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ORIGINAL ARTICLE

Personality traits as a possible factor in the inflammatory response in the first depression episode and in recurrent depressive disorders

M. Talarowska[a,*,1], **K. Bliźniewska**[a,1], **J. Szemraj**[b], **M. Kowalczyk**[a], **P. Gałecki**[a]

[a] *Department of Adult Psychiatry, Medical University of Lodz, Lodz, Poland*
[b] *Department of Medical Biochemistry, Medical University of Lodz, Lodz, Poland*

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Abstract
Background and objectives: Depressive disorders are linked with an increase in the central and peripheral concentration of many pro-inflammatory cytokines, including mainly tumour necrosis factor α (TNF-α) and interleukins (ILs). The aim of the presented work is to verify whether personality traits predisposing to the occurrence of a depression episode are associated with changes in the peripheral expression of genes for selected cytokines.
Methods: 77 individuals, who met the diagnostic criteria for a depression episode were qualified to take part in the study. Personality traits was measured using selected scales of The Minnesota Multiphasic Personality Inventory (MMPI-2). Expression at the mRNA and protein level for IL-1, IL-6, IL-10, IL-12 and TNF-α were examined.
Results: A significant positive dependence was observed in the entire group examined with reference to the intensity of symptoms on the Welsh anxiety scale and the expression at the mRNA and protein level for the IL-12 gene. Analyses conducted separately for the first depressive episode group and the recurrent depression group revealed significant interrelations between the neurotic triad of the MMPI-2 test and the expression for genes IL-1, IL-10 and IL-12.
Conclusions: (1) The intensity of depression episode symptoms, measured using the neurotic triad and the Welsh anxiety scale for the MMPI-2 test, correlate significantly with the expression at the mRNA and protein level for the genes of pro-inflammatory and anti-inflammatory cytokines. (2) Anxiety as a personality trait may be a significant marker of inflammation during a depression episode.

* Corresponding author.
E-mail address: talarowskamonika@wp.pl (M. Talarowska).
[1] Equivalent share of the authors in the compilation of this paper.

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Introduction

Brain diseases belong to the most socially and economically burdening diseases in Europe. Approximately 800 billion euros are spent annually on the fight with the consequences of these diseases.[1] Among all brain diseases, more than 60% of social and economic costs are generated by mental disorders, mainly depressive disorders.[2]

Annual prevalence of depression in the population of adults oscillates between 6% and 12%. Based on numerous sources, it varies from 5% to even 30% among people over the age of 65.[3] According to estimates of the World Health Organisation (WHO), 350 million people around the world present symptoms of depression, while depressive disorders constitute nearly 4.3% of the global burden of all diseases.[4] Depression often accompanies other somatic diseases as a symptom. It means that approximately 10% of all adults (which corresponds to 100 million cases) show signs of depression during a year. Women suffer from depression twice as often as men.[5]

Both physical and psychological (emotional) stress increase the likelihood of occurrence of mental disorders (including depressive disorders)[6,7] owing to the action of a series of hormonal and biochemical[8] as well as epigenetic mechanisms, which has been confirmed in recent times.[9] With the absence of somatic comorbidity, depressive disorders are linked with an increase in the central and peripheral concentration of many pro-inflammatory and anti-inflammatory cytokines, including mainly tumour necrosis factor α (TNF-α) and interleukins (ILs).[10] Changes in the metabolism of biogenic monoamines, i.e. dopamine, noradrenaline and serotonin in mesencephalic nuclei, are considered potential ways of cytokines' impact on the aetiology of depression.[11] Moreover, cytokines lead to excessive secretion of cortisol – directly by means of stimulating the hypothalamic–pituitary–adrenal axis (HPA axis) and indirectly by modifying the sensitivity of glucocorticoid receptors.[11]

A special role in the aetiology of recurrent depression is assigned to three pro-inflammatory interleukins (IL-1, IL-6 and IL-12) as well as IL-10, which is one of anti-inflammatory interleukins.[12,13] On the other hand, TNF-α induces excessive reuptake of monoamines, stimulates pathologic hyperactivity of the HPA axis, and increases the activity of indole 2,3-dioxygenase (IDO); hence, reduces substantially the production of serotonin.[14,15]

In one of our previous papers, we indicated that the premorbid personality structure (mainly anxiety as a constant feature of emotional functioning) may have a significant importance for the effectiveness of applied antidepressant pharmacotherapy.[16]

The aim of the presented work is to verify whether personality traits predisposing to the occurrence of a depression episode are associated with changes in the peripheral expression of genes for selected pro-inflammatory and anti-inflammatory cytokines: IL-1, IL-6, IL-10, IL-12, and TNF-α.

Material and methods

Material

Seventy-seven individuals, aged 18–64 ($M = 47.96$, $SD = 11.23$), meeting the diagnostic criteria for a depression episode and recurrent depressive disorders (F32.0–7.32.2, F33.0–F33.8), were qualified to participate in the experiment.[17,18] All the examined individuals were patients of the Department of Adult Psychiatry of the Medical University of Lodz (the J. Babiński Hospital in Lodz, Poland). All the subjects were examined during their hospitalisation, and no symptoms of concurrent somatic diseases or axis I and II disorders, other than depressive episodes, were diagnosed. Inflammatory or autoimmune disorders, central nervous system traumas, and unwillingness to give informed consent were considered additional exclusion criteria. A case history was obtained from each patient using the standardised Composite International Diagnostic Interview (CIDI)[19] prior to the start of the experiment.

The examined individuals were divided into two groups: the patients diagnosed with the first depression episode (ED-I, $N = 25$) and the patients treated due to a recurrent episode of the disease (recurrent depression episodes group, rDE, $N = 52$). Statistically significant differences were confirmed in the examined groups in terms of age ($Z = 0.117$, $p = 0.011$). No significant differences were found in terms of sex ($X^2 = 0.221$, $p = 0.641$) between the two groups.

Depression severity was evaluated and classified using the 21-item Hamilton Depression Rating Scale (HDRS).[20] Intensity levels of depressive symptoms were measured with the use of the grades presented in the study conducted by Demyttenaere and De Fruyt.[21] Each patient was examined by the same specialist (the same psychiatrist performed the HDRS test, while a clinical psychologist oversaw conducting the MMPI-2 test).

The individuals taking part in the experiment were native Poles from central Poland (not related with one another). They were selected at random without replacement sampling. Participation in the study was voluntary; all personal data and results were kept confidential. Before making a decision to participate in the experiment, the patients were informed about its purpose, assured of the voluntary nature of the experiment, and guaranteed that their personal data would be kept in secret. Written informed consent was given in accordance with the study protocol, approved by the Bioethical Committee of the Medical University of Lodz (No. RNN/272/15/KE).

Methods

The Minnesota Multiphasic Personality Inventory (MMPI-2)

The Polish version of the MMPI-2 by S. Hathaway and J. McKinley, adapted by T. Kucharski was used to evaluate the personality structure of the examined individuals.

The MMPI-2 is a psychological tool used in the diagnostics of various disorders, which is also helpful in determining the mode of planned psychotherapeutic interventions. When applying the MMPI-2 test profilograph during an assessment of depression symptoms, multiple scales and subscales for disposal are used, which are characterised by various degrees of diagnostic accuracy, e.g. the clinical depression scale (D), hypochondria scale (Hs) and the hysteria scale (Hy). The depression, hypochondria and hysteria scales make the 'neurotic triad'.[22,23] High scores in all the three scales are associated with excessive concentration on somatic health status, frequent complaints about physical ailments, lack of energy, sleep problems, impaired attention and concentration, and low self-esteem, diffidence and pessimism. Subjects in this group react to demanding situations with strong somatic symptoms. They are nervous, impatient and live under constant tension.[24,25]

HDRS was applied at the therapy onset (on admission) and after 8 weeks of its continuation. The MMPI-2 test was applied at the beginning of the pharmacological treatment. All the patients were examined on admission, i.e. during the symptomatic phase, before or shortly after a modification of the previous antidepressant drug regime. The blood used to conduct genetic analyses was collected (in volumes of 5 ml) on the day of admission to the experiment.

Evaluation of selected genes expression at the level of protein

Determining protein concentration

Total protein concentration in blood plasma of the patients was determined with the use of Micro BCA™ Protein Assay Kit (ThermoSCIENTIFIC) based on the manufacturer's recommendations. 150 μl of the reaction mixture was added to pits containing 150 μl of serum, diluted 10 times in 10 mM of phosphate buffered saline, pH 7.4, and incubated (2 h, 37 °C). An analytical curve for serum albumin was determined in order to measure protein concentration. Both the examined samples and the reference samples were made parallel in three repetitions. Sample absorbance was measured using Multiskan Ascent Microplate Photometer (Thermo Labsystems) at $\lambda = 570$ nm and total protein concentration was calculated from the standard curve equation.

Enzyme-linked immunosorbent assay (ELISA)

The concentration of proteins IL-1, IL-6, IL-10, IL-12 in the patients' serum was determined using IL-1 Elisa kit (R&D Systems, Inc, Minneapolis, MN, USA), Human IL-6 Elisa kit (R&D Systems, Inc, Minneapolis, MN, USA), Human IL10 (R&D Systems, Inc, Minneapolis, MN, USA), IL-12 Elisa kit (LifeSpan Biosciences, Inc., Seattle, WA, USA) and TNF-α Elisa kit (LifeSpan Biosciences, Inc., Seattle, WA, USA) according to the protocols provided by the manufacturer. β-actin was used for endogenous control of protein concentration in the samples and determined with the help of Human Actin Beta (ACTb) ELISA Kit (BMASSAY) based on the manufacturer's recommendations. 100 μl of serum (ρprotein = 0.5 mg/ml) was added to pits coated with antibodies specific for the analysed proteins and then incubated (1.5 h, 37 °C). The content was removed, and the pits were rinsed three times in 10 mM of phosphate buffered saline and incubated (1 h, 37 °C) with 100 μl of biotinylated antibodies specific for the analysed proteins. Then, the content was removed, and the pits were rinsed three times in 10 mM of phosphate buffered saline and incubated (30 min, 37 °C) with 100 μl of ABC Working Solution. The content was removed, and the pits were rinsed five times in 10 mM of phosphate buffered saline and incubated (10 min, 37 °C) with 90 μl of TMB substrate. After adding 100 μl of TMB Stop Solution, the absorbance of the samples was measured using Multiskan Ascent Microplate Photometer (Thermo Labsystems) at $\lambda = 450$ nm. Analytical curves for the analysed proteins were created in order to determine protein concentration.

Evaluation of selected genes expression at the level of mRNA

Total RNA isolation

Peripheral blood was used as a material in the genotype study (in volumes of 5 ml on EDTA). Total RNA isolation from the patients' blood samples using TRIZOL (Invitrogen Life Technologies) – an RNA extraction reagent – according to the standard acid-guanidinium-phenol-chloroform method, was performed using Chomczyński's modified method.[26] The absorbance of isolated RNA was measured using a spectrophotometer (Picodrop) at $\lambda = 260$ nm with the aim of determining total RNA concentration. Isolated RNA was stored at a temperature of −70 °C.

Quality analysis of isolated RNA

The quality of total RNA was checked with Agilent RNA 6000 Nano Kit (Agilent Technologies) in accordance with the manufacturer's recommendations. 1 μl of RNA 6000 Nano dye was added to a test tube containing 65 μl of Agilent RNA 6000 Nano gel matrix, and then centrifuged (10 min, 13,000×*g*). The gel-fluorescent dye mixture was applied on the surface of a Nano chip placed in a workstation. Then, 5 μl of RNA Nano marker were added to selected pits. Isolated samples of RNA and RNA size marker were subject to denaturation (2 min, 70 °C), and then 1 μl of the sample was pipetted to selected pits of the Nano chip, and mixed (1 min, 2400 rpm). The quality of isolated RNA was checked using 2100 Bioanalyzer (Agilent Technologies). The level of degradation of total RNA was determined with the use of an electrophoretogram and the RIN values recorded. Only the samples with RIN value >7 were subject to further analysis.

RT-PCR reverse transcription

An RT reaction was carried out using TaqMan® RNA Reverse Transcription Kit (Applied Biosystems) based on the manufacturer's recommendations. The samples were incubated (30 min, 16 °C and 30 min, 42 °C) in a thermocycler (Biometra). Reverse transcriptase was inactivated (5 min, 85 °C) and the obtained cDNA was stored at a temperature of −20 °C.

Real-time PCR reaction

A real-time PCR reaction was conducted using TaqMan® Universal PCR Master Mix, No UNG (Applied Biosystems), according to the protocol provided by the manufacturer, delivered by Applied Biosystems. To calculate relative

Table 1 Participants' demographic and clinical features.

Age (years)	All subjects $N = 77$	ED-I $N = 25$	rDE $N = 52$	ED-I vs rDE	
Male/female (%)	46/31 (59.75/40.25)	14/11 (56/34)	32/20 (61.54/38.56)	$\chi^2 = 0.215$	0.641
Age *M*(*SD*)	47.96 (11.23)	43.23 (12.01)	50.23 (10.19)	$Z = -2.451$	0.011*
HDRS-I *M*(*SD*)	23.6 (7.12)	22.96 (7.67)	23.94 (6.89)	$Z = -0.201$	0.841
HDRS-II *M*(*SD*)	6.61 (3.9)	5.87 (3.48)	6.94 (4.19)	$Z = -0.704$	0.481
Number of depression episodes *M*(*SD*)	–	–	7.35 (4.3)	–	–

ED-I – first episode of depression; rDE – recurrent depression episodes; HDRS-I – Hamilton Depression Rating Scale at the onset of therapy; HDRS-II – Hamilton Depression Rating Scale after pharmacological treatment; M – mean; SD – standard deviation.
* – *p* statistically significant.

expression of miRNA genes, the Ct comparative method was used.[27,28]

Statistical analysis

A statistical analysis of the material was performed with the use of both descriptive and inferential statistics. A two-tailed critical region was employed in the testing of the statistical hypothesis. The qualitative characteristics of the groups were expressed as frequencies and shown as percentages. An arithmetical mean (*M*) was calculated to characterise the average values of quantitative features.

Distributions were measured with the use of the Shapiro–Wilk test. The hypothesis referring to the normality of distribution was rejected. The following tests were applied in the comparison of nonparametric variables in the test groups: the Pearson χ^2 for qualitative variables, the Wilcoxon signed-rank test for two related groups for quantitative variables, and the Mann–Whitney *U* test for two independent groups to determine the coincidence of distributions. Spearman's *R* rank order correlation coefficients were estimated, the aim of which was to evaluate the relationships between the analysed variables. Statistical significance was defined as $p < 0.05$[29] in each analysis. All the analyses were conducted using STATISTICA PL, version 12.

Results

The social and demographic characteristics of the examined individuals and the information regarding the course of the disease are presented in Table 1.

Course of the disease

Table 1 shows that disease intensification on the day of admission and after treatment completion was similar in the two groups compared. Statistically significant differences were observed in both examined groups in terms of the intensity of depression symptoms measured at the onset of pharmacotherapy and after 8 weeks. A significant improvement of the patients' mental status was achieved ($Z = 4.281$, $p < 0.001$ for the ED-I group; $Z = 6.261$, $p < 0.001$ for the rDE group, respectively).

Descriptive statistics of the analysed variables

Statistically significant differences in the intensity of symptoms measured with the neurotic triad and the Welsh anxiety scale for the MMPI-2 test were confirmed between the analysed groups. Significantly higher scores were recorded by the subjects hospitalized due to a recurrent depression episode (Table 2) as compared to the individuals treated with antidepressant pharmacotherapy for the first time. No differences were found in the expression at the mRNA and protein level for the analysed variables in the examined groups (Table 2).

Correlations

Spearman's rank correlation coefficient analysis did not reveal any statistically significant relationship between the expression at the mRNA and protein level for IL-1, IL-6, IL-10 and TNF-α for the entire group analysed ($N = 77$). Significant positive dependence was observed in the entire group examined with reference to the intensity of symptoms on the Welsh anxiety scale and expression at the mRNA and protein level for the IL-12 gene ($p < 0.05$).

Results of statistically significant analyses, conducted separately for the ED-I and rDE groups, are presented in Table 3.

Discussion

Personality can be defined as interpersonal behaviour, subjective reactions, feelings and objectives we strive after, typical of each person.[30] Based on the theory of personality development continuity in time, it is assumed that the main traits are relatively constant beginning from the age of three. The traits present in childhood become more intensified at later stages of development (e.g. self-conscious and behaviourally inhibited children are more exposed to the reinforcement of anxiety disorder symptoms, with numerous avoidance strategies, in adolescence and adulthood).[31] The quality of development processes decides about the functioning of a given person in terms of motivation to act, adaptation processes, and experiencing oneself in relations with others.[32]

Mainly limbic structures with the amygdala and the hippocampus, and the prefrontal cortex, as well as the effectiveness of connections between them, have particular relevance in the process of personality shaping.[33] The

Table 2 Descriptive statistics for the analysed variables as divided into examined groups ($N = 77$).

Variable $M(SD)$		All subjects $N = 77$	ED-I $N = 25$	rDE $N = 52$	ED-I vs rDE
Hypochondria scale (Hd)	High scores reflect undefined physical problems, concern for own health, concentration on invented somatic problems, lack of energy, dissatisfaction, sleep problems, complaining, claiming attitude	71.481 (14.22)	66.241 (13.88)	74 (13.82)	−2.165*
Depression scale (D)	High scores reflect depressive mood, low self-esteem and the feeling of being inappropriate, worrying, dissatisfaction with life status, withdrawal	76.416 (12.33)	70.921 (11.32)	79.058 (12.02)	−2.720*
Hysteria scale (Hy)	High scores mean little insight into life problems and emotions, numerous somatic fears, sleep problems, negation, claiming approach, self-concentration	71.494 (14.22)	66.481 (15.64)	73.904 (13.24)	−2.029*
Welsh anxiety	Anxiety intensification as a constant personality trait	73.001 (10.66)	68.913 (11.14)	74.918 (9.98)	−2.488*
IL-1 mRNA ($2^{-\Delta\Delta ct}$)		0.683 (0.09)	0.679 (0.09)	0.684 (0.08)	−0.179
IL-1 protein (pg/ml)		11.373 (1.46)	11.292 (1.62)	11.412 (1.39)	−0.179
IL-6 mRNA ($2^{-\Delta\Delta ct}$)		0.329 (0.05)	0.336 (0.05)	0.326 (0.05)	0.680
IL-6 protein (ng/ml)		5.462 (0.84)	5.584 (0.78)	5.404 (0.86)	0.843
IL-10 mRNA ($2^{-\Delta\Delta ct}$)		0.377 (0.05)	0.384 (0.06)	0.373 (0.05)	0.533
IL-10 protein (ng/ml)		6.257 (0.87)	6.348 (0.97)	6.213 (0.83)	0.386
IL-12 mRNA ($2^{-\Delta\Delta ct}$)		0.932 (0.18)	0.910 (0.19)	0.943 (0.17)	−0.740
IL-12 protein (ng/ml)		15.542 (2.95)	15.172 (3.18)	15.719 (2.86)	−0.783
TNF-α mRNA ($2^{-\Delta\Delta ct}$)		0.676 (0.09)	0.670 (0.09)	0.679 (0.09)	−0.294
TNF-α protein (ng/ml)		11.157 (1.42)	11.052 (1.33)	11.208 (1.48)	−0.479

ED-I – first depression episode; rDE – recurrent depression episodes; M – mean; SD – standard deviation.
* – p statistically significant.

Table 3 Results of Spearman's rank correlation for the variables analysed separately for the ED-I group and the rDE group.

			R Spearman	p
ED-I	IL-1 mRNA ($2^{-\Delta\Delta ct}$)	& Depression	0.402	0.04*
	IL-1 protein (pg/ml)		0.401	0.04*
	IL-10 mRNA ($2^{-\Delta\Delta ct}$)	& Depression	0.423	0.03*
	IL-10 protein (pg/ml)		0.414	0.04*
	IL-10 mRNA ($2^{-\Delta\Delta ct}$)	& Hysteria	0.453	0.02*
	IL-10 protein (pg/ml)		0.439	0.02*
rDE	IL-12 mRNA ($2^{-\Delta\Delta ct}$)	& Depression	0.265	0.05*
	IL-12 protein (pg/ml)		0.273	0.05*
	IL-12 mRNA ($2^{-\Delta\Delta ct}$)	& Welsh anxiety	0.392	0.005*
	IL-12 protein (pg/ml)		0.403	0.004*

ED-I – first depression episode; rDE – recurrent depression episodes.
* – p statistically significant.

moment of maturation of those structures is convergent with the periods critical for the shaping of permanent personality traits of a human being. The hippocampal region reaches maturity close to that of an adult person between week 13 and 20 of pregnancy.[34] Subsequent essential structural changes take place during the first year of life, especially in the dentate gyrus and in the entorhinal cortex. At subsequent ages, a growth in size was noted in all components of the hippocampal formation.[35] Frontal lobes ''mature'' gradually as late as at the age of 20–25,[36] reaching the highest specialisation in this period. Referring to the functional model in the aetiology of depression, which can

be also referred to a shaping personality,[37,38] hyperactivity in the limbic area (the amygdala, hippocampus, anterior cingulate cortex) is not sufficiently controlled by the medial cortex of the frontal lobe in response to emotional stimuli of a negative charge.[39] On the other hand, positive stimuli cause excessive inhibition in the frontal cortex.[40]

Personality shaping is also affected by both genetic and environmental factors, which indicate the direction of the structural and functional development of the brain. They may affect either negatively or positively each of the previously mentioned developmental stages; hence, reduce or increase our resistance and coping skills.[41] The first signal of a disease that affects functions of the brain usually include subtle changes in behaviour,[42] irrespective of whether we are dealing with personality disorders, mood disorders, anxiety disorders, psychosis, or dementia. Established personality traits in the form of anxiety attitude are, on the other hand, a source of constant pro-inflammatory activity of the immune system by means of dysregulating the HPA axis.[43] Through excessive production of neurotoxic compounds (especially the so-called tryptophan Catabolites, TRYCATs), this cascade of mutual feedback loops leads gradually to neurodegenerative processes, which are revealed among others in the form of depression.[44–46]

The epigenetic mechanisms described in the papers dedicated to the aetiology of depression (e.g. miRNA expression, DNA methylation and histone modifications) have a permanent impact on gene expression without modifying the genetic code. They may be the missing link between biological and environmental factors and permanent structural and functional changes taking place in the human brain, which lead to the occurrence of depression.[47,48]

The results obtained by us, which indicate that the scales of the MMPI-2 test associated with the intensification of anxiety symptoms correlate positively with the expression of both pro-inflammatory and anti-inflammatory cytokines, correspond with the phenomena described above. Golimbet et al.[49] (IL-10 and Il-4 were analysed), Sutin et al.[50] (IL-6), and Elliot et al.[51] recorded results that are similar with the results obtained by us. Interestingly, this relationship is observed amongst members of Western cultures, but not amongst the people who live in the East.[52] An increased level of neuroticism – as a personality trait – combined with low conscientiousness and openness to experiences is linked not only with an elevated risk of attempting suicide,[53] but also with a rise in the following indicators of an active inflammatory process: interleukin 6 (Il-6), C-reactive protein (CRP).[50,54–56] A tendency to experiencing often the feeling of anger and hostility is accompanied by an increase in the level of CRP[57] and TNF-α.[58,59] Furthermore, a tendency to having an anxious approach when evaluating reality correlates positively with the level of CRP and negatively with the level of self-control.[60] Additionally, it turns out that a high level of neuroticism is a common feature for the people susceptible to depressive disorders and dementia,[61] while personality changes in the form of intensive fear – as a permanent personality trait – turn out to be a predictor of dementia.[62] Table 4 presents collectively the results of the most important research studies conducted.

We also showed that the level of intensification of an anxiety feature significantly differentiates people with the first and with recurrent episodes of depression. The results recorded are also confirmed in studies and experiments conducted by other centres.[63] Kuznetsova et al.[64] mention interrelations between neuroticism and the intensification of depression symptoms in a group of students, while Smith et al.[65] confirm the same among adolescents. However, this dependence is not typical for young adults. It is also observed in the case of individuals in middle age[66,67] and in the elderly suffering from depressive disorders.[68,61] Moreover, an initially high neuroticism feature increases the risk of attempting a suicide[61] and the risk of disease recurrence.[16,69] In their deliberations, Yoneda et al.[70] went one step further and treated a more intensive neurotic tone of personality in older respondents as an earlier marker of dementia.

Table 4 Inflammatory process indicators versus personality traits.

↑ IL-6	↑ Neuroticism[50,55] ↓ Conscientiousness[50] ↓ Openness to experience[54] ↑ Impulsiveness[53]
↑ CRP	↑ Neuroticism[50] ↓ Conscientiousness[50] ↓ Openness to experience [Luchetti et al., 2014] ↑ Hostility[57] ↑ Impulsiveness[53] ↑ Anxious attitude in reality evaluation[60] ↓ Self-control[60]
↑ TNF-α	↑ Hostility[58,59]

Interesting results of studies conducted on a group of 133 healthy participants were presented by a team of Italian scientists.[71] It turned out that the 5HTTLPR s/s genotype was linked with neuroticism and tension/anxiety symptoms, cognitive anxiety, and emotional arousal control. What is more, neuroticism mediates the association between the 5HTTLPR polymorphism and symptoms of cognitive anxiety and emotional arousal control. Gao et al. recorded comparable results to the ones presented herein for the following genes: OXTR, RORA, GRM8, CHRNA4, IL-1A, CRHR1, MTHFR, DRD2, APOE.[72]

The structure of patients' personality in the presented paper was evaluated only before the start of pharmacotherapy, i.e. during the period of the highest intensification of symptoms. Therefore, a question should be asked whether depression psychopathology itself could have an impact on fear intensification as a situational state. In compliance with the previously mentioned theory of the permanent nature of personality traits,[31] the main foundation of personality does not change during subsequent years of our lives. According to Lopez-Castroman et al.,[73] axis II diagnoses in acutely depressed patients, reassessed after 3 months, are often stable and not associated with remission of or improvement in major depression. A diagnosis of personality disorders (mainly border-line disorders and obsessive-compulsive personality disorders) reduced significantly the period of remission after a clinical improvement had been achieved in the patients suffering from a major depressive disorder (MDD).[74,75]

To sum up, it is justified to once again refer to the phenomenon of epigenetics and underline the results obtained by us, which indicate a connection between anxiety as a constant personality trait with changes in the expression of genes of pro-inflammatory and anti-inflammatory cytokines.

Conclusions

1. The intensity of depression episode symptoms, measured using the neurotic triad and the Welsh anxiety scale for the MMPI-2 test, correlate significantly with the expression at the mRNA and protein level for the genes of pro-inflammatory and anti-inflammatory cytokines.
2. Anxiety as a personality trait may be a significant marker of inflammation during a depression episode.

Limitations

Age differences between the examined groups may be treated as a limitation of the study. However, irrespective of the age differences between the examined groups, statistically significant dependence was confirmed for each group separately.

It is also worth repeating the protocol of the experiment with reference to more numerus groups of subjects. It must also be noted that the research study had an explorational rather than clinical nature.

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Authors' contributions

Monika Talarowska – study design, data collection, data interpretation, manuscript preparation, literature search.

Katarzyna Bliźniewska – data collection, manuscript preparation, literature search.

Małgorzata Kowalczyk – manuscript preparation.

Janusz Szemraj – genetic analysis.

Piotr Gałecki – critical review.

Conflict of interest

The manuscript has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors and by the responsible authorities where the work was carried out. If the manuscript will be accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

References

1. de Sousa RT, Zanetti MV, Brunoni AR, Machado-Vieira R. Challenging treatment-resistant major depressive disorder: a roadmap for improved therapeutics. Curr Neuropharmacol. 2015;13(5):616–35.
2. DiLuca M, Olesen J. The cost of brain diseases: a burden or a challenge? Neuron. 2014;82(6):1205–8.
3. Reynolds CF III, Cuijpers P, Patel V, Cohen A, Dias A, Chowdhary N. Early intervention to reduce the global health and economic burden of major depression in older adults. Annu Rev Public Health. 2012;33:123–35.
4. Docherty AR, Edwards AC, Yang F, Peterson RE, Sawyers C, Adkins DE, et al. Age of onset and family history as indicators of polygenic risk for major depression. Depress Anxiety. 2017;34(5):446–52.
5. Kuehner C. Why is depression more common among women than among men? Lancet Psychiatry. 2017;4(2):146–58.
6. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):676–92.
7. Lindqvist D, Dhabhar FS, James SJ, Hough CM, Jain FA, Bersani FS, et al. Oxidative stress, inflammation and treatment response in major depression. Psychoneuroendocrinology. 2016;76:197–205.
8. Finnell JE, Wood SK. Neuroinflammation at the interface of depression and cardiovascular disease: evidence from rodent models of social stress. Neurobiol Stress. 2016;4:1–14.
9. Babenko O, Kovalchuk I, Metz GA. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev. 2015;48:70–91.
10. Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017;135(5):373–87.
11. Catena-Dell'Osso M, Rotella F, Dell'Osso A, Fagiolini A, Marazziti D. Inflammation, serotonin and major depression. Curr Drug Targets. 2013;14:571–7.
12. Sukoff Rizzo SJ, Neal SJ, Hughes ZA, Beyna M, Rosenzweig-Lipson S, Moss SJ, et al. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl Psychiatry. 2012;2:e199.
13. Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. J Affect Disord. 2014;169:15–20.
14. Lichtblau N, Schmidt FM, Schumann R, Kirkby KC, Himmerich H. Cytokines as biomarkers in depressive disorder: current standing and prospects. Int Rev Psychiatry. 2013;25(5):592–603.
15. Bobińska K, Gałecka E, Szemraj J, Gałecki P, Talarowska M. Is there a link between TNF gene expression and cognitive deficits in depression? Acta Biochim Pol. 2017;64(1):65–73.
16. Talarowska M, Zboralski K, Chamielec M, Gałecki P. The MMPI-2 neurotic triad subscales and depression levels after pharmacological treatment in patients with depressive disorders – clinical study. Psychiatr Danub. 2011;23(4):347–54.
17. International statistical classification of diseases and related health problems 10th revision (ICD-10). Genewa: World Health Organization; 2015.
18. Diagnostic and statistical manual of mental disorders. fifth ed. Washington, DC: APA; 2013.
19. Patten S. Performance of the composite international diagnostic interview short form for major depression in community and clinical samples. Chron Dis Can. 1997;3:18–24.
20. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
21. Demyttenaere K, De Fruyt J. Getting what you ask for: on the selectivity of depression rating scales. Psychothery Psychosom. 2003;72:61–70.

22. Hathaway SR, McKinley JC. The Minnesota multiphasic personality inventory. Minneapolis: University of Minnesota Press; 1943.
23. Biles L. A taxometric analysis of the MMPI/MMPI-2 depression scales. In: A Dissertation Presented to the Faculty of Pacific Graduate School of Psychology Palo Alto; 2005.
24. Kucharski T. Selected issues connected with polish adaptation of the MMPI-2 and the MMPI-A. Toruń: CPKiROZ; 2002.
25. Talarowska M, Florkowski A, Zboralski K, Gałecki P. Differences in the course of depressive disorders among women and men measured by MMPI-2. Psychiatr Pol. 2010;XLIV:319–28.
26. Chomczynski P, Sacchi N. Single – step method of RNA isolation by acid guanidinium thiocyanate–phenol–chloroform extraction. Anal Biochem. 1987;162:156–9.
27. Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative CT method. Nat Protocols. 2008;3:1101–8.
28. Livak K, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta CT}$ method. Methods. 2001;25(4):402–8.
29. Kirkwood B, Sterne J. Essential medical statistics. 2nd ed. Wiley-Bleckwell; 2003.
30. Pingault JB, Falissard B, Côté S, Berthoz S. A new approach of personality and psychiatric disorders: a short version of the Affective Neuroscience Personality Scales. PLOS ONE. 2012;7(7):e41489.
31. Westen D, Shedler J. A prototype matching approach to diagnosing personality disorders: toward DSM-V. J Pers Disord. 2000;14:109–26.
32. Naylor B, Boag S, Gustin SM. New evidence for a pain personality? A critical review of the last 120 years of pain and personality. Scand J Pain. 2017;17:58–67.
33. Davis KL, Panksepp J. The brain's emotional foundations of human personality and the Affective Neuroscience Personality Scales. Neurosci Biobehav Rev. 2011;35(9):1946–58.
34. Kier EL, Kim JH, Fulbright RK, Bronen RA. Embryology of the human fetal hippocampus: MR imaging, anatomy, and histology. AJNR Am J Neuroradiol. 1997;18(3):525–32.
35. Insausti R, Cebada-Sánchez S, Marcos P. Postnatal development of the human hippocampal formation. Adv Anat Embryol Cell Biol. 2010;206:1–86.
36. Morrison KE, Rodgers AB, Morgan CP, Bale TL. Epigenetic mechanisms in pubertal brain maturation. Neuroscience. 2014;264:17–24.
37. Montag C, Widenhorn-Müller K, Panksepp J, Kiefer M. Individual differences in Affective Neuroscience Personality Scale (ANPS) primary emotional traits and depressive tendencies. Compr Psychiatry. 2016;73:136–42.
38. Deris N, Montag C, Reuter M, Weber B, Markett S. Functional connectivity in the resting brain as biological correlate of the Affective Neuroscience Personality Scales. Neuroimage. 2016;147:423–31.
39. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry. 2014;171:829–43.
40. Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. J Affect Disord. 2011;130(1–2):66–74.
41. Mosquera D, Gonzalez A, Leeds AM. Early experience, structural dissociation, and emotional dysregulation in borderline personality disorder: the role of insecure and disorganized attachment. Borderline Personal Disord Emot Dysregul. 2014;1:15.
42. Baryshnikov I, Joffe G, Koivisto M, Melartin T, Aaltonen K, Suominen K, et al. Relationships between self-reported childhood traumatic experiences, attachment style, neuroticism and features of borderline personality disorders in patients with mood disorder. J Affect Disord. 2016;210:82–9.
43. Hodes GE, Ménard C, Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. Neurobiol Stress. 2016;4:15–22.
44. Talarowska M, Galecki P. Cognition and emotions in recurrent depressive disorders – the role of inflammation and the kynurenine pathway. Curr Pharm Des. 2016;22(8):955–62.
45. Morris G, Carvalho AF, Anderson G, Gałecki P, Maes M. The many neuroprogressive actions of tryptophan catabolites (TRYCATs) that may be associated with the pathophysiology of neuro-immune disorders. Curr Pharm Des. 2017;22(8):963–77.
46. Gałecki P, Talarowska M. Neurodevelopmental theory of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2018;80 Pt C:267–72.
47. Paslakis G, Bleich S, Frieling H, Deuschle M. Epigenetic mechanisms in major depression. Nervenarzt. 2011;82(11):1434–8.
48. McCoy CR, Jackson NL, Day J, Clinton SM. Genetic predisposition to high anxiety- and depression-like behavior coincides with diminished DNA methylation in the adult rat amygdala. Behav Brain Res. 2016;320:165–78.
49. Golimbet VE, Alfimova MV, Korovaitseva GI, Lezheiko TV. Analysis of the association of interleukin 4 and interleukin 10 gene variants with basic personality traits. Mol Biol (Mosk). 2016;50(6):953–9.
50. Sutin AR, Terracciano A, Deiana B, Naitza S, Ferrucci L, Uda M, et al. High neuroticism and low conscientiousness are associated with interleukin-6. Psychol Med. 2010;40(9):1485–93.
51. Elliot AJ, Turiano NA, Chapman BP. Socioeconomic status interacts with conscientiousness and neuroticism to predict circulating concentrations of inflammatory markers. Ann Behav Med. 2017;51(2):240–50.
52. Miyamoto Y, Boylan JM, Coe CL, Curhan KB, Levine CS, Markus HR, et al. Negative emotions predict elevated interleukin-6 in the United States but not in Japan. Brain Behav Immun. 2013;34:79–85.
53. Isung J, Aeinehband S, Mobarrez F, Nordström P, Runeson B, Asberg M, et al. High interleukin-6 and impulsivity: determining the role of endophenotypes in attempted suicide. Transl Psychiatry. 2014;4:e470, http://dx.doi.org/10.1038/tp.2014.113.
54. Chapman BP, van Wijngaarden E, Seplaki CL, Talbot N, Duberstein P, Moynihan J. Openness and conscientiousness predict 34-week patterns of Interleukin-6 in older persons. Brain Behav Immun. 2011;25(4):667–73.
55. Turiano NA, Mroczek DK, Moynihan J, Chapman BP. Big 5 personality traits and interleukin-6: evidence for ''healthy Neuroticism'' in a US population sample. Brain Behav Immun. 2013;28:83–9.
56. Luchetti M, Barkley JM, Stephan Y, Terracciano A, Sutin AR. Five-factor model personality traits and inflammatory markers: new data and a meta-analysis. Psychoneuroendocrinology. 2014;50:181–93.
57. Smith TW, Uchino BN, Bosch JA, Kent RG. Trait hostility is associated with systemic inflammation in married couples: an actor-partner analysis. Biol Psychol. 2014;102:51–3.
58. Boisclair Demarble J, Moskowitz DS, Tardif JC, D'Antono B. The relation between hostility and concurrent levels of inflammation is sex, age, and measure dependent. J Psychosom Res. 2014;76(5):384–93.
59. Girard D, Tardif JC, Boisclair Demarble J, D'Antono B. Trait hostility and acute inflammatory responses to stress in the laboratory. PLOS ONE. 2016;11(6):e0156329.
60. Henningsson S, Baghaei F, Rosmond R, Holm G, Landén M, Anckarsäter H, et al. Association between serum levels of C-reactive protein and personality traits in women. Behav Brain Funct. 2008;4:16.

61. Manning KJ, Chan G, Steffens DC. Neuroticism traits selectively impact long term illness course and cognitive decline in late-life depression. Am J Geriatr Psychiatry. 2017;25(3):220–9.
62. Yoneda T, Rush J, Berg AI, Johansson B, Piccinin AM. Trajectories of personality traits preceding dementia diagnosis. J Gerontol B Psychol Sci Soc Sci. 2017;72(6):922–31.
63. Tayefi M, Shafiee M, Kazemi-Bajestani SMR, Esmaeili H, Darroudi S, Khakpouri S, et al. Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study. Psychoneuroendocrinology. 2017;81:63–9.
64. Kuznetsova VB, Knyazev GG, Dorosheva EA, Bocharov AV, Savost'yanov AN. A role of personality and stress in the development of depressive symptoms in students. Zh Nevrol Psikhiatr Im S S Korsakova. 2016;116(12):114–8.
65. Smith KA, Barstead MG, Rubin KH. Neuroticism and conscientiousness as moderators of the relation between social withdrawal and internalizing problems in adolescence. J Youth Adolesc. 2017;46(4):772–86.
66. Paans NP, Bot M, Gibson-Smith D, Van der Does W, Spinhoven P, Brouwer I, et al. The association between personality traits, cognitive reactivity and body mass index is dependent on depressive and/or anxiety status. J Psychosom Res. 2016;89:26–31.
67. van der Veen DC, van Dijk SD, Comijs HC, van Zelst WH, Schoevers RA, Oude Voshaar RC. The importance of personality and life-events in anxious depression: from trait to state anxiety. Aging Ment Health. 2016;4:1–7.
68. van Dijk SD, Hanssen D, Naarding P, Lucassen P, Comijs H, Oude Voshaar R. Big five personality traits and medically unexplained symptoms in later life. Eur Psychiatry. 2016;38:23–30.
69. Bukh JD, Andersen PK, Kessing LV. Personality and the long-term outcome of first-episode depression: a prospective 5-year follow-up study. J Clin Psychiatry. 2016;77(6):e704–10.
70. Yoneda T, Rush J, Berg AI, Johansson B, Piccinin AM. Trajectories of personality traits preceding dementia diagnosis. J Gerontol B Psychol Sci Soc Sci. 2016. March 4. pi**i: gbw006 [Epub ahead of print].
71. Petito A, Altamura M, Iuso S, Padalino FA, Sessa F, D'Andrea G, et al. The relationship between personality traits, the 5HTT polymorphisms, and the occurrence of anxiety and depressive symptoms in elite athletes. PLOS ONE. 2016;11(6):e0156601.
72. Gao J, Davis LK, Hart AB, Sanchez-Roige S, Han L, Cacioppo JT, et al. Genome-wide association study of loneliness demonstrates a role for common variation. Neuropsychopharmacology. 2017;42(4):811–21.
73. Lopez-Castroman J, Galfalvy H, Currier D, Stanley B, Blasco-Fontecilla H, Baca-Garcia E, et al. Personality disorder assessments in acute depressive episodes: stability at follow-up. J Nerv Ment Dis. 2012;200(6):526–30.
74. Grilo CM, Stout RL, Markowitz JC, Sanislow CA, Ansell EB, Skodol AE, et al. Personality disorders predict relapse after remission from an episode of major depressive disorder: a 6-year prospective study. J Clin Psychiatry. 2010;71(12):1629–35.
75. Skodol AE, Grilo CM, Pagano ME, Bender DS, Gunderson JG, Shea MT, et al. Effects of personality disorders on functioning and well being in major depressive disorder. J Psychiatr Pract. 2005;11(6):363–8.