Cytokine levels and fatigue in patients with depression: A case-control study

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Abstract

1. Abstract

Background: Depression represents a highly disabling disease. A relationship between augmented cytokine concentrations and depression has been suggested. Fatigue, frequently being part of depressive symptoms and being associated with infectious diseases and autoimmune diseases, could constitute a link between inflammation mechanisms and depression. The aim of this work was to show the pattern of relationships between depression, fatigue, and inflammation.

Methods: A case-control study with 27 patients and 33 matched controls was conducted. IL-6, IL-1β, TNF-α, IFN-γ and CRP were assessed in venous blood samples. Fatigue was assessed behaviorally with a sustained attention task (SAT) and subjectively with a questionnaire (FIS-D). Depression scores were assessed using a questionnaire (BDI-FS).

Results: IL-6 was higher in the patient group (U test = 304.00; p = 0.045). For the whole sample size, IL-1β concentration differences were found between BDI-FS categories (H (3) = 11.34, p = 0.01). In patients, correlations were found between BDI-FS categories and IL-1β (ρ = 0.409, p = 0.038), psychosocial fatigue and IL-6 (ρ = 0.437, p = 0.029), and somatic fatigue and TNF-α (ρ = 0.390, p = 0.049). However, correlations failed p = 0.05 threshold for controls. Finally, the total number of omitted responses in the SAT and TNF-α were positively correlated in the patient group (ρ = 0.488, p = 0.011) as well as in the control group (ρ = 0.454, p = 0.008).

Conclusions: The results suggest the presence of inflammation in both depression and fatigue. However, each correlates with different pro-inflammatory parameters, indicating potential biological heterogeneity.

2. Background

Depression is a mental health disorder, which is present in 27% of the world population. Depression is associated with a high DALY-metric (1,2). The clinical features are predominantly lowering of mood, reduction of energy, and decrease in activity (3). Among other symptoms, marked tiredness after even minimum effort is common (3).

Well regarded models for depression frequently involve a stress-induced change in behavior. According to these models, stress activates different hypothalamic regions, which promotes higher concentrations of pro-inflammatory cytokines (i.e. Interleukin 1 beta -IL-1β-) (4,5). In some cases, this results in memory deficits and depressive mood symptoms (6,7). This statement was corroborated in two studies who demonstrated a relationship between IL-1β and depressive disorders (8) as well as with cognitive performance (9).

One consequence of the hypothalamic provoked stress is fatigue (5). Fatigue is considered either a common nonspecific symptom or a syndrome. However, there is no uniform definition. In a review based on 38 studies on the chronic fatigue syndrome, Brurberg et al. proposed five domains of fatigue (10). These domains include musculoskeletal pain/tiredness, neurocognitive problems, inflammation, sleep disorders/tiredness, and mood disorders (10). Fatigue has been described as a diminished ability to initiate or maintain activity or to maintain attention (11,12).

Various diseases are associated with fatigue. These include tumor-related fatigue, chronic infectious diseases, autoimmune diseases, fatigue associated with pharmacological treatment, deficiency diseases, endocrine disorders, organ disorders and depression, anxiety disorders, burnout and chronic fatigue syndrome (13,14). For example, chronic diseases such as rheumatoid arthritis (15) or chronic kidney disease (16) develop persistent fatigue that impairs the ability to perform daily activities. This was demonstrated in a study in which higher levels of pro-inflammatory cytokines (i.e., IL-6) were associated with fatigue in patients with chronic kidney disease (16). The presence of inflammation on perceived fatigue indicates possible dysregulation of the hypothalamic axis, as occurs in depressive disorders. However, there are only a few studies dealing with this issue to explain fatigue and inflammatory mechanisms in depression (16,17).

To the best of our knowledge, there are no studies on the relationship of the fatigue dimensions mentioned, which are also present in depression. Only two studies have shown associations between depression, higher cytokine levels and behavioral fatigue, with the latter being operationalized by sustained attention (18,19). As a result, a relationship between fatigue and inflammation can be established, bearing in mind that in depression, pro-inflammatory mechanisms may be present and fatigue is a common manifestation of depression. It has been shown that fatigue correlates with inflammation in some chronic diseases, and it can be argued that in various fatigue dimensions, inflammatory mechanisms are also present in depression (20,21). It would be particularly interesting to investigate whether depression and fatigue, which cannot be completely differentiated in terms of their symptoms, can be differentiated by the involvement of inflammatory parameters. Thus, the aim of this study is to investigate the relationship between cytokine concentration, depression and fatigue.

3. Materials And Methods

3.1. Study design

A case-control study was conducted. 27 patients diagnosed with depression or depressive episode (DE) as defined by ICD-10 and 33 healthy controls (HC), aged between 18 and 60 years, were included in the study. Groups were matched by age and gender. Data collection was performed between November 2018 and February 2019. In the patient group, 27 volunteers with DE but without concomitant psychotic episode or anxiety disorders were included. Patients having another comorbid psychiatric disease (i.e. bipolar disorder, personality disorder, adaptation syndrome and post-traumatic stress disorder) were included as long as a DE was present and predominant during the last 6 months. Exclusion criterion for both patients and controls were insufficient German language

knowledge, somatic limitations that did not allow participation, particularly visual or auditory limitations. Individuals could not participate if they suffered from acute or chronic disease or illness of any type, particularly related to infection, except depression. Latter were assigned to the patient's group. Demographic data are shown in table 1.

All participants were informed about the procedure and gave written informed consent. All experimental procedures were in accordance with the Declaration of Helsinki and were approved by the local ethics committee of the Justus-Liebig University (JLU) medical faculty. The study complies with the APA ethical standards.

3.2. Data collection

3.2.1 Blood Sampling

3 mL fasting venous blood samples were collected between 8:00 am and 12:00 pm with EDTA K blood sample tubes (SARSTEDT, Monovette®) and then centrifuged at 4°C with 176 xg for 15 minutes. After centrifugation, the serum was collected, divided into two 0.5 mL aliquots and immediately stored at -20°C. Every 4 weeks, the blood samples were collectively delivered to an university research facility, which was about 30 km away, and stored at -80°C for further use.

Levels of IL-6, IL-1β, C-reactive Protein (CRP), Tumor necrosis factor-alpha (TNF-α) and Interferon-gamma (IFN-γ) were measured using Quantine-ELISA kits (R&D-Systems Inc., Minneapolis, Minnesota, United States of America) with the detection limits of: IL-6 = 3.13 pg/mL, IL-1β = 3.9 pg/mL, CRP = 0.78 ng/mL, TNF-α = 15.6 pg/mL and IFN-γ = 15.6 pg/mL. Intra- and inter-precision values were < 10%.

IL-1β values below the ELISA detection limit (one participant) were considered to be zero pg/mL and included in the analysis. Maximum serum cytokine values (indicated by the software as '>Max') for IL-6 (one participant), CRP (twelve participants) and IL-1β (two participants) were reported and excluded from the analysis. One participant, who had refused the blood sampling, was excluded from the study.

Cytokine concentrations were calculated using the Magellan Reader Software (Tecan Reader). For the parameter calculation, the Marquardt's 4-parameter estimation method was used.

3.2.2. Depression

DE as defined according to the diagnostic criteria from the International Statistical Classification of Diseases and Related Health Problems, version 10 -ICD-10- (3). The presence of a DE was diagnosed in the psychiatric department of the University Hospital of Giessen and Marburg (Location - Giessen), by clinical experts.

The Beck Depression Inventory – Fast Screening, German Version (BDI-FS) (22) was applied for scoring the severity of the DE. The BDI-FS provides scores in the range between 0 – 21. The highest score indicates a high load of depressive burden. The instrument has good internal consistence (Cronbach's α = 0.84) and a convergent validity with the PHQ-9 of r = 0.67, including that it was validated to a representative German sample (n = 2467). If necessary, the cut-off definitions recommended in the manual were used (cut-off = 5). The categories used were labeled as *minimal* (0 to 3 points), *mild* (4 to 8 points), *moderate* (9 to 12 points), and *severe* (13 to 21 points).

3.2.3. Fatigue dimensions

The extent of fatigue was assessed on both the subjective and the behavioral level. The subjective ratings of fatigue were recorded applying the Fatigue Impact Scale – German Version (FIS-D (23)) in both groups. The FIS-D measures the impact of fatigue on Health-Related Quality of Life (23). The FIS-D consists of three sub-scales, which represent a three dimensional structure of fatigue. These dimensions include a psychosocial dimension (or PSY-F, 20 questions, maximum score 80 points), a somatic dimension (or SOM-F, 10 questions, maximum score 40 points) and a cognitive dimension (or COG-F, 10 questions, maximum score 40 points). The maximum score (TOT-F) that can be acquired is 160 points (4 for each item). As defined in the FIS-D manual, the cut-off values for increased fatigue are over 20 points for the psychosocial dimension, over 10 points for the somatic or cognitive dimension, and over 40 points for the full test.

To assess fatigue at behavioral level, the sustained attention task from the *Testbatterie zur Aufmerksamkeitsprüfung* (Psychological Test Systems, German version 2.3.1.) (24) was applied. Sustained attention is defined by the performance of monitoring frequent target stimuli over time. In many studies sustained attention performance was demonstrated to correlate with levels of fatigue (25–28). The implementation of the sustained attention task in the current study consisted of a sequence of 450 images, each showing a combination of the feature dimensions shape (circle, square, triangle, cross, diamond, oval, rectangle), size (small, middle, big), color (yellow, blue, red, green, purple), and fill (empty, grid, filled). Each stimulus was presented for 500 ms, the interstimulus interval was 1500 ms, and total duration was 15 minutes. The participants were asked to press a button whenever a stimulus matched color or form of the immediately preceding stimulus. The instruction emphasized the importance of both speed and accuracy of the responses. Reaction times were recorded; correct (max.=54) and incorrect responses (false alarm, omission) were counted. For analysis, the task was divided into three epochs of 5 minutes duration. For each epoch as well as for the total task the median of reaction times (RT) and the count of omitted responses to target were computed.

3.3. Statistical Analysis

Statistical analyses were performed using SPSS v. 24.0 (IBM Enterprises) and JASP 0.9.2 (Eric-Jan Wagenmakers, The University of Amsterdam, Department of Psychological Methods).

All sample description statistics, psychological and immunological parameters evaluated are displayed in table 1 and table 2. Quantitative variables approximately fitting a normal distribution are specified as mean ± standard deviation, those with a non-normal distribution were expressed as median with percentile 75 and percentile 25 and the interquartile range (Q3 – Q1; IQR). Categorical variables were specified with numbers and in some cases quotient values.

To evaluate the differences in continuous parametric distributed data, Student`s t-test was used. In case of non-parametric distributed data, U-Mann-Whitney test was used to investigate differences between the two groups. For categorical data, $\chi 2$ or Fisher's exact test was used to evaluate differences between groups.

For the effect sizes, Cohen's d (for parametrical distributed data), Eta-Square (for non-parametrical distributed data) and Cramer's V (for categorical data) tests were used. Cohen's d thresholds were defined as low = 0.2, medium = 0.5, high = 0.8. For the Cramer's V effect size, we used the following thresholds: very low 0 to 0.1, low 0.1 to 0.3, medium 0.3 to 0.5 and high up to 0.5. For the non-parametrical data, Eta-Square (ES) was used under the following formula: $\eta 2 = Z2/N\text{-}1$. The effects were defined as weak whenever $ES \leq 0.04$; ES was defined as medium when $0.04 < ES \leq 0.36$ and as strong when $ES > 0.36$.

The difference between groups was considered 'significant' if the P-value was < 0.05. To evaluate differences between groups, testing was one-tailed.

In order to show differences between cytokine concentrations among to the BDI-FS categories, Kruskal-Wallis test was computed. In this case, data for cytokine concentration were not normally distributed and BDI-FS categories fall into more than two categories. These results are shown in Figure 1.

A Spearman rank correlation (Spearman ρ) between fatigue (subjective and behavioral) and cytokine concentration was performed separately in participants with DE and HC. These results were tabulated and p-values, when significant, were flagged (Table 3).

Potential confounders (age, gender, BMI, cigarette smoking) and demographic characteristics were included in the sample description for each group (Table 1).

4. Results

4.1. General characteristics of the sample

Baseline laboratory and clinical characteristics of the 59 participants included in the study are listed in Table 1. The sample consisted of about twice as many women as men. However, the ratio of men and women did not differ per group (Table 1). The age differed between the groups by about 3 years (median) with the IQR being slightly higher in the depression group (Table 1). More smokers were found in the patient group ($p = 0.018$, Cramer's $V = 0.307$).

4.2. Fatigue (FIS-D, sustained attention task) and Depression (BDI-FS)

The BDI-FS, the total FIS-D, and all three sub-scales (PSY-F, SOM-F, COG-F) showed higher depression scores and higher fatigue scores in DE compared to HC (Table 2). In the SAT, the total sum of omitted responses was higher in DE than in HC (Table 2; Mann-Whitney-U = 261.500; $p = 0.008$). Thereby, the first two 5-minute segments of the continuous task showed a small effect size and the third segment a medium effect size (Table 2).

4.3. Cytokine concentration

Differences between patients with DE and HC: IL-6 concentration was higher in patients (Table 2; Mann-Whitney-U = 304.000, $p = 0.045$) with a small to moderate effect size. No differences between groups were found for the other cytokine concentrations, IL-1β, TNF-α, IFN-γ and CRP.

Differences between the BDI-FS categories: The Kruskal-Wallis H test, combining DE and HC groups, showed a significant difference in IL-1β concentrations between the four BDI-FS categories ($H(3) = 9.128$, $p = 0.028$). Median of IL-1β concentration was 2.41 pg/mL for minimal, 2.42 pg/mL for mild, 6.39 pg/mL for moderate and 9.75 pg/mL for severe BDI-FS categories (Figure 1). The same analyses were carried out for the other cytokines. No differences were found with $p < 0.05$ between the four BDI-FS categories and the other cytokine concentration values (IL-6: $H(3) = 6.114$, $p = 0.106$; TNF-α: $H(3) = 3.592$, $p = 0.309$; IFN-γ: $H(3) = 4.689$, $p = 0.196$; CRP: $H(3) = 0.437$, $p = 0.933$), also the effect sizes were weak.

4.4. Correlation between cytokine concentration, fatigue and BDI-FS categories

Table 3 shows the correlations between fatigue dimensions, BDI-FS categories, and cytokine concentrations.

BDI-FS categories correlated with IL-1β level in the patient group, but not in the control group (Table 3). No substantial correlations were seen between BDI-FS categories and TNF-α, IFN-γ, or CRP (Table 3). Neither for the entire sample ($\rho = 0.106$, $p = 0.426$) nor within the groups did the BDI-FS categories correlate with smoking behavior. The only correlation of smoking behavior with cytokine concentration was a negative correlation with IL-1β concentrations in the control group but not in the patient group (Table 3).

Unlike BDI-FS, both TOT-F and the PSY-F dimension's score correlated significantly with IL-6 levels in the patient group (Table 3). However, SOM-F dimension's scores correlated with TNF-α concentrations in the patient group (Table 3).

Referring to behavioral fatigue –measured with the number of omitted values from the SAT-, we found that TNF-α is positively correlated with the total number of omitted values in the patient group as well as in the control group (Table 3). However, associations failed $p = 0.05$ threshold for correlations between behavioral fatigue and the other assessed cytokines (IL-6, IL-1β, IFN-γ and CRP).

5. Discussion

The results of this study showed, first, that IL-6 concentrations are significantly higher in patients with DE compared to HC. Secondly, significant differences in IL-1β concentrations were found between BDI-FS categories (defined also as depression severity) for the entire participants. Thirdly, in the patient group different variables correlated positively, namely IL-1β concentrations and depression severity, IL-6 and both PSY-F and TOT-F as well as TNF-α and SOM-F. Fourthly, positive correlations were found between TNF-α and behavioral fatigue (total number of omitted responses in the SAT) in both groups. Finally, no significant correlations were found between IFN-γ, CRP, fatigue dimensions and depression in both groups. Smoking behavior, although it was different between patients and control, it did not constitute a major confounding variable.

5.1. Cytokine concentration differences.

IL-6 differences between patients with DE and HC: Respecting the findings of this study, differences of IL-6 concentrations between patients and controls were congruent with two meta-analyses of human studies reported significant differences of peripheral IL-6 levels in patients with depressive disorders compared to HC (29,30). Furthermore, one of the main functions of IL-6 is the synthesis induction of adrenocorticotropic hormone –or HPA- (31,32). This together could suggest that higher peripheral IL-6 levels in depression may be linked with an overstimulation of the hypothalamic axis –or HPA- (4). In this sense, many experimental models have demonstrated that an augmentation of IL-6 overstimulates the HPA, altering the cortisol homeostasis and producing a pro-inflammatory state (33–38). Finally, this cortisol enhance due to higher IL-6 concentrations could explain the obtained differences in this study (Table 1) and in some cases characteristic symptoms of depression (38).

IL-1β and differences among depression severity degrees: The findings of this study revealed statistical differences between among depression severity degrees for the whole sample size. Three studies reported the same direct proportional relation between IL-1β concentrations and depression severity (39–41). This direct proportional relation could be explained through the concentration-dependent anti-neurogenic effect of the IL-1 cytokine family (42). The augmentation of IL-1β in the CNS leads to a reduced neurogenesis in the dentate gyrus, reducing the hippocampal volume and leading to classical depressive symptomatology, following an experimental study in rats (43). This detrimental effects of IL-1β in the neurogenesis are demonstrated to be concentration-dependent, i.e. the higher concentrations of this cytokines the more impairment is produced (44). Although most of these models belong to cognitive and memory performance (45), the presence of cognitive impairment is also related with depression (46) and could explain this direct proportion between both variables.

5.2. Correlations - cytokine concentrations

IL-6 concentration with psychosocial fatigue and total fatigue scores: The results of the present study showed a significant positive correlations between PSY-F and IL-6 concentrations, as well as TOT-F and IL-6 correlations. These were present in the patient group but not in the control group. As mentioned before, there is strong evidence supporting higher peripheral IL-6 values in patients with depression (29), as well as positive correlations with depression and IL-6 concentrations (47). In this case, positive correlations between both variables in the patient group show a direct proportion between subjective fatigue (in this case psychosocial and total values) and IL-6 concentrations, suggesting a IL-6-concentration-dependence-behavior (48,49). Additionally, fatigue has been demonstrated to be related with stress and HPA-dysfunction (14). HPA-dysregulation leads to augmentation of cortisol levels, leading finally to fatigue, as shown in a study with cancer patients (50). This coincides also with the effects of cortisol overproduction due to higher IL-6 concentrations, as mentioned above. Finally, this information suggest that higher IL-6 production in patients with depression could produce HPA-dysregulation, possibly leading to a unbalanced cortisol production and finally developing fatigue, predominantly altering the psychosocial dimension of fatigue.

IL-1β concentration with depression severity scores: This study found statistical differences among the different depression severity scores for the whole sample size. Interestingly, depression severity scores (expressed as BDI-FS categories) correlate significantly with the patient group and not with the control group. For that reason, the raised hypothesis above on the effects of IL-1β on the neuroplasticity could be more related to the patient group and not to the HC individuals. Additionally, the detrimental effects of IL-1β are also time-dependent (42) that means the longer exposition could lead to a stronger neural damage. In this case, most of the depressive patients assessed in this study had a median of seven years of disease (10.50 – 1.76; 8.74), corresponding also to the time-dependent effects of IL-1β in our patient sample.

TNF-α concentration with somatic and behavioral fatigue: The results of this study pointed out first that there is a positive significant correlation between somatic fatigue and TNF-α concentration in the patient group. Secondly, TNF-α positive correlates with behavioral fatigue in both groups. TNF-α is a pleiotropic cytokine, whose main function is the regulation of immune response and the initiation of strong inflammatory response (32). As a consequence of an immune response, the body reacts with sleepiness, decreased motorial activity and general reduction of corporal activity, as well as worsening of the general status (51). This is also described as fatigue and present in different chronic inflammatory disorders (15,52), as well as in depressive disorders (15). In this case, the TNF-α can actively cross the blood-brain barrier (53), having negative effects on neurotransmission and unbalanced HPA-stimulation/desensitization (15). As mentioned before, an unbalanced HPA causes an overproduction of corticoids, which lately will cause the classical symptoms of fatigue. In addition, an experimental model for fatigue demonstrated HPA hyperactivity in depression and also this model fatigue correlated with an increase with CD8+T Cells, which produce mostly TNF-α and IFN-γ (54). Although this model corresponds to patients with multiple sclerosis, this is in line with the results of this study on correlations between fatigue and TNF-α in patients with depression, compared to controls. However, for behavioral fatigue, these results point out a correlation with TNF-α in both groups. This differs with the somatic fatigue, in which TNF-α correlates with somatic fatigue only in the patient group. Because of stronger physiological effects of cortisol on the CNS during an acute reaction (“fight or flight”) and the simultaneous stimulation of pro-inflammatory cytokines (55), correlations are seen in both groups, as showed on Table 3. From this perspective, in a study with healthy subjects, pro-inflammatory cytokines like TNF-α were negative correlated with cognitive performance of the participants, which could also related to behavioral fatigue (56). Nevertheless, studies regarding frequent effects of TNF-α on behavioral fatigue in healthy subjects are still lacking.

5.3. Limitations and future directions

Limitations: This study had different limitations. First, the patient group showed differences in age in comparison to the HC subjects. Although age plays an important role in the augmentation of pro-inflammatory cytokines (57), the assessed participants, allocated in two groups, did not present significant differences in age. Secondly, the sample size was small for generalizing these results beyond the context of the study. However, the power obtained from this study with 59 participants was 1-β = 0.99, value that overcome the 1-β = 0.80 threshold. This means, that the sample size and the study design are adequate to deliver precise results, especially the differences and correlations between inflammatory parameters, fatigue and depression. Thirdly, the higher amount of women in comparison to men for both groups could play an important biological role. Nevertheless, in Germany, the women: men rate for depression is approximately 2 to 1 (58,59). This proportion is also reflected in our study, as delivered in Table 1. Fourthly, the presence of a basement effect in the HC participants. Basement effects are mostly found in psychological test and represent a non-differentiation of the participants due to a gathering of minimum values, contributing finally to a reduced variance. This corresponds mostly to our HC subjects, who did not presented higher values of depression, because they were absent of any mental disease. The latter reflects the selection criteria and the study design, expecting in this case an obtained basement effect from the control group. Additionally, it was selected non-parametric test, not only for the small sample size but also for this basement effect in the HC subjects. Fifthly, the high number of CRP data loss due to twelve participants' blood samples who showed maximal values. As we know, CRP is an acute phase protein with pro-inflammatory effects but mainly unspecific (60). Its values could be elevated, not being necessarily correlated with inflammation processes (60). The undetected values (marked as ">Max") in seven HCs and five participants with depression delivered a loss of data of CRP concentrations specifically and therefore our observations regarding CRP could be influenced by this incident. Finally, we observed that patients differed in a predominant smoking behavior from controls. This could influence the cytokine concentrations. However, we included smoking behavior as a possible confounding factor but did not see significant differences between smokers and non-smokers.

Future directions: Regarding future research directions, the influence of cytokine concentrations in depressive patients over time would be of interest. In addition, the first appearance of depression could be also related with altered cytokine concentrations and searching for possible causality between deregulation of the HPA, inflammation and depressive symptoms is a major goal in the research area. Finally, the elaboration of imaging studies, such as in vivo magnetic resonance spectroscopy, could be helpful to correlate the hypothalamic activity with peripheral serum cytokine concentrations or cerebrospinal fluid cytokine concentrations.

6. Conclusions

We conclude that there are cytokine concentration differences between patients and healthy subjects (IL-6 concentrations) and among depressive severity degrees (IL-1β concentrations). Moreover, we conclude that there exist significant correlations between different cytokine concentrations and different fatigue dimensions in depressive patients. This reflects different correlation patterns for fatigue and inflammation, as well as depression severity and depression. Finally, we conclude that behavioral fatigue correlated positively with TNF-α in both groups. Due to the physiological liaison between pro-inflammatory cytokines and cortisol metabolism, we suggest that this may due to the cognitive impairment and tiredness under higher cortisol levels/production. For this reason, more studies are needed to understand the mechanisms involved between HPA, cortisol, and fatigue dimensions in depressive patients.

Abbreviations

BDI-FS: Beck Depression Inventory – Fast screening.
BMI: Body Mass Index.
CD8+: Cluster of difference 8 positive.
CNS: Central nervous system.
COG-F: Cognitive dimension of fatigue.
CRP: C reactive protein.
DAAD: German academic exchange service.
DALY: Disability-adjusted life years.
DE: Depressive episode.
ELISA: Enzyme-linked immunosorbent assay.
ES: Eta-Squared.
FIS-D: Fatigue Impact Scale, German version.
HC: Healthy control.
HPA: Hypothalamus-pituitary-axis.
IBM: International Business Machines corporation.
ICD-10: International Statistical Classification of Diseases and Related Health Problems, tenth (10th) version.
FN-γ: Interferon gamma.
IL-1: Interleukin 1 family.
IL-1β: Interleukin 1 Beta.
IL-6: Interleukin 6.
IQR: Interquartile range.
JASP: Jeffreys's Amazing Statistics Program.
JLU: Justus-Liebig University.
PHQ-9: Patient healthy questionnaire, ninth (9th) version.

PSY-F: Psychosocial dimension of fatigue.
Q1: First quartile/25th percentile.
Q3: Third quartile/75th percentile.
RT: Reaction time.
SAT: Sustained attention task.
SOM-F: Somatic dimension of fatigue.
SPSS: Statistical package for the social sciences.
TNF-α: Tumor necrosis factor – alpha.
TOT-F: Total fatigue values.

Declarations

Ethical Approval and Consent to participate: This study was approved by the ethic committee of the JLU medical faculty (Annex 1). Additionally, this study is part of a big project to investigate inflammatory factors and fatigue in patients with depression and multiple sclerosis. The code of this project in the ethic committee is AZ 81/18. Attached is the ethical approval and the informed consents (Annex 2, Annex 3) in its original language (German).

Consent for publication: "Not applicable"

Availability of data and materials: The data that support the findings of this study are not publicly available due to the approved law of data protection from the European Union but are available from the corresponding author on strictly grounded reasonable requests.

Competing interests: "The authors declare that they have no competing interests"

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Authors' contributions

BPP: Wrote the introduction, methods, results, discussion and conclusions. Corrected the manuscript, did the data analysis and the literature search.

EN: Corrected the manuscript, helped with the data analysis, mentored the methods (specifically in molecular biology matters) and helped with the discussion of the paper, proofreading and paper mentoring.

GS: Corrected the manuscript for the resubmission, helped with the data analysis, mentored the methods (specifically in topics that corresponded to depression and fatigue) and helped with the discussion, proofreading and paper mentoring.

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Tables

Table 1: Sample size description - General data

racteristic	All subjects (n = 59)	Patients (n = 26)	Controls (n = 33)	P	Effect size
ears)	24 (31 - 21; 10)	26 (39.25 - 22; 17.25)	23 (28 – 20.5; 7.5)	0.052	0.065
: female)	18:41	07:19	11:22	0.595	0.069
n^2)	24.36 ± 4.64	24.81 ± 5.27	24.03 ± 4.12	0.526	0.363
status (yes: no)	14:45	10:16	04:29	0.018	0.307
ause of DE					
E		1			
ate DE		3			
DE		5			
S		11			
ondary to BD		2			
ondary to PTSD		2			
ondary to AD		1			
ondary to BPD		1			

Abbreviations: DE = Depressive Episode; BMI = Body-Mass-Index; NOS = Not otherwise specified; BD = Bipolar disorder; PTSD = Post-Traumatic stress disorder; AD = Adjustment disorder; BPD = Borderline personality disorder; BDI – FS = Beck Depression Inventory – Fast Screening.

Table 2: Fatigue dimensions, BDI-FS categories and Inflammation Parameters

Characteristic	All subjects (n = 59)	Patients (n = 26)	Controls (n = 33)	P	Effect size
FIS-D					
Psychosocial	30.10 ± 19.83	47.54 ± 13.88	16.36 ± 10.97	<0.001	2.529
Somatic	14.31 ± 9.23	20.58 ± 8.36	9.36 ± 6.51	<0.001	1.521
Cognitive	18.39 ± 9.70	25.92 ± 6.91	12.45 ± 7.14	<0.001	1.913
Total	62.80 ± 37.01	94.04 ± 26.28	38.18 ± 22.92	<0.001	2.285
BDI-FS	5 (10 – 1; 9)	10 (11.25 – 7.75; 3.5)	1 (3 - 0; 3)	<0.001	0.633
Minimal (0 - 3)	28	1	27		
Mild (4 - 8)	14	9	5		
Moderate (9 - 12)	14	13	1		
Severe (13 - 21)	3	3	0		
Behavioral fatigue (Sustained attention task – Omitted Response Values)					
0 to 5 min	3 (5 - 2; 3)	3,5 (5.5 - 2; 3.5)	2 (4 – 1.50; 2.5)	0.059	0.042
5 to 10 min	4 (7 - 2; 5)	5 (8 - 2; 6)	4 (4.50 – 2.50; 2)	0.056	0.044
10 to 15 min	3 (6 - 2; 4)	5 (8 - 3; 5)	2 (4 - 1; 3)	0.001	0.163
Total	10 (16 - 6; 10)	15 (19.25 - 8; 11.25)	10 (11.50 - 5; 6.5)	0.007	0.101
Inflammation Parameters					
IL-6 (pg/mL)	3.38 (3.87 – 2.76; 1.11)	3.45 (4.19 – 3.04; 1.16)	3.10 (3.77 - 2.70; 1.07)	0.045	0.051
IL-1β (pg/mL)	3.31 (7.60 – 1.59; 6.01)	5.75 (9.88 – 1.30; 8.58)	2.99 (6.03 – 1.57; 4.46)	0.104	0.028
TNF-α (pg/mL)	16.38 (19.00 – 14.13; 4.87)	17.20 (19.75 – 15.41; 4.34)	16.38 (18.84 – 14.13; 4.71)	0.115	0.025
IFN-γ (pg/mL)	10.36 (11.92 – 9.19; 2.73)	10.46 (11.97 – 9.38; 2.59)	9.97 (11.53 – 9.09; 2.44)	0.132	0.022
CRP (ng/mL)	496.80 (1610.90 – 238.62; 1372.28)	747.61 (1248.75 – 201.26; 1047.50)	471.17 (2049.95 – 245.60; 1804.35)	0.677	0.004

Abbreviations: FIS-D = Fatigue Impact Scale – German Version; BDI – FS = Beck Depression Inventory – Fast Screening; IL-6 = Interleukin 6; TNF-α = Tumor necrosis factor alpha; IL-1β = Interleukin 1 Beta; IFN-γ = Interferon gamma; CRP = C-reactive Protein.

Table 3 – Spearman's correlation between inflammatory parameters, depression severity scores and fatigue

		BDI-FSc	COG-F	SOM-F	PSY-F	TOT-F	TOV	Smoking
IL-6	Patients (n = 25)	*0.254*	*0.384*	*0.272*	**0.437***	**0.432***	*-0.052*	*0.081*
	Controls (n = 33)	*0.140*	*-0.014*	*0.049*	*-0.117*	*-0.031*	*0.017*	*-0.020*
IL-1β	Patients (n = 25)	**0.473***	*0.032*	*-0.245*	*-0.069*	*-0.111*	*-0.224*	*-0.139*
	Controls (n = 33)	*0.201*	*0.204*	*0.342*	*0.225*	*0.281*	*0.162*	**-0.415***
TNF-α	Patients (n = 26)	*-0.312*	*-0.074*	**0.390***	0.072	0.142	**0.488***	*0.137*
	Controls (n = 33)	*-0.067*	*0.178*	*0.266*	*0.072*	*0.167*	**0.454****	*0.010*
IFN-γ	Patients (n = 26)	*0.292*	*-0.075*	*-0.122*	*0.119*	*-0.019*	*0.130*	*-0.111*
	Controls (n = 33)	*0.170*	*0.192*	*0.174*	*-0.002*	*0.123*	*0.136*	*-0.210*
CRP	Patients (n = 21)	*0.092*	*-0.025*	*0.043*	*0.240*	*0.131*	*0.157*	*0.250*
	Controls (n = 26)	*0.058*	*-0.341*	*-0.239*	*-0.331*	*-0.370*	*-0.051*	*-0.152*
BDI-FSc	Patients (n = 26)	----------	**0.410***	*0.070*	**0.501****	**0.402***	*-0.214*	*-0.289*
	Controls (n = 33)	----------	**0.474****	**0.537****	**0.451****	**0.487****	*0.131*	*-0.175*

*Significance levels are indicated for: ** p < 0,01 (two-tailed).*

*Significance levels are indicated for: *p < 0,05 (two-tailed).*

Spearman correlation table. Values indicate Spearman's rho (p).

Abbreviations: BDI – FSc = Categories from Beck Depression Inventory – Fast Screening; COG-F = Cognitive fatigue component scores (FIS-D); SOM-F = Somatic fatigue component scores (FIS-D); PSY-F = Psychosocial fatigue component scores (FIS-D); TOT-F = Total fatigue component scores; TOV = Total omitted values – sustained attention task; IL-6 = Interleukin 6; TNF-α = Tumor necrosis factor alpha; IL-1β = Interleukin 1 Beta; IFN-γ = Interferon gamma; CRP = C-reactive Protein.

Figures

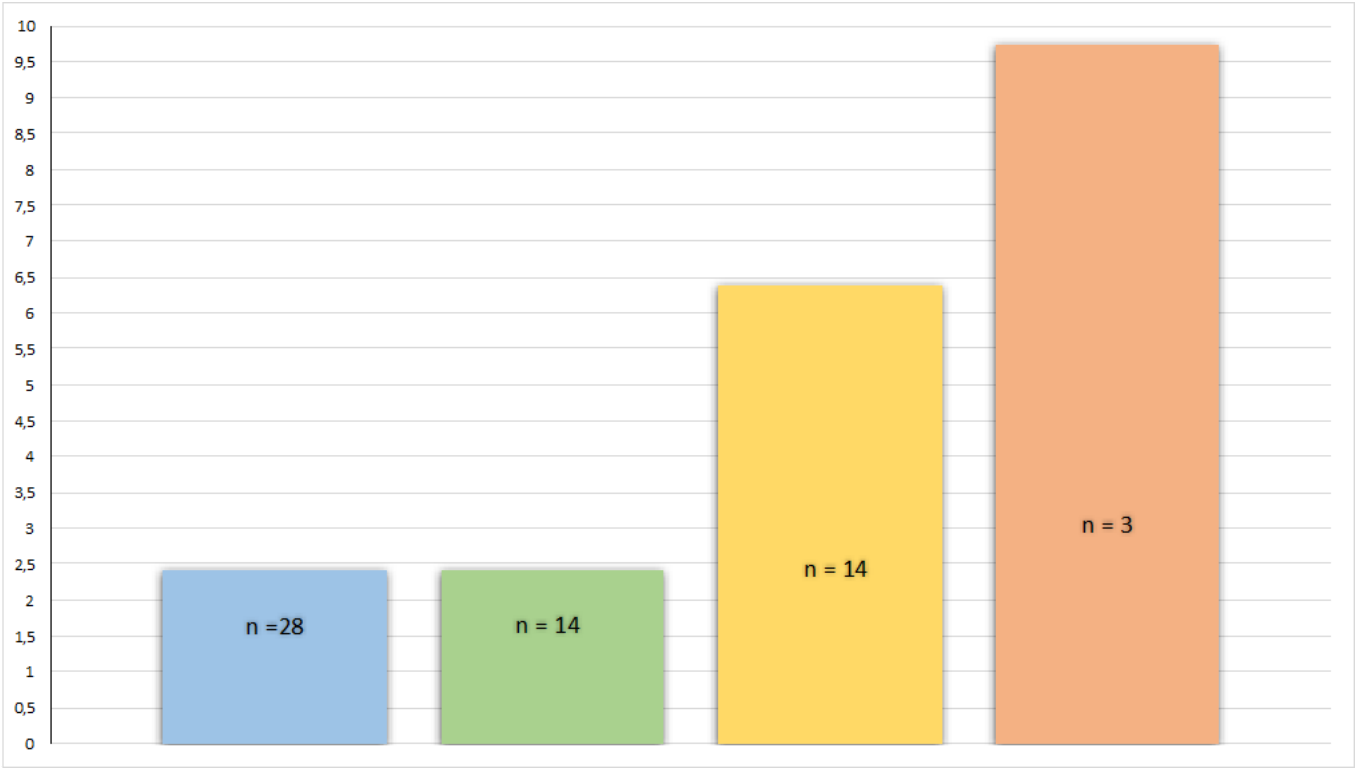

Figure 1

Median IL-1β concentration values and depression severity scores Legend: - Blue: Minimal (0 – 3) - Green: Mild (4 – 8) - Yellow: Moderate (9 – 12) - Red: Severe (13 – 21) - Y-Axis: Median values for IL-1β concentrations (pg/mL) - X-Axis: Depression severity degree (BDI-FS)

Supplementary Files

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