Affective temperament in inflammatory bowel diseases: Another brick in the wall of differentiation

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Abstract

Psychiatric disorders are significantly common complications among patients suffering from inflammatory bowel diseases (IBD). Affective temperament is a concept of core personality traits, which can describe the vulnerability to mood disorders, therefore its evaluation might convey useful information about patients’ mental status in autoimmune disorders. The aim of the study was to evaluate the affective temperament in patients with Crohn’s disease (CD) and ulcerative colitis (UC) as characteristic features of these diseases, but also in the clinical course and the severity of anxiety and depression. Due to our knowledge this is the first study of this kind. The study enrolled 130 patients with IBD, including 68 with CD and 62 with UC. We used TEMPS-A to evaluate affective temperament and HADS scales to assess the intensity of depressive and anxiety symptoms. Harvey Bradshaw scale, Crohn’s Disease Activity Index (CDAI) and Mayo Score were used to evaluate clinical severity of the diseases. We observed significantly higher prevalence of depressive, cyclothymic and anxiety temperaments in CD patients compared to the control group. Harvey Bradshaw scale, CDAI and Mayo Self Report showed statistically significant outcomes, including significant positive correlations with depressive, cyclothymic and anxiety subscales of TEMPS-A, and negative correlation with the hyperthymic temperament in CD subjects. Our findings indicate significant differences between CD and UC due to temperament traits, and suggest distinct pathogenesis of mood disorders in IBD.

Introduction

Inflammatory Bowel Disease (IBD), such as Crohn’s Disease (CD) and Ulcerative Colitis (UC) are chronic and relapsing gastrointestinal disorders with crucial implications. This issue requires greater attention provided that the number of patients with IBD is still significantly...
increasing, especially in the western industrialized countries. The occurrence rate of IBD in adult Europeans can reach even 140 per 100,000 inhabitants [1].

IBD may lead to several considerable complications associated not only with gastrointestinal manifestation, but can also affect other relevant systems [2–6]. This contributes to poor quality of life (QoL) in IBD patients. They present worries and concerns regarding complications, stigmatization or intimacy, as well as management plans or effective treatment interventions [7]. According to many studies, impaired QoL depends on the disease activity [8,9].

Epidemiological studies have established that anxiety and depression are the most prevalent psychiatric disorders among IBD patients [10–13]. Also patients suffering from other immune-mediated inflammatory diseases, such as multiple sclerosis or rheumatoid arthritis, are at the increased risk of psychiatric comorbidity [14,15]. The incidence of mood disorders in IBD is not well understood, although the risk of falling for depression or anxiety gets higher, as QoL decreases [15]. It has been noted, that long-term stress may change the course of the disease resulting in higher risk of exacerbations [16]. Therefore, in the case of enhanced symptoms during the course of IBD, it is crucial to take into account patient's mental health and stress levels [17].

Hagop Akiskal has developed the novel concept of affective temperament; it comprises inherited personality traits which may become the extreme manifestations of affective disorders. Affective temperament might be considered as a phenotype which derives from genetic and biological bases. It remains rather stable over time, however dysregulations of the temperament may predispose to the development of affective disorders, like depression or bipolar disease [18–20,21]. Hence, affective temperament may be considered as a factor predisposing to psychiatry diseases, such as depression or anxiety.

Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) is a self-report instrument used in order to assess five affective temperaments in subjects: hyperthymic, depressive, irritable, cyclothymic and anxious [22]. Recent studies show numerous correlations between greater scores of temperaments which show liability to mood disorders and the prevalence of depressive or anxiety symptoms [23]. TEMPS-A has been proved useful in the temperament evaluation in context of both depressive and anxiety symptoms in autoimmune disorders [24–26]. However, currently there is no study describing temperament in patients suffering from IBD. Thus, the aim of this study was to evaluate the prevalence of five traits of affective temperament, by means of TEMPS-A, in IBD patients in relation to the intensity of depression and anxiety and clinical manifestation of the diseases in both UC and CD patients. We hypothesized that patients with IBD show specific affective temperament profile, which may be associated with clinical manifestation of the diseases, including neuropsychiatric symptoms e.g. depression and anxiety. To our knowledge, this is the first study laying the emphasis on the affective temperament in IBD, and its relation to the intensity of clinical factors affecting the course of both CD and UC.

Materials and methods

Participants

The study involved 130 patients; 68 with CD (30 women and 38 men) and 62 with UC (31 women and 31 men). They were of Polish nationality and white ethnicity. The mean age of participants was 28.5 years (range, 22–36.5 years) for CD group and 31 years (range, 21–50 years) for UC group. The patients were treated outpatient at the Clinic of Intestinal Diseases and, according to the consent of the bioethical commission, they were recruited on the basis of the proposal of a gastroenterologist. During the observation, the diagnosis has not been changed. Demographic factors are shown in Table 1.
The inclusion criteria were the diagnosis of IBD and the signing of the Informed Consent Form for participation in the study. The diagnosis of IBD was determined based on diagnostic criteria, including clinical presentation, laboratory, endoscopic and imaginary studies, as well as histological results.

In order to determine differences in the expression of temperament dimensions, the control group of healthy people was selected in terms of sex and age for the study groups.

Participants with a severe somatic or psychiatric disorder per Diagnostic and Statistical Manual of Mental Disorders, 4th edition, or with diagnosed any neurological abnormality, addiction to illicit drugs or alcohol were excluded from the study.

**Ethical statement**

Permission for the study was obtained from the Bioethical Commission of the Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz. The subjects demonstrated their willingness to participate in the study by signing the Informed Consent Form. All the patients were informed about the goals and processes of the study, potential risks, anonymity of the data and the possibility to cancel their participation at any moment.

**Assessments**

The procedure of examination shown below was conducted once and consisted of clinical, biochemical and psychological assessment.

**Clinical assessment**

Clinical evaluation was based on physical examination and medical history as well as filling out a questionnaire concerning the course of the disease and individual factors. We evaluated

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### Table 1. Basic demographic and clinical parameters in subgroups of patients with CD and CU.

|                        | CD (n = 68)          | UC (n = 62)          | p     | Cohen’s d |
|------------------------|----------------------|----------------------|-------|-----------|
| **Age (y)**            | 28.5 (22.0–36.5)     | 31.0 (21.0–50.0)     | 0.41  | 0.30      |
| **Gender**             | ♀ 30 (44%)           | ♀ 31 (50%)           | 0.63  | -         |
| **Duration of illness (y)** | 5.0 (3.0–8.0)       | 6.0 (2.0–8.0)       | 0.74  | 0.007     |
| **Biometrics**         |                      |                      |       |           |
| BMI (kg/m²)            | 22.1 (19.2–24.8)     | 22.5 (20.2–26.3)     | 0.19  | 0.36      |
| Waist (cm)             | 81.0 (76.0–89.0)     | 83.0 (76.0–90.0)     | 0.55  | 0.27      |
| **Education**          |                      |                      |       |           |
| Basic (n,% )           | 4 (6%)               | 4 (6.5%)             | 0.82  | -         |
| Vocational (n,% )      | 11 (16%)             | 8 (13%)              |       |           |
| Secondary (n,% )       | 33 (48.5%)           | 31 (50%)             |       |           |
| Higher (n,% )          | 20 (29.5%)           | 19 (30.5%)           |       |           |
| **Physical Activity**  |                      |                      |       |           |
| None (n,% )            | 25 (37%)             | 24 (39%)             | 0.60  | -         |
| < 1/week               | 8 (12%)              | 14 (22.5%)           |       |           |
| 2-3/week               | 31 (45.5%)           | 16 (26%)             |       |           |
| >3/week                | 4 (5.5%)             | 8 (12.5%)            |       |           |
| **Cigarette smoking (n, %)** | 11 (16%)         | 14 (23%)             | 0.81  | -         |

Values are expressed as the median (25–75%) or as number of patients (n). Significance of differences between groups was determined by Mann–Whitney U Test. BMI: Body Mass Index.
demographic factors (age, sex, education, place of residence etc.), parameters related to illness: disease type, duration, other diseases, risk factors of IBD or exacerbations, anthropometric parameters etc.

**Assessment of disease activity**

For the assessment of clinical activity and course of the disease, we utilized Crohn’s Disease Activity Index (CDAI) and Harvey-Bradshaw Index for CD. For UC activity evaluation we used Mayo Classification.

**Crohn’s Disease Activity Index.** CDAI is a standard questionnaire used in research studies in order to assess disease activity. Calculation of CDAI involves 8 items such as hematocrit, physical examination outcomes, and 1-week diary data of the number of liquid stools, the intensity of abdominal pain and general well-being. Every parameter is evaluated in numeric scale and increasing number of points is associated with disease exacerbation. Another item involves the occurrence of concurrent complications such as arthritis, uveitis, erythema nodosum, fistulas or abscesses. Moreover CDAI includes the usage of anti-diarrhea drugs, and the presence of abdominal mass which is evaluate during physical examination. The disease activity is calculated building on the total amount of obtained points [27].

**Harvey-Bradshaw Index.** Harvey-Bradshaw Index is simplified alternative to the CDAI, designed for easier data collection and calculations in evaluating CD’s activity. In comparison to CDAI, this scale does not require a 7-day data collection from the patient and is based on the assessment from the 1-day observations. Evaluated items consist of general well-being, the intensity of abdominal pain, the daily number of liquid stools, the occurrence of abdominal mass and concurrent complications associated with UC. The disease activity is determined based on overall obtained points. Patients with score < 5 are likely to be in remission; scores over 5 points suggest exacerbation [28]. Studies show positive correlations between both CDAI and Harvey-Bradshaw index in CD activity assessment. [29–31].

**The Mayo Score.** The Mayo Score is used to assess the activity of UC. The scale shows patient’s symptoms (such as abdominal pain, rectal bleeding, the number of liquid stools), the appearance of the moid mucosa in endoscopic studies and other findings during physical examination. The sum of all obtained scores reflects disease activity [32].

**Psychological assessment**

We used Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) to assess affective temperament in our group of patients. The anxiety and depressive symptoms intensity were evaluated using the HADS scale (Hospital Anxiety and Depression Scale) with the cut-off score as over 8.

**Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A).** TEMPS-A measures affective temperament traits, represented by five dimensions: depressive, cyclothyemic, anxious, irritable and hyperthymic. The tool consists of 110 items; version for males contains 109 questions. Questions regarding each dimension require simple “yes” (score 1) or “no” (score 0) answers, and are grouped together in following manner:

1. questions 1 to 21 (21 points) relate to depressive temperament;
2. questions 22 to 42 (21 points) relate to cyclothyemic temperament;
3. questions 43 to 63 (21 points) relate to hyperthymic temperament;
4. questions 64 to 84 (21 points, 20 points in the version for men) relate to irritable temperament;
5. questions 85 to 110 (26 points) relate to anxious temperament. Points scored for each temperament are summed up and then divided by the number of questions pertained to each dimension. Based on that, the severity of each temperament is measured [18,33]. In our study, the Polish version of TEMPS-A was utilized [34].

Hospital Anxiety and Depression Scale (HADS). HADS is a simple tool for the assessment of anxiety and depression in patients who suffer from somatic diseases [35]. The auto-questionnaire contains two parts: seven questions to evaluate the severity of depressive symptoms, and another seven questions applying to anxiety symptoms. Results for anxiety and depression are summed up separately, albeit the questions of each part are interspersed. We used following cut-off points established for Polish population: 0–7 –no disorders; 8–10 –mild intensity; 11–21 –severe intensity [36].

Statistical analysis

STATISTICA 12.5 was used for statistical analyses; it was conducted for two groups. Using the Shapiro-Wilk test, it was found that the test group does not meet the normal distribution criteria. To assess the significance of the differences between groups the Mann-Whitney U test was used. Effect size was expressed using Cohen’s d. The R-Spearman test was used to determine correlations between non-parametrical variables. Differences and correlations were considered significant for \( p < 0.05 \).

Results

The initial analysis of affective temperament showed that patients with CD have significantly more depressive (\( p = 0.018 \), d-Cohen = 0.51), cyclothymic (\( p = 0.026 \), d-Cohen = 0.32) and irritable (\( p = 0.029 \), d-Cohen = 0.27) dimensions in relation to patients with UC (Table 2). Similar analyzes were carried out regarding the subgroup results of patients with CD and UC to the results of the control group matched according to gender, age and level of education to the patients groups (Table 3). The results indicated higher prevalence of depressive (\( p = 0.0004 \), d-Cohen = 0.43), cyclothymic ((\( p = 0.0001 \), d-Cohen = 0.27) and anxiety (\( p = 0.001 \), d-Cohen = 0.52) temperaments among CD patients compared to the control group. In contrast, patients with UC were only characterized by a significantly lower scores of irritability in TEMPS-A.

The study of the correlation of the TEMPS-A scale with the total score of the CDAI clinical scale did not show significant results. However, a similar analysis with the total result of the Harvey Bradshaw scale, the higher the score expresses the greater the activity of the disease, showed significant positive correlations with depressive (\( p = 0.025 \)), cyclothymic (\( p = 0.049 \)) and anxiety (\( p = 0.007 \)) affective temperaments, as well as negative ones with the hyperthymic dimension (Table 4). The number of surgical procedures was not related to the TEMPS-A subscales for both IBD groups.

In the next step, the correlations between TEMPS-A and the clinical self-assessment parameters of CDAI and Harvey Bradshaw indices were analyzed (Table 5). Significant correlation of TEMPS-A only with the number of stools has been found. The higher scores on depressive (\( p = 0.003 \) for CDAI and \( p = 0.015 \) for HBS) and anxiety (\( p = 0.031 \) for CDAI and \( p = 0.012 \) for HBS) dimensions were associated with a higher number of stools, while the higher scores on hyperthymic temperament were associated with a significantly smaller number of stools (\( p = 0.024 \) for CDAI and \( p = 0.008 \) for HBS). Similar analysis was then carried out for the results of patients with UC and Mayo Clinical scale, divided into a medical evaluation and self-assessment (Table 6). Significant correlations were associated only with self-assessment.
parameters. More pronounced subjective symptoms of the disease were significantly positively correlated with cyclothymic ($p = 0.038$) and anxiety ($0.031$) dimensions of TEMPS-A. The positive correlation of the depressive scale remained in the trend. The negative significant correlation was related to the hyperthymic temperament ($p = 0.034$).

Table 7 presents the results of the correlation between the severity of anxiety and depression symptoms measured with HADS and the dimensions of affective temperament. Hyperthymic temperament in both study subgroups was associated with lower symptoms of anxiety and depression, however, significant correlations were related only to the severity of anxiety. The other dimensions of affective temperament exhibited statistically significant positive correlations with the severity of anxiety and depression, except for the irritable temperament, which did not reach significance in patients with CD.

| Table 2. HADS and TEMPS-A results in subgroups of patients with CD and UC. |
|---------------------------------|-----------------|-----------------|-----|-----|
|                                | CD (n = 68)     | UC (n = 62)     | p   | Cohen’s d |
| HADS_A                         | 7.0 (5.0–9.0)   | 6.0 (2.0–7.0)   | 0.69| 0.09 |
| HADS_D                         | 4.0 (2.0–7.0)   | 4.0 (2.0–7.0)   | 0.90| 0.12 |
| TEMPS_depressive               | 0.38 (0.28–0.48)| 0.33 (0.19–0.43)| 0.018| 0.51 |
| TEMPS_cyclothymic              | 0.43 (0.26–0.57)| 0.28 (0.14–0.57)| 0.026| 0.32 |
| TEMPS_hyperthymic              | 0.52 (0.33–0.57)| 0.52 (0.38–0.67)| 0.47 | 0.09 |
| TEMPS_irritable                | 0.22 (0.1–0.35) | 0.15 (0.09–0.23) | 0.029| 0.27 |
| TEMPS_anxious                  | 0.35 (0.19–0.58)| 0.27 (0.15–0.44)| 0.13 | 0.25 |

Values are expressed as the median (25–75%) or as number of patients (n). Significance of differences between subgroups was determined by Mann–Whitney U Test.

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Table 3. TEMPS-A results in subgroups of patients with CD and UC and in control group.

| Table 3. TEMPS-A results in subgroups of patients with CD and UC and in control group. |
|---------------------------------|-----------------|-----------------|-----|-----|
|                                | CD (n = 68)     | Control (n = 132) | P   | UC (n = 62) | Control (n = 132) | p   |
| Age (y)                        | 28.5 (22.0–37.0)| 25.0 (24.0–30.0)| 0.47| 31.0 (20.0–50.0)| 25.0 (24.0–30.0)| 0.31|
| Gender (F/M, n, %)             | ♀ 30 (44%)      | ♀ 73 (55%)      | 0.11| ♀ 31 (50%) | ♀ 59 (45%) | 0.39|
|                               | ♂ 38 (56%)      | ♂ 59 (45%)      |     | ♂ 59 (45%) | ♂ 59 (45%) |     |
| TEMPS_depressive               | 0.38 (0.28–0.48)| 0.28 (0.19–0.43)| 0.0004| 0.33 (0.19–0.43)| 0.28 (0.19–0.43)| 0.51|
| TEMPS_cyclothymic              | 0.43 (0.26–0.57)| 0.26 (0.14–0.45)| 0.0001| 0.28 (0.14–0.45)| 0.26 (0.14–0.45)| 0.34|
| TEMPS_hyperthymic              | 0.52 (0.33–0.57)| 0.52 (0.33–0.67)| 0.27| 0.52 (0.38–0.67)| 0.52 (0.33–0.67)| 0.57|
| TEMPS_irritable                | 0.22 (0.1–0.35)| 0.19 (0.09–0.30)| 0.55| 0.15 (0.09–0.23)| 0.19 (0.09–0.30)| 0.039|
| TEMPS_anxious                  | 0.35 (0.19–0.58)| 0.23 (0.12–0.38)| 0.001| 0.27 (0.15–0.44)| 0.23 (0.12–0.38)| 0.10|

Values are expressed as the median (25–75%) or as number of patients (n). Significance of differences between subgroups and controls was determined by Mann–Whitney U Test.

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An analysis of covariance was also carried out for the effects assessment of gender, age and education on HADS results and parameters related to disease activity. In the CD group of patients, gender was the only parameter which affected the model with statistical significance ($F = 3.8$, $p = 0.008$). However, among patients with CU model was significantly affected by gender ($F = 12.9$, $p = 0.004$) and education ($F = 3.6$, $p = 0.008$).

**Discussion**

Temperament displays the relatively stable biological and genetic basis of personality which can putatively affect the risk of psychiatric comorbidities [22]. Mood disorders are very prevalent among IBD patients and by their intensity create two-dimensional dependencies with the clinical course. Hence TEMPS-A, as a simple tool, can be very useful in assessing patient’s morbidity to psychiatric disorders [37]. To our knowledge, this is the first study scrutinizing affective temperament in patients suffering from CD and UC.

As was shown in Table 2, CD patients scores were significantly higher in depressive, cyclothymic and irritable temperaments in comparison to UC patients. This may imply that patients suffering from CD may be more vulnerable to mood disorders, such as depression and anxiety, than UC patients. However, we have not observed any differences in HADS scales between those diseases. Researches describing mood disorders in IBD, usually assess both UC and CD collectively (as IBD) instead of evaluating them individually [38–40]. Our findings suggest that the origin of psychiatric symptoms in CD and UC may ensue from different mechanisms. More research is needed in this regard to invent adjusted strategies aiming to treat psychiatric comorbidities in particular group of IBD patients.

Subsequently, we compared TEMPS-A scales in CD and UC patients versus control groups. The results indicated that more strongly expressed depressive, cyclothymic and anxious affective temperaments are characteristic to Crohn’s disease, while UC patients did not differ in regard to these temperaments from the control group. Those findings accentuate the differences of the temperament profile in both diseases and therefore support the potential theory that the pathogenesis of mood disorders in both IBDs may have separate basis.

Depression is a heterogeneous condition triggered by various etiological factors, including genetic (neurotransmitter polymorphisms) and environmental ones (e.g. stress, immune infections). It has been suggested that chronic stress may cause alterations in synaptic transmission or change the morphology of neuron’s structure—i.e. impair neuroplasticity processes—within particular brain regions, resulting in the development of depressive symptoms. Diminished 5-HT neurotransmission might attenuate hippocampal neurogenesis, and thus, contribute to the occurrence of depressive symptoms [41]. In IBD, which is a condition characterized by chronic inflammation, stress-related factors might affect neuroplasticity in central nervous

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Table 4. TEMPS-A correlation with clinical factors in CD.

| CD          | No of surgical interventions | CDAI       | Harvey-Bradshaw Scale |
|-------------|------------------------------|------------|-----------------------|
|             | R   | p    | R   | p    | R  | p    |
| TEMPS_depressive | 0.105 | 0.39 | 0.218 | 0.07 | 0.27 | 0.025 |
| TEMPS_cyclothymic     | 0.052 | 0.68 | 0.064 | 0.62 | 0.245 | 0.043 |
| TEMPS_hyperthymic     | 0.125 | 0.33 | -0.085 | 0.51 | -0.239 | 0.049 |
| TEMPS_irritable       | 0.11  | 0.37 | -0.127 | 0.29 | 0.071 | 0.57  |
| TEMPS_anxious         | 0.179 | 0.14 | 0.125 | 0.33 | 0.322 | 0.007 |

R—Spearman correlations

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system and hence predispose to mood disorders. In their study Hong et al. observed significant differences in CT scans between UC and healthy controls. Authors suggest that the reorganization of grey matter in IBD may stem from chronic gut inflammation processes [42]. However, more research needs to be done in regard to this field.

Depressive temperament exhibits low energy, non-assertiveness, negative cognition or being shy, highly pessimistic and gloomy [20,43]. Individuals with higher cyclothymic temperament have tendencies to rapid mood shifts between the depressive and hyperthymic traits—between high and low moods [44]. They are instable considering their energy, self-esteem, as well as activity in social life [45]. Patients with high scores on anxious temperament displays behavioral and emotional response to the potential threats in the environment, i.e. the tendency to excessive worrying and inability to relax [22].

Hypertymic temperament seems to be independent of other temperaments. It is suggested that affective temperaments are grouped into “cyclothymic-sensitive” with dysthymic, cyclothymic, irritable, anxious temperaments and into independent hypertimic temperament. In this way, a different role of hypertimic temperament is explained in the process of modifying the clinical course of various diseases [46].

Many studies have assessed the relation between affective temperament and the susceptibility to depressive and anxiety disorders [19,43–45].

Table 5 presents the correlation between affective temperaments and both HADS-A and HADS-D scales in CD and UC individuals. Our findings are consistent with the literature describing the association between affective temperaments (depressive, anxious, cyclothymic and irritable) with the high prevalence of anxiety and depression [44,48]. Results from the study of Kesebir et al. indicate that higher scores of depressive, anxious, cyclothymic and irritable dimensions are significantly higher in depressive individuals than in healthy ones [47].

### Table 5. TEMPS-A correlation with the dimensions of subjective symptoms of scales assessing the clinical course of the Crohn Disease.

| CD | No of soft stools | Abdominal pain | General well-being | No of soft stools | General well-being |
|---|---|---|---|---|---|
| TEMPS_depressive, | 0.352 | 0.054 | 0.163 | 0.292 | 0.222 |
| TEMPS_cyclothymic | 0.232 | -0.054 | -0.018 | 0.230 | 0.187 |
| TEMPS_hyperthymic | -0.273 | -0.150 | 0.077 | -0.318 | -0.081 |
| TEMPS_irritable | 0.099 | -0.066 | -0.137 | 0.061 | -0.004 |
| TEMPS_anxious | 0.261 | 0.107 | 0.115 | 0.303 | 0.226 |

### Table 6. TEMPS-A correlation with clinical factors in Ulcerative Colitis. R—Spearman correlations.

| UC | No of surgical interventions | Mayo-Physicians assessment | Mayo-Self assessment |
|---|---|---|---|
| TEMPS_depressive, | -0.056 | 0.66 | -0.036 | 0.78 | 0.226 | 0.077 |
| TEMPS_cyclothymic | 0.073 | 0.57 | 0.183 | 0.15 | 0.264 | 0.038 |
| TEMPS_hyperthymic | -0.09 | 0.48 | -0.113 | 0.38 | -0.27 | 0.034 |
| TEMPS_irritable | -0.128 | 0.32 | 0.128 | 0.32 | 0.191 | 0.13 |
| TEMPS_anxious | -0.186 | 0.14 | 0.034 | 0.79 | 0.273 | 0.031 |

R—Spearman correlations
Research evaluating ankylosing spondylitis (AS) yield following results: depressive, cyclothymic, irritable and anxious temperament scores correlated with Beck Anxiety Inventory and Beck Depressive Inventory, hence greater scores of depressive and anxiety scales [25]. Based on the abovementioned literature, we assume that the greater scores of depressive, cyclothymic, irritable and anxious temperaments in TEMPS-A the higher vulnerability to falling for mood disorders in IBD patients. Our group of patients did not qualified as depressed or anxious according to the results of HADS scales, however we suggest that the regular monitoring of CD patients is needed due to their TEMPS-A results, and following proneness to developing mood disorders.

Interestingly, UC patients showed significantly lower scores in irritable temperament in comparison to CD and control group. Irritable temperament is portrayed as an unstable mixture of dysthymic and hyperthymic features. This suggests that UC patients may be less dysphoric and aggressive, show less criticism, are less complaining in comparison to control and CD groups [45]. Irritable temperament has been reported to be a predictor of depression in many studies, also in the group of patients suffering from a polycystic ovary syndrome [49]. According to our data, UC patients are less likely to develop depressive symptoms on the basis of their core personality traits showed by TEMPS-A.

Hyperthymic temperament displays exuberant, high self-esteem, narcissism and higher sociability [50]. In our results hyperthymic temperament negatively correlated with both HADS scales. Those results are consistent with the literature describing the potential protective effect of hyperthymic temperament on mood disorders [51].

Literature presents many correlations between affective temperament and autoimmune diseases such as psoriasis, AS or rheumathoid arthritis [25,26,52]. The study evaluating patients with psoriasis did not show any significant temperament differences with control group. However, depressive and anxious temperaments were associated with stressful factor of the disease in a group of women [26]. Also in the study assessing TEMPS-A scores in the group of AS patients, researchers did not observe any differences in temperament between AS and control group [25]. However, results showed positive correlation between depressive, cyclothymic, anxious temperament and AS activity index. Described temperaments were also associated with greater pain, measured in visual analogue scale (VAS), in contrast to hyperthymic dimension which showed negative correlation to VAS. Affective temperament is associated with disease activity and pain in AS patients and could be a risk factor for depression and anxiety in this group of patients [25].

These examples are consistent with results of our study displayed in Tables 4 and 7. Depressive, cyclothymic and anxious temperaments showed positive correlation with scores of subjective aspects of Harvey-Bradshaw Scale, Crohn Disease Activity Index and Mayo Self Report

| Table 7. TEMPS-A correlation with anxiety and depression (HADS). |
|---------------------------------------------------------------|
|                  | CD (n = 68)          | HADS_A | HADS_D | UC (n = 62)         | HADS_A | HADS_D |
| TEMPS_depressive | R 0.43, p = 0.002    | R 0.31, p = 0.01 | R 0.41, p = 0.0009 | R 0.53, p < 0.0001 |
| TEMPS_cyclothymic | R 0.47, p < 0.0001   | R 0.33, p = 0.006 | R 0.49, p < 0.0001 | R 0.56, p < 0.0001 |
| TEMPS_hyperthymic | R -0.16, p = 0.19    | R -0.40, p = 0.0007 | R -0.10, p = 0.44 | R -0.45, p = 0.0002 |
| TEMPS_irritable  | R 0.41, p < 0.0001   | R 0.14, p = 0.25 | R 0.34, p = 0.007 | R 0.33, p = 0.009 |
| TEMPS_anxious    | R 0.58, p < 0.0001   | R 0.37, p = 0.002 | R 0.53, p < 0.0001 | R 0.58, p < 0.0001 |

R—Spearman correlations

https://doi.org/10.1371/journal.pone.0205606.t007
utilized in assessing the activity of CD and UC. Interestingly, we did not observe any correlation between affective temperament and objective scales. Affective temperament significantly affects stress-related processes like in autoimmune diseases [53]. Individuals who present more vulnerable temperament traits, according to TEMPS-A scores, may acquire greater negative consequences of the stressor than those with more protective temperament [54]. We assume, that in this regard temperament can be identified as a specific risk factor to the development of mood disorders. Our findings imply that the course of the disease may be more harmful for patients possessing such personality traits and they may be more vulnerable in developing mood disorders. Additionally, in all scales hyperthymic temperament showed the negative correlation proving it’s protective effects.

Affective temperament is perceived as being heritable [55]. A meta-analysis of CD and UC genome-wide association scans observed that IBD loci overlapped with immune-mediated diseases; the largest pertained to AS and psoriasis [56]. Therefore, it is very interesting that we have received similar temperament results like in studies which evaluated affective temperament in both diseases. It may suggest that those disorders share common genes encoding temperament traits, resulting in greater risk of psychiatric comorbidities. We have observed the significant temperament differences between CD and UC. Hence, we suggest that more genetic studies are needed to extract more data about common loci of UC and other immune-related diseases. Presumably, only CD shares the same genes responsible for affective temperament unlike UC.

The intestinal serotonergic signaling system plays an important and multifactorial role in IBD, e.g. affects inflammatory processes and the intensity of symptoms [57]. Gonda et al. showed the association between affective temperaments and S-allele of 5-HTTLPR polymorphism of the serotonin transporter (SERT) gene [58]. Hyperthymic component was the only one which did not show such association. S-allele of 5-HTTLPR is considered to be related with higher predisposition to depression [59]. Table 6 shows the positive correlation between both cyclothymic and anxious temperaments, and the number of soft stools, however hyperthymic temperament showed negative correlation in this aspect. Such results indicate the overt connection between affective temperament and the serotonergic system in CD. Unfortunately, the association between SERT expression in IBD still requires more data, due to scarce literature. More comprehensive investigations are needed, especially those focusing on CD and UC separately, not collectively. Especially, that results of TEMPS-A imply significant differences in the serotonergic transmission in those two disorders.

Conclusions

In conclusions, to our knowledge, this is the first study evaluating the affective temperament via TEMPS-A in both CD and UC patients. The results of our study indicate significant differences between CD and UC due to temperament traits, and suggest distinct pathogenesis of mood disorders in IBD. Our findings show strong association between cyclothymic, depressive and anxious temperament and CD group in comparison to control groups. Also these temperaments positively correlated with subjective scales assessing the activity of UC and CD, and the number of loose stools in regard to CD scales. We have observed negative correlation of hyperthymic temperament in this regard, showing it’s putatively protective effect on the disease course. We suggest that the mechanisms responsible for such findings are related to genetic polymorphisms and changes in serotonergic neurotransmission, however more studies are needed to prove this association. TEMPS-A constitutes the simple tool, which could be utilized in the assessment of the vulnerability to psychiatric disorders and prognostic evaluation in IBD patients. Our results also indicate that analysis of affective temperament
may contribute to genetic studies in identifying genes responsible for the development of affective disorders in IBD population. Creating more homogenous groups of patients regarding clinical manifestation and genetic profile, might result in administration of individualized and better adjusted treatment strategies against mood disorders in both CD and UC patients.

**Limitations**

Main limitations of our study are: the cross-sectional type of the study, which does not allow the generalization of the findings and relatively small sample of patients for better assessment of the affective temperament. We also did not collect the data about participants who declined participating in the study or who were excluded from the research including their demographic, clinical or psychological characteristics. We were also unable to display exact mechanisms which could explain our findings, due to very complex network of dependencies.

**Supporting information**

- **S1 File. gastro TEMPS_3 anonim_ENG.xlsx.** Data base of affective temperament in IBD patients. (XLSX)
- **S2 File. gastro baza_12 anonim_ENG.xlsx.** Data base of clinical factors and surgical treatment of IBD patients. (XLSX)

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**References**

1. Lucendo AJ, Hervías D, Roncero Ó, Lorente R, Bouhmid A, Anqueira T, et al. Epidemiology and temporal trends (2000–2012) of inflammatory bowel disease in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol*. 2014; 26:1399–407. https://doi.org/10.1097/MEG.0000000000000226 PMID: 25341061
2. Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juram BD, Lazaridis KN. Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD. *Am J Gastroenterol*. 2016; 111:705–11. https://doi.org/10.1038/ajg.2016.55 PMID: 27002801
13. Ananthakrishnan AN, Gainer VS, Cai T, Perez RG, Cheng SC, Savova G, et al. Similar risk of depression and anxiety following surgery or hospitalization for Crohn’s disease. *BMJ Case Rep.* 2018; pii: bcr-2017-222946.

14. Ramsey M, Krishna SG, Stanich PP, Husain S, Levine EJ, Conwell D, et al. Inflammatory Bowel Disease Adversely Impacts Colorectal Cancer Surgery Short-term Outcomes and Health-Care Resource Utilization. *Clin Transl Gastroenterol.* 2017; 8: e127. https://doi.org/10.1038/ctg.2017.54 PMID: 29189768

15. Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, et al. Stress and exacerbation in inflammatory bowel disease. *Inflamm Bowel Dis.* 2005; 11:272–86. PMID: 15735434

16. Janke KH, Klump B, Gregor M, Meisner C, Haeuser. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis.* 2015; 21:1397–404. https://doi.org/10.1002/ibd.22533 PMID: 25913119

17. Lünfors S, Vermeire S, Greco M, Hommes D, Bell C, Avedano L. IBD and health-related quality of life—discovering the true impact. *J Crohns Colitis.* 2015; 9:1230–48. https://doi.org/10.1136/gutjnl-2014-306371 PMCID: 29126510

18. Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, Sussman DA. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. *Am J Gastroenterol.* 2008; 103:1989–97. https://doi.org/10.1111/j.1572-0241.2008.01980.x PMID: 18796096

19. Verma S, Tsai HH, Giaffer MH. Does better disease-related education improve quality of life? A survey of IBD patients. *Dig Dis Sci.* 2001; 46:865–869. PMID: 11330426

20. Bielinski J, Liebert A, Lesiewska N, Bielinski M, Mieczkowski A, Sopońska-Brzosczyk S, et al. Depressive and anxiety symptoms among patients with inflammatory bowel diseases. *Mel Res J.* 2017; 2:6–12.

21. Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, et al. The Manitoba IBD cohort study: A population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol.* 2008; 103:1989–97. https://doi.org/10.1111/j.1572-0241.2008.01980.x PMID: 18796096

22. Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, Sussman DA. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. *Aliment Pharmacol Ther.* 2014; 39:802–10. https://doi.org/10.1111/apt.12669 PMID: 24588323

23. Ananthakrishnan AN, Gainer VS, Cai T, Perez RG, Cheng SC, Savova G, et al. Similar risk of depression and anxiety following surgery or hospitalization for Crohn’s disease and ulcerative colitis. *Am J Gastroenterol.* 2013; 108:594–601. https://doi.org/10.1038/ajg.2012.471 PMID: 23337479

24. Marrie RA, Walld R, Bolton JM, Sareen J, Walker JR, Patten SB, et al. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. *J Psychosom Res.* 2017; 101:17–23. https://doi.org/10.1016/j.jpsychores.2017.07.015 PMID: 28867419

25. Kim MC, Jung YS, Song YS, Lee JI, Park JH, Sohn CI, et al. Factors Associated with Anxiety and Depression in Korean Patients with Inactive Inflammatory Bowel Disease. *Gut Liver.* 2016; 10:399–405. https://doi.org/10.5009/gnl15188 PMID: 26470768

26. Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol.* 2000; 95:1213–20. https://doi.org/10.1111/j.1572-0241.2000.02012.x PMID: 10811330

27. Bernstein CN. Psychological Stress and Depression: Risk Factors for IBD? *Dig Dis.* 2016; 34:58–63. https://doi.org/10.1159/000429299 PMID: 26983009

28. Akiskal HS, Akiskal KK. Special issue: TEMPS: temperament evaluation of Memphis, Pisa, Paris and San Diego. *J Affect Disord.* 2005; 85:1–242. https://doi.org/10.1016/j.jad.2004.12.003 PMID: 15780670

29. Akiskal HS, Akiskal K. Cyclothymic, hyperthymic and depressive temperaments as subaffective variants of mood disorders. In: Tasman A., Riba M.B. (Eds.) *American Psychiatric Press.* 1992; 2:43–62.

30. Von Zerssen D, Akiskal HS. Personality factors in affective disorders: historical developments and current issues with special reference to the concepts of temperament and character. *J Affect Disord.* 1998; 51: 1–5. PMID: 9879798

31. Goodwin FK, Redfield Jamison K. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. New York: Oxford University Press; 2007.

32. Akiskal HS, Akiskal KK, Haykal RF, Haykal RF, Manning JS, Connor PD. TEMPS-A: progress towards validation of a self-rated clinical version of the temperament evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. *J Affect Disord.* 2005; 85:3–16. https://doi.org/10.1016/j.jad.2004.12.001 PMID: 15780671
23. Eory A, Gonda X, Lang Z, Torzsa P, Kalman J Jr, Kalabay L, Rihmer Z. Personality and cardiovascular risk: association between hypertension and affective temperaments-a cross-sectional observational study in primary care settings. *Eur J Gen Pract.* 2014; 20:247–52. https://doi.org/10.3109/13814788.2013.868431 PMID: 24456347

24. Hall PA, Coons MJ, Valls TM. Anxious temperament and disease progression at diagnosis: the case of type 2 diabetes. *Psychosom Med.* 2008; 70:837–843. https://doi.org/10.1097/PSY.0b013e1817b8e6 PMID: 18606721

25. Yildirim T, Solmaz D, Emul M, Akgol G, Yalvac D, Ersoy Y. Affective temperament profile in ankylosing spondylitis patients using TEMPS-A. *J Phys Ther Sci.* 2017; 29:394–400. https://doi.org/10.1589/jpts.29.394 PMID: 28356618

26. Litaiem N, Youssef S, El Kefi H, Jabeur K, Dhaoui MR, Doss N. Affective temperament profile in psoriasis patients in Tunisia using TEMPS-A. *J Affect Disord.* 2013; 151:321–4. https://doi.org/10.1016/j.jad.2013.05.099 PMID: 23830858

27. Best WR, Becktel JM, Singleton JW. (1979) Rederived values of the eight coefficients of the Crohn’s Disease Activity Index (CDAI). *Gastroenterology.* 1979; 77: 843–846. PMID: 467941

28. Harvey RF, Bradshaw MJ. Measuring Crohn’s disease activity. *Lancet.* 1980; 1: 1134–1135.

29. Best WR. Predicting the Crohn’s disease activity index from the Harvey-Bradshaw Index. *Inflamm Bowel Dis.* 2006; 12: 304–310.

30. Guyatt HL, Bundy DA. Estimating prevalence of community morbidity due to intestinal helminths: prevalence of infection as an indicator of the prevalence of disease. *Trans R Soc Trop Med Hyg.* 1991; 85:778–782. PMID: 1801353

31. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn’s disease activity and Harvey-Bradshaw indices in assessing Crohn’s disease severity. *Clin Gastroenterol Hepatol.* 2010; 8: 357–363. https://doi.org/10.1016/j.cgh.2010.01.001 PMID: 2096379

32. Schroeder KW, Tremaine WJ, Istrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987; 317:1625–1629. https://doi.org/10.1056/NEJM198712243172603 PMID: 3317057

33. Dębnińska-Krajewski D, Rybakowski J. The Temperament Evaluation of Memphis, Pisa, and San Diego Auto-questionnaire (TEMPS-A)—an important tool to study affective temperament. *J Psychiatr Pol.* 2014; 48: 261–276.

34. Borkowska A, Rybakowski JK, Dróżdż W, Bielinski M, Kosmowska M, Rajewska-Rager A, et al. Polish validation of the TEMPS-A: the profile of affective temperaments in a college student population. *J Affect Disord.* 2010; 123: 36–41. https://doi.org/10.1016/j.jad.2009.09.024 PMID: 19880192

35. Stern AF. The hospital anxiety and depression scale. *Occup Med (Lond).* 2014; 64: 393–394.

36. Wichowicz HM, Wieczorek D. Screening post-stroke depression using the Hospital Anxiety and Depression Scale. *J Psychiatr Pol.* 2011; 45: 505–514.

37. Vázquez GH, Gonda X, Lolic M, Tondo L, Baldessarini RJ. Suicidal Risk and Affective Temperaments, Evaluated with the TEMPS-A Scale: A Systematic Review. *Harm Rev Psychiatry.* 2018; 28:8–18. https://doi.org/10.1097/HRP.0000000000000153 PMID: 29303918

38. Martin-Subero M, Anderson G, Kanchanatawan B, Berk M, Maes M. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. *CNS Spectr.* 2016; 21:184–198. https://doi.org/10.1017/S1092852915000449 PMID: 26307347

39. Bennebroek Evertsz’ F, Sprangers MAG, Sitnikova K, Sitnikova K, Stokkers PCF, Ponsioen CY, Bartelsman JFW, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. *J Consult Clin Psychol.* 2017; 85:918–25. https://doi.org/10.1037/ccp0000227 PMID: 28857595

40. Ish-Hak WW, Pan D, Steiner AJ, Feldman E, Mann A, Mirocha J, et al. Patient-Reported Outcomes of Quality of Life, Functioning, and GI/Psychiatric Symptom Severity in Patients with Inflammatory Bowel Disease (IBD). *Inflamm Bowel Dis.* 2017; 23:798–803. https://doi.org/10.1097/MIB.0000000000001060 PMID: 28301432

41. Serafini G, Hayley S, Pomplii M, Dwivedi Y, Brahmacari G, Girardi P, et al. Hippocampal neurogenesis, neurotrophic factors and depression: possible therapeutic targets? *CNS Neurol Drug Targets.* 2014; 13: 1708–1721. PMID: 25470403

42. Hong JY, Labus JS, Jiang Z, Ashe-Mcalley C, Dinov I, Gupta A, et al. Regional neuroplastic brain changes in patients with chronic inflammatory and non-inflammatory visceral pain. *PLOS One.* 2014; 9: e84564. https://doi.org/10.1371/journal.pone.0084564 PMID: 24416245
43. Mella LF, Bertolo MB, Dalgalarrondo P. Depressive symptoms in rheumatoid arthritis. *Rev Bras Psiquiatr*. 2010; 32:257–263. PMID: 20694442

44. Mendelowicz MV, Jean-Louis G, Kelsoe JR, Akiskal HS. A comparison of recovered bipolar patients, healthy relatives of bipolar probands, and normal controls using the short TEMPS-A. *J Affect Disord*. 2005; 85:147–151. https://doi.org/10.1016/j.jad.2004.01.012 PMID: 15780685

45. Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, et al. Switching from unipolar to bipolar II: An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry*. 1995; 52:114–23. PMID: 7848047

46. Greenwood TA, Akiskal HS, Akiskal KK. Bipolar Genome Study, Kelsoe JR. Genome-wide association study of temperament in bipolar disorder reveals significant associations with three novel Loci. *Biol Psychiatry*. 2012; 72: 303–310. https://doi.org/10.1016/j.biopsych.2012.01.018 PMID: 23357651

47. Kesebir S, Gündoğar D, Küçüksubaşı Y, Talıdil Yaylacı E. The relation between affective temperament and resilience in depression: a controlled study. *J Affect Disord*. 2013; 148:352–356. https://doi.org/10.1016/j.jad.2012.12.023 PMID: 23357656

48. Aguiar Ferreira AD, Vasconcelos AG, Neves FS, Laks, Correa H. Affective temperaments: familiality and clinical use in mood disorders. *J Affect Disord*. 2013; 148:53–6. https://doi.org/10.1016/j.jad.2012.11.047 PMID: 23245466

49. Asik M, Altınbaş K, Eroğlu M, Karahanmet E, Erbaq G, Ertekin H, Sen H. Evaluation of affective temperament and anxiety-depression levels of patients with polycystic ovary syndrome. *J Affect Disord*. 2015; 185:214–18. https://doi.org/10.1016/j.jad.2015.06.043 PMID: 26241866

50. Gois C, Barbosa A, Ferro A, Santos AL, Sousa F, Akiskal H, et al. The role of affective temperaments in metabolic control in patients with type 2 diabetes. *J Affect Disord*. 2011; 134:52–58. https://doi.org/10.1016/j.jad.2011.05.021 PMID: 21641045

51. Karam EG, Salamoun MM, Yeretzian JS, Mneimneh ZN, Karam AN, Fayyad J, et al. The role of anxious and hyperthymic temperaments in mental disorders: a national epidemiologic study. *World Psychiatry*. 2010; 9:103–10. PMID: 20671899

52. Rezvani A, Aytüre L, Arslan M, Kurt E, Eroğlu Demir S, Karacan I. Affective temperaments in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2014; 17:34–38. https://doi.org/10.1111/1756-185X.12033 PMID: 24472264

53. Jaffe CL, Grimaldi G Jr, McMahon-Pratt D. The cultivation and cloning of Leishmania. In: Morel CM, editors. *Genes and Antigens of Parasites: A Laboratory Manual*, 2nd ed. Rio de Janeiro: FIOCRUZ. 1984. pp 47–91.

54. Janowski K, Steuden S. Severity of psoriasis and health-related quality of life: the moderating effects of temperament. *Br J Dermatol*. 2008; 158:633–635. https://doi.org/10.1111/j.1365-2133.2007.08381.x PMID: 18081895

55. Evans L, Akiskal HS, Keck PE Jr, McElroy SL, Sadovnick AD, Remick RA, et al. Familiality of temperament in bipolar disorder: support for a genetic spectrum. *J Affect Disord*. 2005; 85:153–168. https://doi.org/10.1016/j.jad.2003.10.015 PMID: 15780686

56. Jostins L, Ripke S, Weerema RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012; 491:119–124, https://doi.org/10.1038/nature11582 PMID: 23128233

57. Coates MD, Tekin I, Vrana KE, Vrana KE, Mawe GM. Review article: the many potential roles of intestinal serotonin (5-hydroxytryptamine, 5-HT) signalling in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017; 46:569–580. https://doi.org/10.1111/apt.14226 PMID: 28737264

58. Gonda X, Rihmer Z, Zsombok T, Bagdy G, Akiskal KK, Akiskal HS. The 5HTTLPR polymorphism of the serotonin transporter gene is associated with affective temperaments as measured by TEMPS-A. *J Affect Disord*. 2006; 91:125–31, https://doi.org/10.1016/j.jad.2005.12.048 PMID: 16464506

59. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010; 167:509–527. https://doi.org/10.1176/appi.ajp.2010.09101452 PMID: 20231323