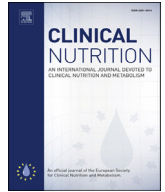




Contents lists available at ScienceDirect

## Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

## Original article

## The role of tryptophan metabolism and food craving in the relationship between obesity and bipolar disorder

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## ARTICLE INFO

## Article history:

Received 15 February 2017

Accepted 25 June 2017

## Keywords:

Food craving  
Tryptophan breakdown  
Overweight  
Obesity  
Bipolar disorder

## SUMMARY

**Background & aims:** Individuals with bipolar disorder (BD) have a significantly increased risk of obesity-related conditions. The imbalance between food intake and energy expenditure is assumed to be a major risk factor for obesity in BD. This study analyzed food craving in relation to anthropometric, metabolic, and neurobiological parameters in a well-characterized cohort of euthymic individuals with BD.

**Methods:** One-hundred-thirty-five patients completed the Food-Craving Inventory assessing four categories of food craving (fat, fast-food, sweets and carbohydrate craving). Additionally, clinical, metabolic and anthropometric parameters were assessed.

**Results:** Higher levels of fat craving were observed in males, *versus* females, with BD. High levels of carbohydrate craving positively correlated with kynurenine and the kynurenine-to-tryptophan ratio. Higher serum nitrite and neopterin levels were related to fat craving. Parameters of fat metabolism (triglycerides, high-density lipoprotein) were associated with fat and fast-food craving. Anthropometric measures of obesity (e.g. body mass index, waist-to-hip-ratio) were not related to food craving.

**Conclusions:** Overweight/obese individuals with BD show an increased driving of tryptophan down the kynurenine pathways, as indicated by an increase in the serum kynurenine-to-tryptophan ratio. The driving of tryptophan down the kynurenine pathway is mediated by immune-inflammatory activity and stress. The correlation of increased kynurenine with food craving, especially carbohydrate craving, probably indicates a regulatory deficit in the maintenance of chronic inflammatory processes in obesity and BD. Food craving seems to be of clinical importance in the treatment of metabolic disturbances in BD, although not associated with anthropometric measures of obesity. Rather, food craving correlates with blood metabolic parameters and an increased activation of the kynurenine pathway, both of which are linked to higher affective symptomatology and the development of cardiovascular diseases.

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## 1. Introduction

Bipolar disorder (BD) is a serious psychiatric illness, often with depressive and (hypo-)manic episodes, interspersed with relatively stable euthymic states [1]. Beside affective and psychomotor

symptoms, eating dysregulation is very common in BD [2]. BD shows a high co-occurrence of eating disorders, especially binge eating behavior [3], both of which are associated with an earlier age of BD onset and a poorer disease course [4–6]. BD has a considerable increased risk for obesity and metabolic disturbances, contributing to the heightened cardiovascular morbidity and mortality [7–10]. Further medical complications of obesity in BD include neurocognitive impairments [11,12], a more complex illness presentation and poorer treatment outcome [13–15].

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<http://dx.doi.org/10.1016/j.clnu.2017.06.024>

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### 1.1. Obesity in BD

Obesity occurs when energy intake is greater than energy expenditure [16], with a number of factors proposed to underpin this in BD, including: Psychopharmacological medication [17,18], genetic factors [19], serotonergic dysfunction [20], inflammatory mediators [21], and higher levels of oxidative stress [22]. Such factors have all been proposed to contribute to the onset and maintenance of obesity in BD. Likewise, behavioral determinants, such as a sedentary lifestyle and poor eating habits may increase obesity in individuals with BD [23].

The current literature has highlighted a significant role for chronic low-grade inflammation, in interaction with other physiological processes, including oxidative and nitrosative stress, metabolic dysregulation, pro-inflammatory cytokines, and heightened activity of the kynurenine pathway, in mediating the association between obesity and BD [22,24].

### 1.2. Food craving

Food craving is defined as a profound desire to consume a specific kind of food. It is described as a multidimensional concept, including cognitive (e.g. thoughts about food); emotional (e.g. intense desire to eat); behavioral (e.g. seeking food); and physiological (e.g. salivation) processes [25]. Food craving is the subject of intense interest, underpinning healthy weight maintenance, as well as overweight/obesity [26–29], snacking behavior, binge eating, the consumption of particular types of foods [30–32], cognitive reappraisal strategies [33], reward sensitivity [34], plasma insulin, and hippocampal activation [35]. Environmental factors, including stressors, also contribute to food craving [36]. Carbohydrates craving, in particular, has been associated with serotonergic dysfunction, and thereby to dysphoric mood [37] and depressive symptomatology [38]. A wide body of data shows that food craving is generally more prevalent in women than in men [39,40]. In BD patients, carbohydrate craving can be stimulated by mood stabilizers, including lithium and valproate, as well as some second generation antipsychotics [41].

### 1.3. Tryptophan metabolism

The  $\alpha$ -amino acid, tryptophan (TRP), is the precursor for two crucial biochemical pathways that are related to inflammatory processes in neuropsychiatric, and other medical, disorders: (a) the generation of serotonin and melatonin, and (b) the production of kynurenine (KYN) and KYN derivatives, which ultimately can lead to nicotinamide adenine dinucleotide production. A relative increase of KYN, and therefore the KYN/TRP ratio, has been found in numerous inflammatory and neuropsychiatric diseases. Such increases in the KYN/TRP ratio arise from pro-inflammatory cytokine driven indoleamine-2,3-dioxygenase (IDO) and stress/cortisol driven tryptophan-2,3-dioxygenase (TDO), which drive TRP down the KYN pathway and away from serotonin and melatonin synthesis [24]. Disturbed TRP metabolism also associates with overweight/obesity [42], where increased levels of pro-inflammatory factors are evident. TRP via serotonin and melatonin, are involved in the regulation of satiety and caloric intake [42,43,62]. Serotonin, by regulating carbohydrate and fat intake, can lower caloric intake [44,45], as well as relieving stress [46], and inhibiting neuropeptide Y, which is one of the most potent hypothalamic orexigenic peptides [47]. An increase in the KYN/TRP ratio is associated with a higher likelihood of fatal cardiovascular events, which are more prevalent in individuals with BD [48].

In the etiology and course of BD, alterations in the levels of KYN pathway products, in inverse correlation with changes in the

serotonergic and melatonergic pathways, have been proposed to be of clinical relevance in both poles of BD [49].

Neopterin is another marker of immune-inflammatory activity, and correlates with changes of TRP and KYN pathway activation [50]. Neopterin is produced in macrophages following stimulation with the pro-inflammatory cytokine, interferon- $\gamma$  (IFN- $\gamma$ ), which is considered as sensitive marker for the development, expansion, and persistence of inflammation and the immune response [51]. In BD, raised IFN- $\gamma$  levels during a manic episode positively correlate with symptom severity, possibly in association with IDO induction [49]. Increased levels of oxidative and nitrosative stress may be intimately linked to higher levels of immune-inflammatory activity, with high serum nitrite levels predictive of metabolic syndrome in females, but not in males, suggesting serum nitrite as a potential biomarker for cardio-metabolic disorders in females [52]. As such, oxidative and nitrosative stress, neopterin, IDO, IFN- $\gamma$  and changes in relative activity of the KYN, *versus* serotonergic and melatonergic, may be intimately linked, with relevance to the pathophysiology of both BD and obesity.

Given such evidence implicating multiple interacting pathways in the development of overweight/obesity in BD, this study aimed to assess the potential role of food craving in such process. We were especially interested in the relationship between food craving with certain metabolic risk factors (e.g. central obesity, insulin resistance, lipid abnormality), and inflammation related parameters (TRP pathway) in euthymic BD patients. We hypothesized that overweight/obese individuals will have greater food craving that is linked to metabolic risk factors and alterations in TRP metabolism. Moreover, this study aimed to identify sex differences in this context. This is the first study to examine food craving and metabolic risk factors in euthymic BD patients.

## 2. Materials and methods

### 2.1. Participants

One-hundred-thirty five individuals with BD, diagnosed according to the Diagnostic and Statistical Manual of mental disorders (DSM-IV) [53], were drawn from a dedicated outpatient center at the Department of Psychiatry of the Medical University of Graz. All patients met the inclusion criteria for euthymia: a score on the *Hamilton Depression Scale* (HAM-D) [54] below 11 and a score on the *Young Mania Rating Scale* (YMRS) [55] below 9.

The current investigation was a secondary analysis of data from a cohort study that was originally intended for other purposes, the BIPFAT study, which explored the shared pathophysiological pathways of obesity and altered brain function in BD. The BIPFAT study design comprises clinical and laboratory diagnostics, neuropsychological measures, electroencephalography, and magnet resonance imaging. A detailed description of the study protocol and the study procedure can be found in previous reports by Lackner et al. [8,12] or Reininghaus et al. [20].

### 2.2. Measurements

All participants completed a German version of the *Food-Craving Inventory* (FCI) [32], designed to measure the total amount of food craving on four domains (fat/carbohydrates/sweets/fast-food). The *Structured Clinical Interview* according to DSM-IV (SCID-I), containing the GAF score (*Global Assessment of Functioning*) [56], the HAM-D, and the YMRS were administered by a trained interviewer. A detailed medical and psychiatric history was taken and participants completed the *Beck Depression Inventory* (BDI-II) [57]. A fasting blood sample was collected, allowing the analysis of levels of glucose, hemoglobin A1c (HbA1c) and homocysteine, as well as

lipids, including triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Serum TRP and KYN concentrations were measured by high performance liquid chromatography [58], with neopterin levels determined by enzyme-linked immunosorbent assay (BRAHMS Diagnostics). To assess overweight and obesity, anthropometric parameters were collected, including body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-height-ratio (WHtR). The BMI was calculated from the body weight (kg) divided by the square of height in meters ( $m^2$ ). The measurement of waist and hip circumference was done in a standing position. Waist circumference was measured midway between the iliac crest and the lower costal margin. Hip circumference was measured at the widest portion of the buttocks [35]. Normal-weight, overweight and obesity were defined using the BMI cut-offs, according to the World Health Organization [59], as follows: normal-weight: BMI = 18.50–24.99; overweight: BMI = 25.0–29.9; obesity: BMI  $\geq$  30.00. The study has been endorsed by the local ethics committee and satisfies the standards of the current revision of the Declaration of Helsinki (EC-number: 24-123 ex 11/12).

### 2.3. Statistics

Pearson correlations were calculated among clinical and socio-demographic measures to assess the need for inclusion of proposed control variables in the analysis. Associations between metabolic risk factors (blood glucose, HbA1c, homocysteine, total cholesterol, HDL, LDL, triglycerides) and food craving parameters were calculated using partial correlation analyses, introducing age, BMI, mood stabilizing medication (lithium, anticonvulsants, atypical antipsychotics, typical antipsychotics), and smoking (yes/no) as co-variables. Associations between anthropometric variables (BMI, waist circumference, WHR, WHtR) and food craving were conducted using age, smoking (yes/no), and mood stabilizing medication (lithium, anticonvulsants, atypical antipsychotics, typical antipsychotics) as co-variables. For association analyses with TRP metabolites, data from 70 bipolar patients were available, with age, BMI, smoking (yes/no), and mood stabilizing medication (lithium, anticonvulsants, atypical antipsychotics, typical antipsychotics) introduced as co-variables.

To measure differences in food craving between overweight/obese and normal-weight patients in relation to sex, a multivariate analysis of co-variance (MANCOVA) with the independent factors overweight/obesity (normal-weight vs. overweight vs. obese) and sex were performed using key co-variables including age, smoking, and mood stabilizing medication.

## 3. Results

Participants showed a high prevalence of overweight (31.9%) and obesity (32.6%). Metabolic characteristics and TRP metabolites in normal-weight and overweight/obese patients are displayed in Table 1, where means and standard deviations of group comparisons are shown.

Table 2 lists clinical characteristics in BD patients and distribution of mood stabilizing medication in the sample.

### 3.1. Foods commonly craved

Overall, individuals with BD had a median FCI-score of 66 (Min = 30, Max = 102). Pasta (41.5%) and chocolate (40.7%) were the foods most commonly craved by BD participants (both normal-weight and overweight). Sausages were significantly more likely to be craved by overweight/obese participants than by normal-weight participants ( $\chi^2(3/1) = 9.13, p = .028$ ).

### 3.2. Association of food craving with clinical characteristics

When correlating food craving scores with clinical variables, significant, positive correlations of age at first episode with food craving were evident (food craving sum score:  $r = .22, p = .015$ ; fast-food craving:  $r = .20, p = .027$ ; sweets craving:  $r = .18, p = .045$ ), whilst a trend was evident between fast-food craving and BDI sum score ( $r = .17, p = .053$ ). No significant associations were found for the other clinical parameters (number of manic/depressive episodes, sleep disorder, binge eating, substance/alcohol abuse, HAMD, YMRS, GAF).

### 3.3. Associations of food craving with metabolic risk factors

Raised triglyceride levels were significantly associated with fast-food craving ( $r = .18, p = .047$ ), and fat craving ( $r = .22, p = .012$ ), whilst a trend was evident with carbohydrate craving ( $r = .17, p = .065$ ). HDL cholesterol was related significantly to fat craving ( $r = -.22, p = .014$ ).

### 3.4. Associations of food craving with tryptophan–kynurenine metabolites

KYN/TRP ratio, as well as KYN concentrations, were positively correlated with carbohydrate craving (KYN/TRP ratio:  $r = .27, p = .032$ ; KYN:  $r = .26, p = .039$ ). Nitrite levels were associated with fat craving ( $r = .25, p = .046$ ) and neopterin levels were associated with fat craving ( $r = -.28, p = .026$ ) and fast food craving ( $r = -.27, p = .033$ ).

### 3.5. Association of food craving with anthropometric measures of overweight/obesity

No significant correlations were evident between food craving and anthropometric measures (BMI:  $r = .09, p = .345$ , waist circumference:  $r = .12, p = .186$ ; WHR:  $r = .08, p = .122$ , and WHtR:  $r = .12, p = .178$ ) in individuals with BD.

### 3.6. Differences in food craving between men and women as well as overweight and normal-weight patients

The MANCOVA indicated a significant sex effect ( $F(4/116) = 2.51, p = .046, \eta^2 = .080$ ) demonstrating higher levels of fat craving in males, versus females, with BD ( $F = 6.43, p = .013, \eta^2 = .051$ ). No significant multivariate effect was found for the factor overweight/obesity ( $F(4/116) = 1.77, p = .084, \eta^2 = .057$ ), although there was a tendency for higher fast-food craving in obese, compared to normal-weight or overweight individuals, in the univariate analyses ( $F = 3.28, p = .041, \eta^2 = .052$ ). No interaction between overweight and sex was found ( $F(4/116) = 1.15, p = .331, \eta^2 = .038$ ). Smoking was identified as significant confounder ( $F(4/116) = 3.94, p = .005, \eta^2 = .120$ ) for fat craving ( $F = 6.67, p = .011, \eta^2 = .053$ ) as well as fast-food craving ( $F = 8.39, p = .004, \eta^2 = .066$ ). Neither mood stabilizing medication nor age was significant confounders. Table 3 shows means and standard deviations are displayed.

## 4. Discussion

This study addressed the question as to the relationship between obesity-related parameters (lipometabolism, TRP metabolism, anthropometrics) and food craving in a well-characterized sample of euthymic individuals with BD. The main finding of this study indicates that food craving is associated with TRP-KYN metabolites, which are markers of immune-inflammatory processes. In addition, correlations with lipid alterations are also evident,

**Table 1**  
Metabolic characteristics and tryptophan metabolites in normal-weight and overweight/obese patients.

|  | Normal-weight (n = 45) | Overweight/obesity (n = 88) | Statistics | p     |
|--|------------------------|-----------------------------|------------|-------|
| Age  | 41.2 (13.9)            | 46.4 (13.4)                 | −2.10      | .038  |
| Males/Females (n)                                | 17/28                  | 51/37                       | 4.85       | .028  |
| <b>Anthropometric measures</b>                   |                        |                             |            |       |
| BMI  | 22.4 (1.9)             | 31.3 (5.9)                  | −9.81      | <.001 |
| Waist circumference                              | 80.7 (8.0)             | 104.7 (14.5)                | −12.3      | <.001 |
| WHR  | .87 (.08)              | .96 (.09)                   | −5.43      | <.001 |
| WHtR   | .47 (.04)              | .61 (.08)                   | −10.29     | <.001 |
| Metabolic Syndrome (yes, n)                      | 3                      | 43                          | 22.34      | <.000 |
| <b>Metabolic parameters</b>                      |                        |                             |            |       |
| Smoking (yes, n)                                 | 21                     | 40                          | .061       | .805  |
| Hypertension (yes, n)                            | 0                      | 29                          | 18.58      | <.001 |
| Diabetes (yes, n)                                | 1                      | 9                           | 2.65       | .103  |
| Total cholesterol (mg/dl)                        | 198 (43.8)             | 192 (44.6)                  | .700       | .485  |
| HDL (mg/dL)                                      | 66.9 (19.2)            | 51.1 (13.9)                 | 5.37       | <.001 |
| LDL (mg/dL)                                      | 110 (36.5)             | 112 (38.4)                  | −.343      | .732  |
| Triglycerides (mg/dL)                            | 103 (72.8)             | 139 (72.1)                  | −2.69      | .008  |
| Blood glucose (mg/dL)                            | 91.8 (10.7)            | 100 (21.6)                  | −2.37      | .009  |
| HbA1c (mmol/mol)                                 | 33.6 (3.8)             | 36.9 (7.2)                  | −2.68      | .019  |
| Homocysteine (μmol/L)                            | 12.7 (6.2)             | 12.9 (3.2)                  | −.207      | .836  |
| <b>Tryptophan–kynurenine metabolites (serum)</b> |                        |                             |            |       |
| Tryptophan (μmol/l)                              | 54.5 (9.2)             | 60.5 (9.0)                  | −2.57      | .012  |
| Kynurenine (μmol/l)                              | 2.5 (.82)              | 3.4 (.98)                   | −3.87      | <.000 |
| Kynurenine/tryptophan ratio                      | 46.7 (17.0)            | 56.7 (15.5)                 | −2.46      | .016  |
| Neopterin (μmol/l)                               | 6.6 (7.9)              | 7.2 (4.6)                   | −.40       | .691  |
| Nitrite (μmol/l)                                 | 14.1 (16.5)            | 21.6 (21.02)                | −1.48      | .144  |

Note: Hemoglobin A1c (Hb A 1c), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Body mass index (BMI), Waist-to-hip-ratio (WHR), Waist-to-height-ratio (WHtR). Statistics are Mann–Whitney U-Tests, Chi-squared tests, and independent t-tests.

**Table 2**  
Clinical characteristics and mood stabilizers in normal-weight and overweight/obese patients.

|                                    | Normal-weight | Overweight/Obesity | Statistics | p    |
|------------------------------------|---------------|--------------------|------------|------|
| <b>Clinical characteristics</b>    |               |                    |            |      |
| BD-I/BD-II (n)                     | 27/17         | 57/31              | .147       | .701 |
| Illness duration (years)           | 19.0 (10.7)   | 19.8 (13.5)        | −.347      | .729 |
| Age of first episode (years)       | 21.4 (9.6)    | 26.1 (10.9)        | −2.41      | .018 |
| Number of manic/hypomanic episodes | 8.3 (9.1)     | 11.3 (16.0)        | −1.40      | .165 |
| Number of depressive episodes      | 13.4 (12.1)   | 15.5 (20.5)        | −.621      | .535 |
| Sleep disorder (yes, n)            | 33            | 67                 | .218       | .640 |
| Binge eating (yes, n)              | 1             | 4                  | −1.46      | .152 |
| Substance abuse (yes, n)           | 7             | 8                  | 1.47       | .225 |
| Alcohol abuse (yes, n)             | 4             | 15                 | 1.40       | .237 |
| HAMD                               | 6.4 (4.9)     | 5.3 (4.3)          | 1.31       | .193 |
| YMRS                               | 1.1 (1.9)     | 1.8 (4.0)          | −1.49      | .138 |
| BDI                                | 12.8 (10.0)   | 15.0 (11.3)        | −1.10      | .272 |
| GAF                                | 70.3 (14.1)   | 67.3 (13.3)        | 1.20       | .232 |
| <b>Mood stabilizing medication</b> |               |                    |            |      |
| Antidepressant (yes, n)            | 16            | 24                 | .815       | .367 |
| Lithium (yes, n)                   | 12            | 30                 | .916       | .339 |
| Anticonvulsants (yes, n)           | 16            | 26                 | .384       | .535 |
| Atypical antipsychotic (yes, n)    | 25            | 56                 | 1.14       | .285 |
| Typical antipsychotic (yes, n)     | 6             | 14                 | .198       | .656 |
| Combination therapy (yes, n)       | 13            | 31                 | .678       | .410 |

Note: Bipolar disorder type I (BD-I), Bipolar disorder type II (BD-II), Hamilton Depression Scale (HAMD), Young Mania Rating Scale (YMRS), Beck Depression Inventory (BDI), Global Level of Functioning (GAF). Statistics are Mann–Whitney U-Tests, Chi-squared tests, and independent t-tests.

**Table 3**  
Comparison of food craving scores between normal-weight, overweight and obese patients, separately for men and women.

|                      | Normal-weight (M, SD) |             | Overweight (M, SD) |             | Obesity (M, SD) |             |
|----------------------|-----------------------|-------------|--------------------|-------------|-----------------|-------------|
|                      | Males                 | Females     | Males              | Females     | Males           | Females     |
|                      | n = 18                | n = 28      | n = 28             | n = 15      | n = 22          | n = 22      |
| <b>Food craving</b>  |                       |             |                    |             |                 |             |
| Total food craving   | 64.2 (15.7)           | 64.4 (16.7) | 68.9 (11.9)        | 65.5 (13.6) | 69.1 (10.5)     | 69.4 (13.7) |
| Sweets craving       | 16.9 (6.2)            | 20.9 (8.8)  | 20.6 (6.3)         | 21.4 (5.7)  | 21.4 (4.5)      | 21.7 (6.7)  |
| Carbohydrate craving | 18.9 (5.0)            | 18.3 (5.3)  | 18.6 (3.7)         | 18.9 (5.4)  | 18.9 (4.2)      | 20.5 (4.7)  |
| Fat craving          | 18.1 (6.3)            | 16.1 (4.8)  | 20.9 (4.7)         | 16.8 (5.1)  | 18.5 (5.5)      | 17.4 (5.1)  |
| Fast-food craving    | 10.3 (3.2)            | 9.0 (3.3)   | 8.9 (3.0)          | 8.3 (3.5)   | 10.3 (2.3)      | 9.9 (3.2)   |

Note: Bipolar disorder (BD).



giving links to metabolic syndrome [60]. Cravings for carbohydrates, fat and fast-food were of greater importance. Anthropometric parameters (e.g. BMI, waist circumference) seem to play a minor part in this relationship. The detected connections between food craving and the analyzed parameters of obesity, metabolic parameters and TRP breakdown in BD are shown in Fig. 1.

Recent data on TRP breakdown in BD [20], found blood KYN concentration, as well as the KYN/TRP ratio, to be significantly higher in euthymic BD, *versus* healthy controls, which was even more evident in the subsample of overweight/obese BD patients. This is supported by the results of the present study. Increased TRP breakdown indicates an increase in pro-inflammatory cytokines associated with heightened levels of immune-inflammation, which is proposed to contribute to the high occurrence of medical comorbidities, and increased mortality, in BD. Previous data shows TRP metabolism to be important to the maintenance of obesity, including by influencing the reward sensitivity system and behavioral inhibition [61,62].

Wider nutritional interactions with immune-linked processes are likely. For example, multiple pathways underpin the gut–brain axis, including brain biochemistry, the vagus nerve, and pro-inflammatory cytokines, as well as TRP metabolism [63]. The KYN pathway is activated following increased pro-inflammatory cytokines and reactive oxygen species, which therefore lead to a decrease in TRP availability as a precursor for serotonin, N-acetylserotonin and melatonin production [49]. Poor diet in obesity can increase gut permeability, thereby contributing to an increase in gut-linked immune-inflammatory processes, with increased pro-inflammatory cytokines feeding back to further increase gut permeability [64]. Gut permeability is increased by stress-induced cortisol as well as dietary factors, such as binge-drinking and saturated fats [24], which are also factors that are implicated in the pathophysiology of BD [65,66]. The microbiome can influence emotional behavior, including by altering central serotonin and dopamine transmission [66], whilst the products of the gut microbiome can also influence host antioxidative defense [67]. Overall, the gut microbiome and alterations in gut permeability may be an important contributor to increased immune-inflammatory activity in BD, including from the consequences of changes in food craving.

The night-time triggered release of pineal melatonin is an important regulator of the circadian rhythm, including in the regulation of caloric intake. Sleep deprivation perturbs orexin

activity, which leads to neuropeptide Y activation and hunger induction [49,68,69]. Such circadian dysregulation may be especially important in BD, as circadian rhythm disruption is evident in all BD phases. Melatonin is also very highly produced in the gut, at levels far higher than the pineal circadian peak, with gut melatonin thought to contribute maintaining gut barrier integrity [49]. As such, pro-inflammatory cytokines and stress, by increasing kynurenine synthesis at the expense of serotonin and melatonin, may contribute to alterations in many organs, including in the gut. It is also of note that melatonin decreases mood stabilizer/antipsychotic-induced weight-gain in BD patients [70,71].

TRP is an essential amino acid that can only be obtained from nutrition. Although it readily crosses the blood–brain barrier, the amount of TRP depends on the ability to compete with other large neutral amino acids (LNAA). Consequently, a diet of TRP-rich foods that are also rich in other LNAA may even decrease TRP availability in the brain. For instance, a carbohydrate-rich/protein-poor diet can increase the plasma TRP–LNAA ratio [45,72]. Since the release of insulin after ingestion of non-fructose carbohydrate can shift this ratio towards TRP, an individual with decreased levels of serotonin would crave carbohydrate-rich foods like pasta and chocolate, as compensatory to serotonin depletion. Buwalda et al. [46] found that 5-HT<sub>1A</sub> serotonin receptors in the central nervous system were desensitized in animals receiving a carbohydrate-based diet. This illustrates one aspect of the “reward deficiency syndrome”: the more carbohydrates a person eats, the more desensitized he or she will become to serotonin, experiencing delayed satiety, and thus eating more [73]. A recent review of the neurobiological foundation of carbohydrate craving proposed a role for brain serotonin due to: (a) increases in brain serotonin levels improve mood and reduce stress and anxiety, and therefore (b) carbohydrate intake is an attempt at self-treatment, given the increase in brain serotonin that occurs after carbohydrate intake [74]. The authors refer to findings showing that TRP levels after a meal rich in carbohydrates tend to increase along with serotonin, due to a 42% rise in brain TRP, *versus* diets rich in protein and low in carbohydrates [75]. Strasser and Fuchs [76] recommended TRP supplementation to assist in the treatment of unrestricted weight gain and in managing vulnerability for depressive episodes.

The correlation between carbohydrate craving and KYN levels provide indirect evidence of increased activity of TRP-degrading IDO, and perhaps TDO, in euthymic BD patients showing high food craving levels. This further emphasizes the significant role of stress and inflammatory agents in the development and/or perpetuation of eating dysregulations and obesity in BD.

In our investigation, associations between neopterin, an indicator of T-helper (Th)1-type immunity, with fat and fast-food craving were evident. The Th-1/Th-2 cell ratio is linked to many medical conditions, including in the susceptibility of atherosclerotic plaques [77,78]. Levels of serum/plasma nitrite correlate with formation of nitric oxide [79], which, when in excess, has many negative associations, including nicotine craving [80]. Furthermore, serum nitrite is significantly linked to diabetes in men, including in hyperglycemia-induced endothelial dysfunction [81]. High serum nitrite levels are potential risk factors for cardio-vascular and metabolic diseases [52].

In contrast to much of the existing literature, male, *versus* female, BD patients have a higher fat craving. In contrast to our assumptions, no significant difference in food craving between normal-weight, overweight or obese individuals with BD were evident. Although previous findings indicate a relationship between food craving and BMI [30], the craving for food is not necessarily equivalent to the consumption of food [82]. Accordingly, early attempts to prove this relationship have also failed [32].

The association of food craving with obesity-related parameters in individuals with bipolar disorder

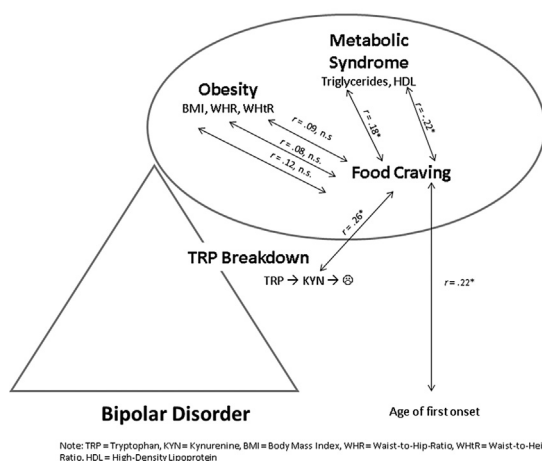


Fig. 1. Food craving and obesity-related parameters in individuals with bipolar disorder.

However, our results showed that fat craving was related to elevated triglycerides levels and higher HDL, two indicators of metabolic syndrome. It is worth mentioning that normal-weight individuals can also develop metabolic syndrome, including a significant higher cardiovascular risk [60].

#### 4.1. Limitations

Self-report measures, including of food craving have inherent limitations [83], especially in regard to issues of validity, including the assessment of idiosyncratic data or the motivation to report. Furthermore, we cannot be sure if participants used the same concept of food craving. Most inventories, including the FCI, evaluate common cravings related to specific categories of food, and are therefore limited. The FCI may be further limited by the absence of any distinction between state, *versus* trait, food cravings. It is also of note that physical activity was not controlled for, which may influence eating behavior and hunger [84], as well as TRP metabolism [85,86]. In addition, some patients were treated by various medications, which can adversely interact and which often have striking orexigenic effects, such as lithium [17,18]. As we had no control group, it cannot be inferred that any of the findings are specific in any way to BD. However, preliminary analyses with healthy controls revealed higher food craving in individuals with BD ( $n = 50$ ) *versus* controls ( $n = 50$ ) [87]. As we have no data on real food intake, the influence of food craving on actual consumption may be another complication that requires clarification. Additional research should also determine how levels of food craving vary during different stages of the disease (depression, hypomania, mania). Based on detected sex differences, future studies should assess as to whether food craving is influenced by the menstrual cycle. As some recent data suggest that the increase in pro-inflammatory cytokines in mood disorders is primarily linked to the reporting of early abusive events [88], this could suggest an increase in pro-inflammatory cytokine-induced IDO in those with a history of early trauma. Future studies on circulating pro-inflammatory cytokines in BD should additionally assess data on early abuse/neglect events, which can also increase the risk of obesity in adolescents with BD [89]. To link such data to some measure of alterations in the gut microbiome and/or in gut permeability could also be very promising.

#### 5. Conclusions

In euthymic individuals with BD, food craving, especially carbohydrate craving, was related to TRP conversion to KYN, an important indicator of immune-mediated inflammation. Consequently, the low serotonin availability will affect brain appetite regulation centers, leading to increased endorphins production, following carbohydrate and fat consumption [44,45]. A higher metabolic risk (manifest in disturbed lipid metabolism) is associated with fat craving. However, the present results indicate that higher levels of overweight/obesity in BD cannot be explained exclusively by high levels of food craving.

There are many factors that may influence obesity, including genetic, epigenetic, early developmental and lifestyle, which interact to co-ordinate subjective food craving with pathophysiological mechanisms that underpin metabolic dysregulation in BD. Given the high obesity rates in BD, and how these may interact with BD pathophysiology via such mechanisms as the gut–brain axis, nutrition-based programs may have clinical efficacy in the management of obesity as well as in BD pathophysiology, *per se*. Overall, BD and obesity share common pathophysiological pathways, including increased levels of immune-inflammatory activity. Prospectively, the diagnosis and management of BD requires

dysregulated TRP metabolism to be considered, including the relevance of alterations in dietary habits.

#### Statement of authorship

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

#### Conflict of interest

The authors report no financial or other relationship relevant to the subject of this article.

#### Funding sources

None.

#### Acknowledgments

We would like to thank Renate Unterweger and our scientific staff members at the Department of Psychiatry who contributed to data collection. Portions of these data were presented at the 23rd European Congress of Psychiatry in Vienna, March, 28–31, 2015.

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