publ. Int. Soc. Psychiatr. Genet. 125B, 63–68.

Nakamura, T., Niimi, S., Nawa, K., Noda, C., Ichihara, A., Takagi, Y., Anai, M., Sakaki, Y., 1987. Multihormonal regulation of transcription of the tryptophan 2,3-dioxygenase gene in primary cultures of adult rat hepatocytes with special reference to the presence of a transcriptional protein mediating the action of glucocorticoids. J. Biol. Chem. 262, 727–733.

Ogawa, S., Fujii, T., Koga, N., Hori, H., Teraishi, T., Hattori, K., Noda, T., Higuchi, T., Motohashi, N., Kunugi, H., 2014. Plasma l-tryptophan concentration in major depressive disorder: new data and meta-analysis. J. Clin. Psychiatry 75, e906–e915.

Ott, M., Litzenburger, U.M., Rauschenbach, K.J., Bunse, L., Ochs, K., Sahm, F., Pusch, S., Opitz, C.A., Blaes, J., von Deimling, A., Wick, W., Platten, M., 2015. Suppression of TDO-mediated tryptophan catabolism in glioblastoma cells by a steroid-responsive FKBP52-dependent pathway. Glia 63, 78–90.

Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 31, 464–468.

Parsey, R.V., Ogden, R.T., Miller, J.M., Tin, A., Hesselgrave, N., Goldstein, E., Mikhno, A., Milak, M., Zanderigo, F., Sullivan, G.M., Oquendo, M.A., Mann, J.J., 2010. Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations. Biol. Psychiatry 68, 170–178.

Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong Peter, J., Van Marwijk Harm, W.J., Assendelft, W.J.J., van der Meer, K., Verhaak, P., Wensing, M., de Graaf, R., Hoogendijk, W.J., Ormel, J., van Dyck, R., 2008. The Netherlands study of depression and anxiety (NESDA): rationale, objectives and methods. Int. J. Methods Psychiatr. Res. 17, 121–140.

Plat, L., Leproult, R., L'Hermite-Baleriaux, M., Fery, F., Mockel, J., Polonsky, K.S., Van Cauter, E., 1999. Metabolic effects of short-term elevations of plasma cortisol are more pronounced in the evening than in the morning. J. Clin. Endocrinol. Metab. 84, 3082–3092.

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916–931.

Quak, J., Doornbos, B., Roest, A.M., Duivis, H.E., Vogelzangs, N., Nolen, W.A., Penninx, B.W.J.H., Kema, I.P., Jonge Peter, De, 2014. Does tryptophan degradation along the kynurenine pathway mediate the association between pro-inflammatory immune activity and depressive symptoms? Psychoneuroendocrinology 45, 202–210.

Ruhé, H.G., Mason, N.S., Schene, A.H., 2007. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol. Psychiatry 12, 331–359.

Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol. Med. 26, 477–486.

Salter, M., Hazelwood, R., Pogson, C.I., Iyer, R., Madge, D.J., Jones, H.T., Cooper, B.R., Cox, R.F., Wang, C.M., Wiard, R.P., 1995. The effects of an inhibitor of tryptophan 2,3-dioxygenase and a combined inhibitor of reuptake in the rat. Neuropharmacology 34, 211–221.

Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci. 13, 465–477.

Soichot, M., Vaast, A., Vignau, J., Guillemin, G.J., Lhermitte, M., Broly, F., Allorge, D.,

2013. Characterization of functional polymorphisms and glucocorticoid-responsive elements in the promoter of TDO2, a candidate gene for ethanol-induced behavioural disorders. Alcohol Alcohol. 48, 415–425.
Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom. Med. 73, 114–126.
Suzuki, Y., Suda, T., Furuhashi, K., Suzuki, M., Fujie, M., Hahimoto, D., Nakamura, Y., Inui, N., Nakamura, H., Chida, K., 2010. Increased serum kynurenine/tryptophan ratio correlates with disease progression in lung cancer. Lung Cancer 67, 361–365.
Theofylaktopoulou, D., Midttun, Ulvik, A., Ueland, P.M., Tell, G.S., Vollset, S.E., Nygård, O., Eussen, S.J.P.M., 2013. A community-based study on determinants of circulating markers of cellular immune activation and kynurenines: the Hordaland health study. Clin. Exp. Immunol. 173, 121–130.
Too, L.K., Li, K.M., Suarna, C., Maghzal, G.J., Stocker, R., McGregor, I.S., Hunt, N.H., 2016. Deletion of TDO2, IDO-1 and IDO-2 differentially affects mouse behavior and cognitive function. Behav. Brain Res. 312, 102–117.
Vogelzangs, N., Duivis, H.E., Beekman, A.T., Kluft, C., Neuteboom, J., Hoogendijk, W., Smit, J.H., de Jonge, P., Penninx, B.W., 2012. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl. Psychiatry 2, e79.
Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch. Gen. Psychiatry 66, 617–626.
Vreeburg, S.A., Hoogendijk, W.J.G., DeRijk, R.H., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W.J.H., 2013. Salivary cortisol levels and the 2-year course of depressive and anxiety disorders. Psychoneuroendocrinology 38, 1494–1502.
Vrshek-Schallhorn, S., Doane, L.D., Mineka, S., Zinbarg, R.E., Craske, M.G., Adam, E.K., 2012. The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. Psychol. Med. 1–11.
Wittchen, H.U., 1994. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J. Psychiatr. Res. 28, 57–84.
World Health Organization, 2008. The Global Burden of Disease: 2004 Update, 146.
Young, S.N., 1981. Mechanism of decline in rat brain 5-hydroxytryptamine after induction of liver tryptophan pyrrolase by hydrocortisone: roles of tryptophan catabolism and kynurenine synthesis. Br. J. Pharmacol. 74, 695–700.