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Chronic fatigue and fibromyalgia symptoms are key components of deficit schizophrenia and are strongly associated with activated immune-inflammatory pathways.

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Abstract

A subset of patients with schizophrenia experience physio-somatic symptoms reminiscent of chronic fatigue and fibromyalgia. In schizophrenia, these symptoms contribute to impaired quality of life, and are strongly related to neuro-cognitive deficits, and increased IgA responses to tryptophan catabolites. Negative and PHEM (psychosis, hostility, excitation, mannerism) symptoms, psychomotor retardation (PMR) and formal thought disorders, appear to be manifestations of a single trait reflecting overall severity of schizophrenia (OSOS). In this study, 120 patients with deficit schizophrenia (DEFSCZ) and 54 healthy subjects were assessed with the FibroFatigue (FF) rating scale, and the above-mentioned symptom domains as well as neuro-cognitive tests and biomarkers were measured. In DEFSCZ, there were robust associations between the FF score and all above-mentioned symptom domains, and impairments in semantic and episodic memory and executive functions. Furthermore, the FF score loaded highly on an OSOS latent vector (LV), which showed adequate convergent validity, internal consistency reliability and predictive relevance and fitted a reflective model. Soft Independent Modelling of Class Analogy (SIMCA) showed that the FF items discriminated DEFSCZ from controls with an overall accuracy of 100%. Interleukin IL-1β, IL-1 receptor antagonist (sIL-1RA), tumour necrosis factor (TNF)-α and CCL-11 (eotaxin) explained 66.8% of the variance in the FF score and 59.4% of the variance in OSOS. In conclusion, these data show that physio-somatic symptoms are a core component of the phenomenology of DEFSCZ and are largely mediated by neurotoxic effects of activated immune pathways, including aberrations in CCL-11, IL-1β and TNF-α signalling.

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Introduction

Classically, schizophrenia is thought to be characterized by two major symptoms domains namely a) positive symptoms (including hallucinations, delusions, conceptual disorganization, aggression and hostility); and b) negative symptoms (including blunted affect, apathy, anhedonia, alogia, and social withdrawal) (Crow, 1985; Mellor, 1991; Cuesta and Peralta, 1995). Recently, we have shown that positive symptoms should be dissected into relevant symptom areas namely psychotic, hostility, excitation and mannerism (PHEM) symptoms (Maes et al., 2019a; Sirivichayakul et al., 2019a; Almulla et al., 2019). Moreover, in stable phase schizophrenia, PHEM and negative symptoms are strongly associated with psychomotor retardation (PMR) and formal thought disorders (FTD), which are other hallmarks of schizophrenia and especially of deficit schizophrenia (Maes et al., 2019a; Sirivichayakul et al., 2019a; Almulla et al., 2019). PMR is a symptom complex consisting of impairments in fine and gross motor performance, extended response latency, slowing in motor responses and movements, bradykinesia and even catatonia in more extreme cases (Almulla et al., 2019a; Maes et al., 2019a). FTD refers to a deterioration in abstract and concrete thinking with disorganized, illogical and inadequate thought processes coupled with intrusions, fluid thinking and loosened associations (Andreasen and Grove, 1986; Bachman and Cannon, 2012; Kircher et al., 2018). The strong intercorrelations between PHEM and negative symptoms, PMR and FTD are also indicated by our findings that a single latent trait may be extracted from those different symptom areas thereby reflecting overall severity of schizophrenia (OSOS) (Almulla et al., 2019).

Other core symptom domains of schizophrenia are affective symptoms and cognitive impairments. Firstly, depressive and anxiety symptoms are present in an important subset of individuals with schizophrenia (Emsley et al., 1999; Kanchanatawan et al., 2018g). Secondly,

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cognitive impairments often comprise both subjective cognitive complaints (SCCs) and objective neurocognitive deficits including impairments in executive functions, episodic and semantic memory, spatial working memory and attention (Reichenberg 2010; Yu et al. 2015; Keefe and Harvey 2012; Seidman et al. 2003; Grillon et al. 2010; Kanchanatawan et al., 2018f; Sirivichayakul et al., 2019b). In schizophrenia, neurocognitive and affective symptoms are strongly associated with both PHEM and negative symptoms (Kanchanatawan et al., 2017; 2018f; Sirivichayakul et al., 2019b). Recently, we found that a meaningful subset of schizophrenia patients exhibit physio-somatic symptoms reminiscent of chronic fatigue syndrome (CFS) and fibromyalgia, including chronic fatigue, muscle pain, muscle tension, autonomic and a flu-like malaise (Kanchanatawan et al., 2017; 2018g). A study showed that these CFS- and fibromyalgia-like symptoms are together with anxiety disorders the most important predictors of lowered health-related quality of life (HR-Qol) in patients with schizophrenia, thereby suggesting that those symptom complexes could be more relevant than PHEM and negative symptoms in predicting HR-QoL in this population (Kanchanatawan et al., 2019). Furthermore, those burdensome physio-somatic symptoms were significantly associated with PHEM and negative symptoms (Kanchanatawan et al., 2018g).

There is now evidence that schizophrenia is a neuro-immune disoder characterized by a simultaneous upregulation of the immune-inflammatory response system (IRS) and the compensatory immune-regulatory system (CIRS) (Roomruangwong et al., 2018). Activation of the IRS is illustrated by increased activity of M1 macrophage and T-helper (Th)-1 cells and increased plasma levels of pro-inflammatory cytokines/chemokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP-1 or CCL-2) and eotaxin (CCL-11) while activation of the CIRS in schizophrenia in indicated by increased plasma concentrations of soluble IL-1 receptor antagonist (sIL1RA), sTNFR1, sTNFR2, and sIL-

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2R (Maes et al., 1996; 2002; Roomruangwong et al., 2019; Noto et al., 2019; Al-Hakeim et al., 2019). Immune products of both IRS and CIRS components may have neurotoxic, cytotoxic and excitotoxic effects on brain cells thereby causing deleterious effects on neuroplasticity, synaptic sampling, synaptic and neuronal functioning, apoptosis, neurogenesis and neuroprotection (Smith and Maes, 1995; Roomruangwong et al., 2018). Most importantly, products of IRS/CIRS including IL-1β, TNF-α, and CCL-11 are strongly associated with PHEM, negative, affective and neurocognitive symptoms suggesting that their neurotoxic effects may be associated with the phenomenology of schizophrenia (Sirivichayakul et al., 2019a; 2019b; Al-Hakeim et al., 2019). Moreover, IRS activation in schizophrenia (including Th-1 and M1 macrophage) may cause stimulation of peripheral IDO (indoleamine 2,3-dioxygenase), which causes an increased catabolism of tryptophan into tryptophan catabolites (TRYCATs), some of which are neurotoxic, e.g. picolinic acid (PA), xanthurenic acid (XA), kynurenine (KYN) and quinolinic acid (QA) (Kanchanatawan et al., 2018c; 2018d). Importantly, increased levels of IgA directed to those TRYCATs (indicating TRYCAT pathway activation) in schizophrenia are significantly associated not only with PHEM, negative, affective and neurocognitive symptoms but also with physio-somatic symptoms (Kanchanatawan et al., 2017; 2018a; 2018b; 2018g), indicating that the latter may be immune-mediated. Nevertheless, to our knowledge no previous study investigated whether physio-somatic symptoms belong to the same latent vector (OSOS) which underlies the key symptom areas of schizophrenia, namely PHEM and negative symptoms, and FTD, and PMR; and whether physio-somatic symptoms are associated with increased levels of neurotoxic cytokines/chemokines.

Thus, in the present work we sought to examine whether physio-somatic symptoms of schizophrenia are associated with both the above-mentioned symptom clusters and also with

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increased levels of cytokines/chemokines with well-known neurotoxic activities.

Methods

Participants

The current study enrolled 120 patients with deficit schizophrenia (DEFSCZ) and 54 healthy control subjects participated. Patients were recruited at the Ibn-Rushd Training Hospital for Psychiatric Medicine, Baghdad, Iraq from December 2018 to February 2019. We used the diagnostic criteria of DSM-IV-Text revised to make the diagnosis of schizophrenia, the Schedule of Deficit Schizophrenia (SDS) to make the diagnosis of DEFSCZ (Kirkpatrick et al., 1989) and the diagnostic criteria described in (Kanchanatawan et al., 2018e) to make the diagnosis of Major Neurocognitive Psychosis (MNP), which are more restrictive than the SDS criteria. However, in the present study all patients with DEFSCZ also met the MNP criteria. Controls were recruited by word of mouth including family, friends or acquaintances of staff members and both controls and patients were recruited from the same catchment area in Baghdad city, Iraq.

Patients and controls presenting with the following conditions were excluded from this study: a) neurodegenerative and neuro-inflammatory disorders including multiple sclerosis, stroke, Alzheimer's and Parkinson's disease; and b) immune-mediated diseases including COPD, psoriasis, rheumatoid arthritis, diabetes type 1, and inflammatory bowel disease. We also excluded patients and controls who had a life-time history of treatments with immune-modulatory drugs including glucocorticoids, methotrexate or immunosuppressants; and subjects who had taken therapeutic doses of antioxidant supplements or ω3-polyunsaturated fatty acids in the months prior to the study. Furthermore, participants with overwhelming peripheral inflammation indicated by CRP values >6 mg/dL were also excluded. We included only patients who were at least 12 weeks

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in the same stable condition. Participants who had a lifetime history of other axis-I disorders including bipolar disorder, schizoaffective disorder, psycho-organic disorders, primary major depression, OCD and substance use disorders (except nicotine use) were also excluded. Finally, controls with any axis-I disorder and those who with a positive family history for schizophrenia were excluded.

All participants as well as the guardians of patients (first degree family members) provided written informed consent prior to participation in the current study. The study was carried out in accordance to the Iraq and international ethics and privacy laws. Approval for the study was obtained from the Institutional Review Board of the University of Kufa (347/2019), which is in compliance with the International Guidelines for Human Research protection as required by the Declaration of Helsinki, The Belmont Report, Council for International Organizations of Medical Sciences (CIOMS) Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Measurements

Clinical assessments

The clinical diagnoses were made by one and the same senior psychiatrist specialized in schizophrenia using DSM-IV-Text Revision criteria and the Mini-International Neuropsychiatric Interview (M.I.N.I.). On the same day, the same senior psychiatrist completed the FibroFatigue scale to assess severity of fibromyalgia and chronic fatigue in patients and controls (Zachrisson et al., 2002). In addition, a semi-structured interview to check clinical and socio-demographic data in controls and patients as well as the Scale for the Assessments of Negative Symptoms (SANS) (Andreasen 1989), SDS (Kirkpatrick et al., 1989), the Brief Psychiatric Rating Scale (BPRS)

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(Overall & Gorham 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Hamilton Depression and Anxiety Rating Scales (HAM-D and HAM-A) (Hamilton, 1959; 1960) were also completed by the same research psychiatrist. The drug state of the patients was also recorded as some patients were taking risperidone (n=109), olanzapine (n=11), or fluphenazine (n=68). On the same day, a well-trained research psychologist, blinded to the clinical assessments and diagnosis, performed neuropsychological tests using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). In brief, the BACS comprises different tests, namely List Learning, which assesses verbal episodic memory; Digit Sequencing Task, which assesses working memory; Category Instances, which probes semantic and verbal fluency; Control Oral Word Association, which probes letter and verbal fluency; Symbol Coding, which assesses attention; and the Tower of London, which assesses executive functions and problem solving. The same psychologist also assessed the Mini-Mental State Examination (MMSE). The diagnosis of Tobacco Use Disorder (TUD) was made using the DSM-IV Text Revision. Body mass index (BMI) was computed as body weight (kg) / length (m^2).

Based on our previous publications (Almulla et al., 2019; Maes et al., 2019a), we computed z-unit weighted composite scores based on BPRS, HDRS, PANSS and SANS items denoting PHEM, FTD, and PMR while severity of negative symptoms was assessed using total scores on the SANS and PANSS negative subscale score.

Assays

In the early morning hours fasting venous blood was collected from all participants. Blood was left at room temperature for 15 min for clotting, centrifuged at 3000 rpm for 10 min, and then serum was separated and transported into Eppendorf tubes to be stored at -80 °C until assays were

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conducted. Serum CRP was measured using a kit supplied by Spinreact®, Spain. The test is based on the principle of the latex agglutination. Commercial ELISA sandwich kits were used to measure serum CCL-11, MCP-1, IL-1β, sIL-1RA, sTNFR1, sTNFR2, and TNF-α (Elabscience, Inc. CA, USA). For samples with highly concentrated biomarkers, we used sample dilution as required. The intra-assay coefficients of variation (CV) (precision within-assay) were < 7.0%.

Statistical analysis

We employed analysis of variance (ANOVA) to check differences in continuous variables among diagnostic categories and analysis of contingence tables (χ^2-test) to assess associations among categorical variables. Correlations between the FF score and other symptom domains, cognitive tests and biomarkers were assessed using partial correlation coefficients. Univariate and multivariate general linear model (GLM) analysis were used to assess the effects of diagnosis while controlling for confounding variables including sex, age, education, TUD, and BMI. Pairwise comparisons among treatment means were assessed using the protected LSD tests. Consequently, we computed model-generated estimated marginal mean (SE) values (adjusted for the significant confounders). Results of multiple comparisons and correlations were p corrected for false discovery rate (FDR) (Benjamini & Hochberg 1995). We used multiple regression analysis (automatic method with p-to-entry of 0.05 and p-to-remove of 0.06) to assess the significant biomarkers that predicted total FF scores. These regression analyses were checked for collinearity using VIF and tolerance and we checked for homoscedasticity using the White and Breusch-Pagan tests. In case homoscedasticity was rejected we employed robust SE or heteroscedasticity-consistent standard error (SE) (HCSE) estimates using the HC3 method. Moreover, all analyses were bootstrapped using 2000 bootstrap samples and we report the bootstrapped results when

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differences among the classical and bootstrapped approaches were observed. We transformed biomarkers to normalize the distribution as assessed using the Kolmogorov-Smirnov test; sIL-1RA and CCL11 were processed in square root transformation while IL-1β, TNF-α, sTNFR1, sTNFR2 and MCP-1 were processed in Ln transformation. Tests were 2-tailed and a p-value of <0.05 was considered for statistical significance. All statistical analyses were performed using IBM SPSS windows version 25, 2017. As machine learning techniques we used Neural Networks (NN) (SPSS version 25), Soft Independent Modeling of Class Analogy or Statistical Isolinear Multiple Component Analysis (SIMCA) (the Unscrambler, CAMO) and Partial Least Squares (PLS) path analysis (SmartPLS, 2019). We have previously described the use of those techniques elsewhere (Almulla et al., 2019).

Results

Socio-demographic and clinical data

Table 1 shows demographic data of patients and controls who took part in the current study. Patients were divided into two groups as determined by the median-split FF score value, namely 23.5, yielding three study groups, namely controls and patients with and without increased FF score. There were no significant differences in age, sex ratio, BMI, marital status, TUD and urban/rural residence between the three study groups. Education was significantly lower in both groups of schizophrenia patients and more schizophrenia patients were also more likely to be unemployed than controls. The same table also depicts the measurements of the clinical rating scales. All clinical rating scales were significantly different between the three study groups and their scores increased from controls → DEFSCZ with lower FF score → DEFSCZ with higher FF score.

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Table 1 shows the measurements of the different cognitive tests. These data were analysed using univariate GLM analysis with age, sex, and education as covariates. All scores on the neurocognitive tests were significantly lower in both patient groups compared to controls, while there were no significant differences among both DEFSCZ subgroups (i.e. those with high versus low FF scores). Table 1 shows the measurements of the biomarkers which were analysed using univariate GLM analysis with age, sex, BMI, education and TUD as covariates. Levels of all biomarkers were significantly higher in both schizophrenia groups as compared to controls, whilst there were no significant differences in the levels of those biomarkers between both patient subgroups.

Differences in FF scores between DEFSCZ and controls

Multivariate GLM analysis (with age, sex and education as covariates) showed that there was a highly significant association ($F=106.31$, $df=12/157$, $p<0.001$) between the 12 FF items and the diagnosis DEFSCZ with an effect size of 0.890. All FF items were significantly higher in DEFSCZ as compared with controls (all $p<0.001$ after p-correction for FDR). There were no significant effects of sex ($F=0.23$, $df=12/157$, $p=0.996$), age ($F=1.58$, $df=12/157$, $p=0.103$) and education ($F=0.88$, $df=12/157$, $p=0.570$) on the FF items' scores. Moreover, there were no significant effects of risperidone ($F=0.99$, $df=12/157$, $p<0.001$), olanzapine ($F=1.00$, $df=12/157$, $p=0.456$), and fluphenazine ($F=1.03$, $df=12/157$, $p=0.426$) on the 12 FF items (results of multivariate GLM analysis).

In order to delineate the FF symptom fingerprint of DEFSCZ we performed SIMCA analysis. Using the training set (50% of controls and 50% of DEFSCZ patients), the 12 FF items were used as modelling/discriminatory variables to build the PCA models surrounding controls

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and DEFSCZ patients. PCA showed that there were no outliers either in the control group or in the patient group. The control group was modelled employing 2 PCs, while the DEFSCZ group was modelled with 7 PCs. All 12 items displayed significant modelling power in both controls and patients (all > 0.4384). **Figure 1** shows the discrimination plot with the discriminatory power of the 12 FF items. The top-5 items with the highest discriminatory power were in descending order: sadness, concentration disorders, fatigue, a flu-like malaise and sleep disorders. The intra-class distance was 738. The classification table shows that all controls and all DEFSCZ patients were authenticated as belonging to their target class while there were no aliens, namely controls or DEFSCZ patients intruding into the critical limits of the alternative class. As such the accuracy of the 12 FF items for DEFSCZ and the control group is 100%, with a 100% sensitivity and 100% specificity for DEFSCZ.

Factor and PC analysis.

Figure 2 shows a PC plot obtained by PCA performed on the 12 FF items. This plot shows the distribution of patients (red dots) and control subjects (blue squares) along PC1 and PC2. The first PC explained 71% of the variance and the second PC 5% of the variance in the 12 FF items. DEFSCZ patients are clearly separated from controls with a very large boundary between both groups showing that there is no overlap between both classes. **Figure 3** shows the correlation loading plot of the 12 FF items on the same PCs. All FF items are located between the outer and inner ellipses and group together indicating that all 12 FF items contribute significantly to the discrimination of patients and controls especially along PC1.

Table 2 displays the results of two explanatory factor analysis (EFAs) performed on all symptom dimensions of schizophrenia (including the FF total score), one performed in the total

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study group (controls + patients) and a second in patients only. The EFA performed on the DEFSCZ group (right column) shows a good Kaiser-Meyer-Olkin Test (KMO), that measures sampling adequacy for each variable in the model and for the complete model, and a significant Bartlett's test for homogeneity of variances (χ^2=1346, df=666, p<0.00001) indicating that the correlation matrix has adequate factorability. In addition, we found that only one eigenvalue was greater than 1 (namely 8.02004). Three different tests, i.e. Parallel Analysis, Hull test and BIC test, showed that one factor fits the data. Moreover, the UNICO, ECV and MIREAL values show that the 12 FF items set should be treated as unidimensional. Table 2 shows that all symptom domains loaded highly on the first factor. FF items showed the lowest loading which, however, was still sufficient to be included in the model. GFI and AGFI showed a good fit of the model, while the high FDI values indicate a good quality of the factor scores estimates. The high values obtained for the H index show a good performance across studies as well as good construct replicability. Table 2 (left column) shows the results of a similar EFA but now performed in patients and controls combined. Overall the results are quite similar as those in DEFSCZ patients only, but most tests showed even better model quality data and also the loadings on the first factor (including the FF score) were higher. The results show again that there is one factor which is essentially unidimensional.

Associations of the FF score with other symptom domains and cognitive test results.

Table 3 shows the partial correlation coefficients (adjusted for age, sex and education) between the total FF score and the other different symptom domains in the combined group of patients and controls as well as in DEFSCZ patients separately. In DEFSCZ patients, there were significant correlations between the total FF score and all other symptom domains (at p<0.001

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after FDR p correction). The partial correlation coefficients in the combined study group were higher than in DEFSCZ patients and all were significant at p<0.0001 (after p correction for FDR).

Table 4 shows the results of stepwise multiple regression analysis, whereby the total FF score was entered as the dependent variable and the other symptom domains as well as age, sex and education as explanatory variables. In the total study group, 94.9% of the variance in the FF score was predicted by SDS and HAM-D scores combined. Consequently, we have examined which negative items of the SDS were significantly associated with the SDS score. Multiple regression showed that flattening, anhedonia, poverty of speech, restricted affect and diminished sense of purpose explained 94.6% of the variance in the total FF score.

Partial correlations (adjusted for age, sex and education) showed that in the total study sample there were significant associations (all at p<0.001 after p-correction for FDR, all n=169) between the total FF score and test scores on MMSE (r=-0.674), List learning (r=-0.726), digit sequencing task (r=-0.724), category instances (r=-0.568), controlled oral word association (r=-0.874), symbol coding (r=-0.786) and Tower of London (r=-0.698). **Table 5** shows the results of a stepwise multiple regression analysis whereby 85.4% of the variance in the FF score was associated by the scores on a single test, namely controlled oral word association. Nevertheless, no significant associations could be detected between the FF score and any of the cognitive probes in the restricted DEFSCZ group.

Associations the FF score and biomarkers.

Partial correlations (adjusted for age, sex, education, BMI and smoking) showed that in the total study sample there were significant associations (all at p<0.001 after p-correction for FDR and all n=167) between the total FF score and IL-1β (r=0.449), sIL-1RA (r=0.726), TNF-α

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(r=0.452), sTNFR1 (r=0.319), sTNFR2 (r=0.307), MCP-1 (r=0.287) and CCL-11 (r=0.548). **Table 5** shows the results of a stepwise multiple regression analysis whereby 66.7% of the variance in the FF score was predicted by the combination of CCL-11, TNF-α, IL-1β, sIL-1RA and sTNFR1. **Figure 4** shows the partial correlation between the total FF score and CCL-11 in the total study group. No significant correlations were found in the restricted DEFSCZ group between the FF score and any of the biomarkers.

Using PLS path analysis (**Figure 5**) (complete and consistent bootstrapping with 5000 bootstrap samples) we examined the significant biomarker predictors (input variables) of the 12 FF items (output variables). We obtained a very good model fit with SRMR = 0.044 (95% CI: 0.044-0.049). The latent construct FF (overall severity of FF) showed excellent quality criteria including Cronbach alpha (0.963 ±0.004), rho_A (0.965 ±0.004), composite reliability (0.963 ±0.004) and AVE (0.6853 ±0.025) and all loadings on this were significant at $p<0.0001$ and higher than 0.675. Also, the discriminant validity was more than adequate as established with the Fornell-Larcker criterion, cross-loadings and the HTMT ratio. Figure 5 shows that 66.8% of the variance in the FF LV was explained by sIL-1RA, IL-1β, TNF-α and CCL-11.

Figure 6 shows the results of a second PLS analysis with a LV extracted from the 12 symptom domains (including total FF score) as output variable and the 7 biomarkers as input variables. This PLS model shows an excellent fit with SRMR=0.018 (0.022-0.024). The LV extracted from the 12 symptom domains (denoted as overall severity of psychosis - OSOS) showed very good quality criteria with Cronbach alpha (0.986 ±0.001), rho_A (0.992 ±0.001), composite reliability (0.988 ±0.001) and AVE (0.871 ±0.010). Moreover, all 12 symptom domains were highly loaded on this LV (all > 0.800 at $p<0.0001$). Confirmatory Tetrad Analysis shows that the OSOS LV fits a reflective model. Blindfolding showed a good cross-validated redundancy of

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0.470. About 59.4% of the variance in the OSOS LV was explained by sIL-1RA, IL-1β, TNF-α and CCL-11.

In order to examine the combined effects of the symptom domains, biomarkers and cognition on the FF score in subjects with DEFSCZ we used a Neural Network. The latter machine learning method entered the FF score as output variable and 7 biomarkers, cognitive test results (entered as the first PC extracted from the 7 cognitive tests and explaining 84.31% of the variance) and 12 symptom domains as input variables. The model was trained with 2 hidden layers with each 2 units whereby the first layer was trained using hyperbolic tangent as activation function while the output layer used identity as activation factor. During the training, the error term (sum of squares) was minimized from 15.672 to 10.344 which shows that the NN model learnt to generalize from the trend. Moreover, the relative error terms were fairly constant in the training (0.514), testing (0.597) and holdout (0.525) samples indicating that the model is not overfitted. The correlation between the model-predicted FF value and the FF score was r=0.681 ($p<0.001$). **Figure 7** displays the relevance chart showing the (normalized) importance of all input variables. The SDS score was the most important determinant of the predictive model, followed at a distance by HAM-A, psychosis, SANS and sIL-1RA, and again at a distance by sTNFR1, PMR and CCL-11.

Discussion

The first major finding of this study is that the total FF score and all FF items are significantly increased in deficit schizophrenia or "Major Neuro-Cognitive Psychosis" when compared with controls. SIMCA showed that sadness, concentration disorders, fatigue, a flu-like malaise and sleep disorders were the top-5 features of the FF score that discriminated schizophrenia patients from controls. These findings extend those of a previous report indicating

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that patients with deficit schizophrenia show increased scores on the FF scale compared to controls (Kanchanatawan et al., 2017). Therefore, it appears that deficit patients show symptoms such as changes in pain perception and hyperalgesia which are similar in magnitude to those observed in fibromyalgia (Zachrisson et al., 2002). Previously, we have shown that SCCs in schizophrenia are associated with objective neurocognitive test scores as measured with CERAD (Sirivichayakul et al., 2019b). Patients with schizophrenia repeatedly complain from fatigue (Skapinakis et al., 2000) while a meaningful subset of those patients show higher fatigue scores (Hedlund et al., 2015). Furthermore, many schizophrenia patients exhibit reduced energy levels and sleep disturbances (Palmese et al. 2011; Hedlund et al 2015) as well as gastro-intestinal symptoms (Chen 2016). Moreover, in the present study we found that the total FF score was significantly associated with all other symptom domains. These results corroborate those of a previous paper reporting that FF symptom are not only associated with affective symptoms, but also with PHEM and negative symptoms (Kanchanatawan et al., 2018g).

The second major finding of this study is that (in both deficit patients and the total study group including controls) FF symptoms belong to a same latent vector together with PMR, FTD, negative symptoms, PHEM symptoms, and HAM-D and HAM-A scores. Furthermore, this latent vector, which comprises FF symptoms, is essentially unidimensional and displays adequate internal consistency reliability, predictive relevance and convergent validity. Moreover, Confirmatory Tetrad analysis showed that this latent vector fits a reflective model indicating that the single latent trait is a common cause for all symptom manifestations, including FF symptoms, which are to a large extent mediated by the underlying trait. As such, FF symptoms belong to the overall severity of schizophrenia (OSOS) latent vector and are together with the other symptom clusters reflective manifestations of OSOS. Nevertheless, previously Kanchanatawan et al.

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(2018g) found in a combined group of deficit and non-deficit schizophrenia patients and controls that PHEM and negative symptoms belong to one factor while HAM-D, HAM-A and FF data belong to another factor (although both components are strongly inter-related). These differences may be explained by differences in selection and exclusion criteria of both studies. Thus, Kanchanatawan et al. (2018g) excluded subjects with current major depression, while the current study did not a priori exclude patients with secondary major depression.

The third major finding of this study is that, using the 12 FF symptoms as discriminatory variables, deficit schizophrenia is modelled and discriminated from controls with a 100% accuracy indicating that this condition is a qualitatively distinct entity with regard to physio-somatic symptoms. At first sight those findings on qualitative or categorical differences are difficult to reconcile with our findings that FF symptoms belong to the same OSOS latent vector, which increases all over a continuum. Therefore, it is possible that the frequency of FF symptoms increases with severity of negative and PHEM symptoms to shape and model deficit schizophrenia as a distinct nosological entity. However, it is important to stress that physio-somatic symptoms are not only a key component of deficit schizophrenia (this study) but also of non-deficit schizophrenia (Kanchanatawan et al., 2017).

The fourth major finding of this study is that FF symptoms are significantly associated with objective cognitive test scores and that impairments in the Controlled Oral Word Association (COWA) test were the most important cognitive correlates of the total FF score, indicating that FF symptoms appear especially in subjects with impairments in semantic memory and verbal fluency. In this regard it is interesting to consider that cognitive impairments, including in memory and attention, may increase risk to generate false memories and psychosis and negative symptoms as well (Tamminga et al., 1998; Harvey et al., 2006; Corlett et al., 2007). In this regard it should be

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noted that CFS is associated with neurocognitive impairments including in concentration, memory, working memory, thought processes, and information processing speed (Jason et al., 2002; Deluca et al., 2004; Lange et al 2005). Cook et al. (2007) reported a significant relationship between mental fatigue and brain activity during a fatiguing cognitive task. Patients with CFS show moderate to more profound impairments in straightforward and complex information processing speed and in assignments requiring working memory over a supported timeframe (Cockshell et al., 2010). CFS is also accompanied by a working memory deficit suggesting that executive functions are impaired and may mediate fatigue (Dobbs et al., 2001).

The fifth major finding of this study is that immune-inflammatory biomarkers are strongly associated with FF symptoms. PLS path analysis showed that IL-1β and sIL-1RA levels (indicating increased IL-1 signalling) combined with increased TNF-α and CCL-11 levels explained a staggering 66.8% of the variance in FF symptoms. Moreover, the same immune indicants explained 59.4% of the variance in the OSOS index, which comprises FF symptoms together with all other symptom manifestations of deficit schizophrenia. Previous research showed that physio-somatic and affective symptoms as well as negative and PHEM symptoms are strongly associated with changes in IgA/IgM responses to TRYCATs (including PA, XA and KYN) indicating increased production and altered regulation of noxious TRYCATs (Kanchanatawan et al. 2017; 2018g). Moreover, it was observed that increased IgA responses to those neurotoxic TRYCATs mediate the effects of immune activation (as measured by increased levels of IL-10, sIL-1RA and MIP-1) on schizophrenia phenomenology (Sirivichayakul et al. 2019a). There is now evidence that CFS is a neuro-immune disorder characterized by (amongst other) increased levels of pro-inflammatory cytokines including IL-1 and TNF-α (Maes and Twisk, 2010; Maes et al., 2012). Montoya et al. (2017) examined 17 cytokines/chemokines, including CCL-11, and found a general

elevation in pro-inflammatory cytokine/chemokine levels in CFS patients as compared to controls and, additionally, that these biomarkers were associated with the severity of CFS. Roerink et al. (2017) found that MCP-1 and CCL-11 were among the chemokines that were associated with CFS. Moreover, in the current study we found that, using neural networks, the total FF score was highly predicted by a combination of schizophrenia symptoms (especially negative, affective and psychotic symptoms), biomarkers (especially increased IL-1, TNF-α and CCL-11 signalling) and to a lesser degree also by cognitive deficits. Our results indicate that schizophrenia patients are primed to develop FF symptoms in part via activated immune-inflammatory pathways.

The results of our study should be interpreted in the light of its limitations. First, this is a case-control study and therefore no causal inferences can be firmly drawn. Further research should examine when FF symptoms appear during the course of illness. Second, this study was performed in patients in a stable phase of schizophrenia and, consequently, our results cannot be generalized to the acute phase of illness. Further research should examine the correlations among FF and other symptoms of schizophrenia during an acute psychotic episode. Third, it would have been even more interesting if we had measured other biomarkers of deficit schizophrenia including lowered natural IgM and indices of the breakdown of gut and blood brain paracellular and vascular pathways (Maes et al., 2019a; 2019b).

The findings of the current study may have clinical implications. First, increased FF scores are, in schizophrenia, together with anxiety symptoms better predictors of lowered quality of life than PHEM, negative and depressive symptoms (Kanchanatawan et al., 2019). It is known that fatigue and sleep disturbances may affect quality of life in schizophrenia patients (De Martinis & Winokur 2007) while fatigue and CFS are well-known to affect quality of life in the general population (Roberts 2018). Therefore, clinicians treating schizophrenia should recognize FF

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symptoms as being a core component of schizophrenia. Second, our findings indicate that FF symptoms should be part of rating scales constructed to measure HR-QoL and overall severity of schizophrenia. In addition, our results show that such rating scales should be constructed as reflective scales and not as composite scales as most scale are constructed. For example, the BPRS did not take into account FF symptoms and is a composite scale. Also the PANSS is constructed as a composite scale while the SANS and SDS only measure negative symptoms and therefore do only partly reflect OSOS. Finally, our results have also some implications for CFS because it appears that a syndrome comprising CFS symptoms may appear during schizophrenia. Nevertheless, our results do not show that schizophrenia patients suffer from the clinical syndrome CFS as one of the exclusion criteria of most case definitions is secondary CFS due to schizophrenia. Previously, we have shown that CFS may appear during the acute phase of major depression, another neuro-immune disorder, and that this comorbidity is accompanied by greater neuro-immune aberrations (Maes et al., 2012). These findings further corroborate that CFS-like syndromes are neuro-immune conditions be it as secondary syndromes in neuro-immune disorders (major depression and schizophrenia) or as Myalgic Encephalomyelitis (ME/CFS) (Maes and Twisk, 2010; Morris and Maes, 2012). Future research should examine whether the CFS symptom cluster in schizophrenia, CFS in major depression and ME/CFS have a common immune etiology including breakdown of the gut paracellular tight junctions, for example (Maes et al., 2007; 2019b; Slyepchenko et al., 2017).

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Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Author's contributions

All the contributing authors have participated in preparation of the manuscript.

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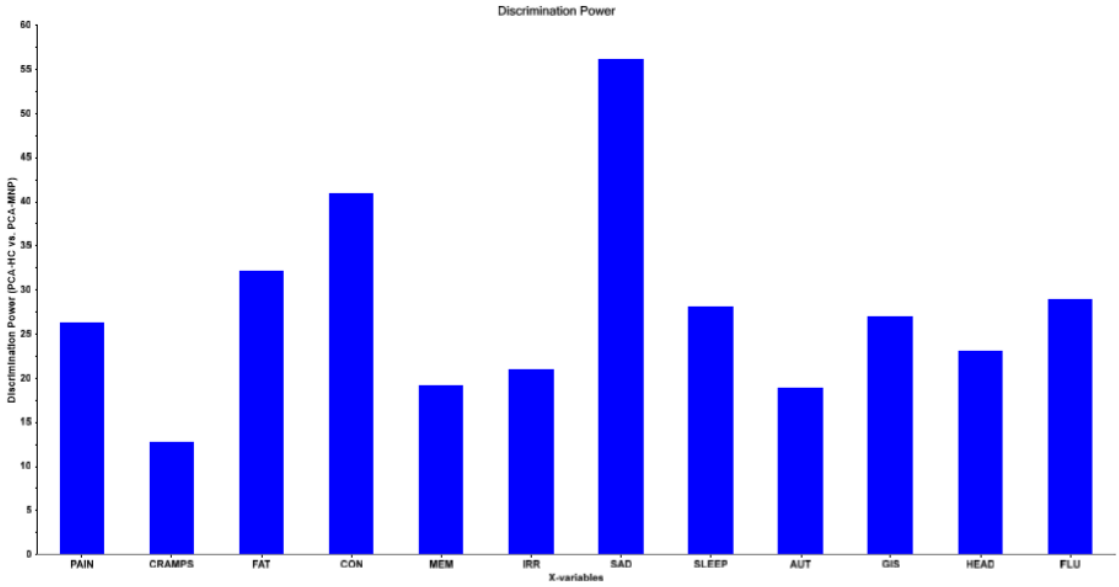
ESF Figure 1 Results of Soft Independent Modelling of Class Analogy. Shown is the discrimination plot with the discriminatory power of the 12 FibroFatigue items.

Pain: muscle pain; Cramps: muscle cramps; Fat: fatigue; Con: concentration disorders; Mem: memory impairments; Irr: irritability; Sad: sadness; Sleep: sleep disorders; Aut: autonomic symptoms; GIS: gastro-intestinal symptoms; Head: headache; Flu: flu-like malaise



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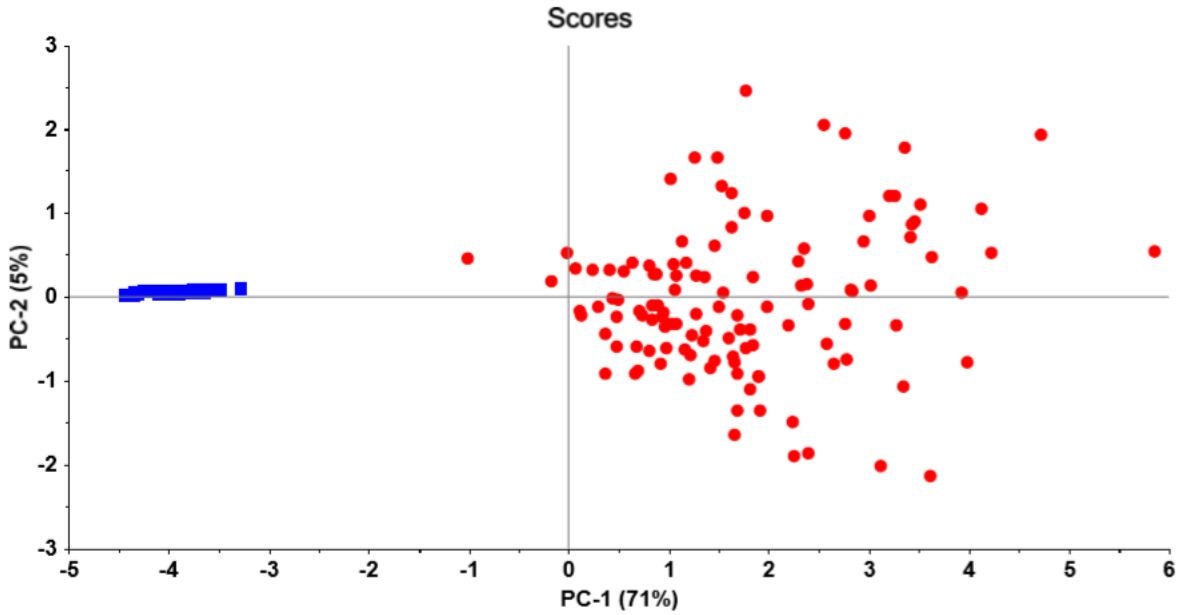
ESF Figure 2 Principal component (PC) plot obtained by PC analysis (PCA) performed on the 12 FibroFatigue items. Patients are shown as red dots and healthy controls as blue squares.



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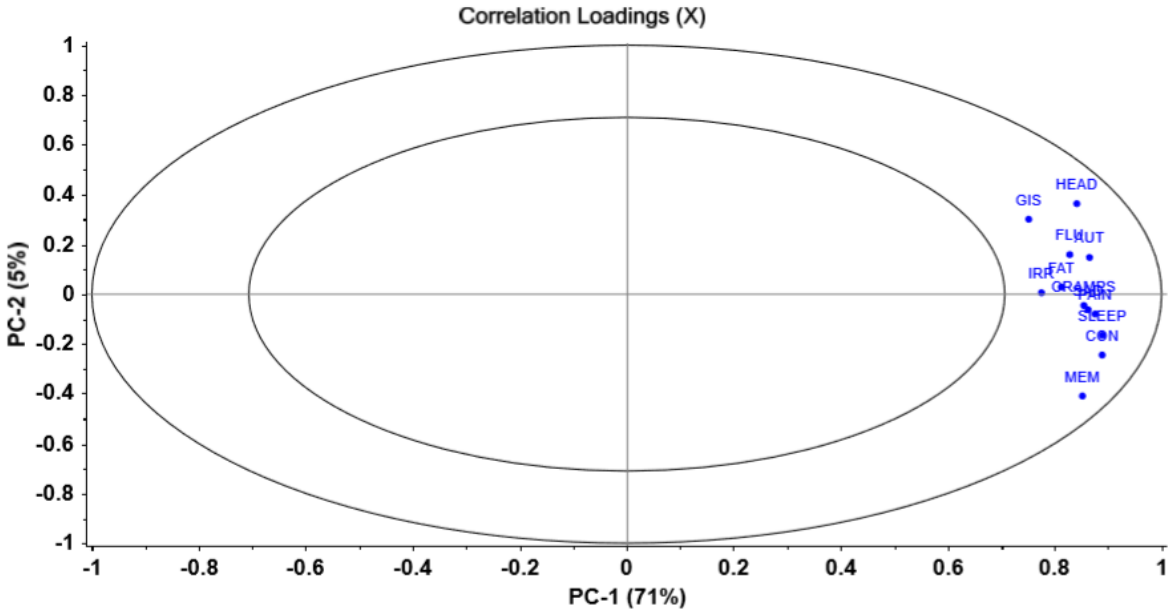
ESF Figure 3 Correlation loading plot of the 12 FibroFatigue items. All FibroFatigue items are located between the outer and inner ellipses and group together indicating that all items contribute significantly to the discrimination of patients and healthy controls as shown in ESF Figure 2.

Pain: muscle pain; Cramps: muscle cramps; Fat: fatigue; Con: concentration disorders; Mem: memory impairments; Irr: irritability; Sad: sadness; Sleep: sleep disorders; Aut: autonomic symptoms; GIS: gastro-intestinal symptoms; Head: headache; Flu: flu-like malaise



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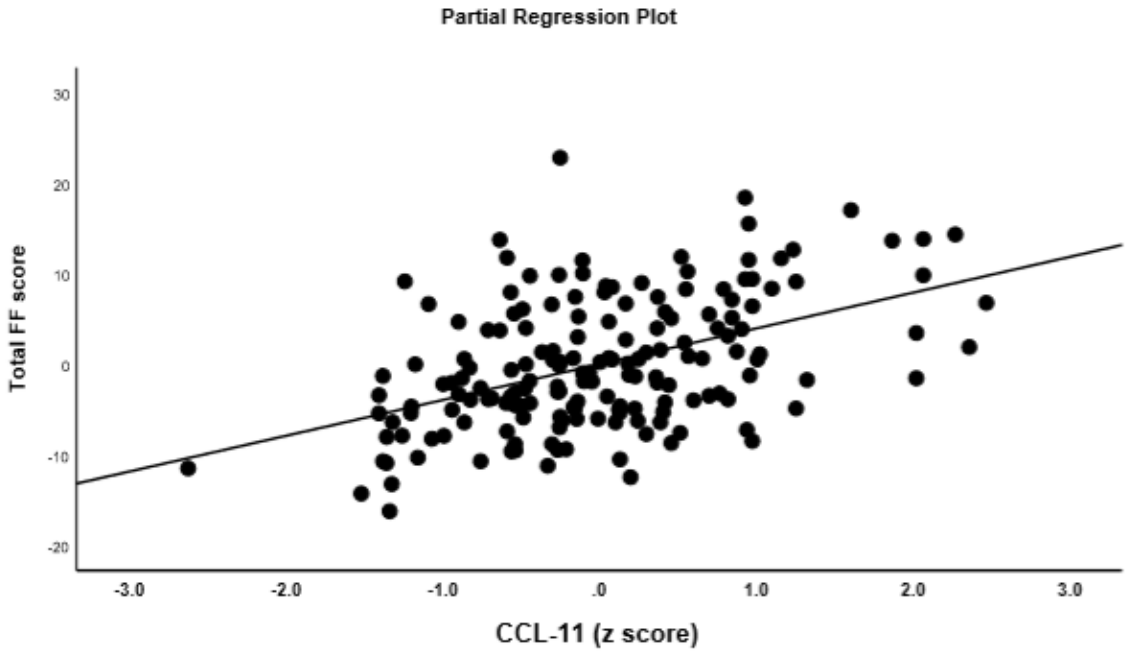
ESF Figure 4 Partial correlation between the total FibroFatigue score and CCL-11 (eotaxin) in the total study group.



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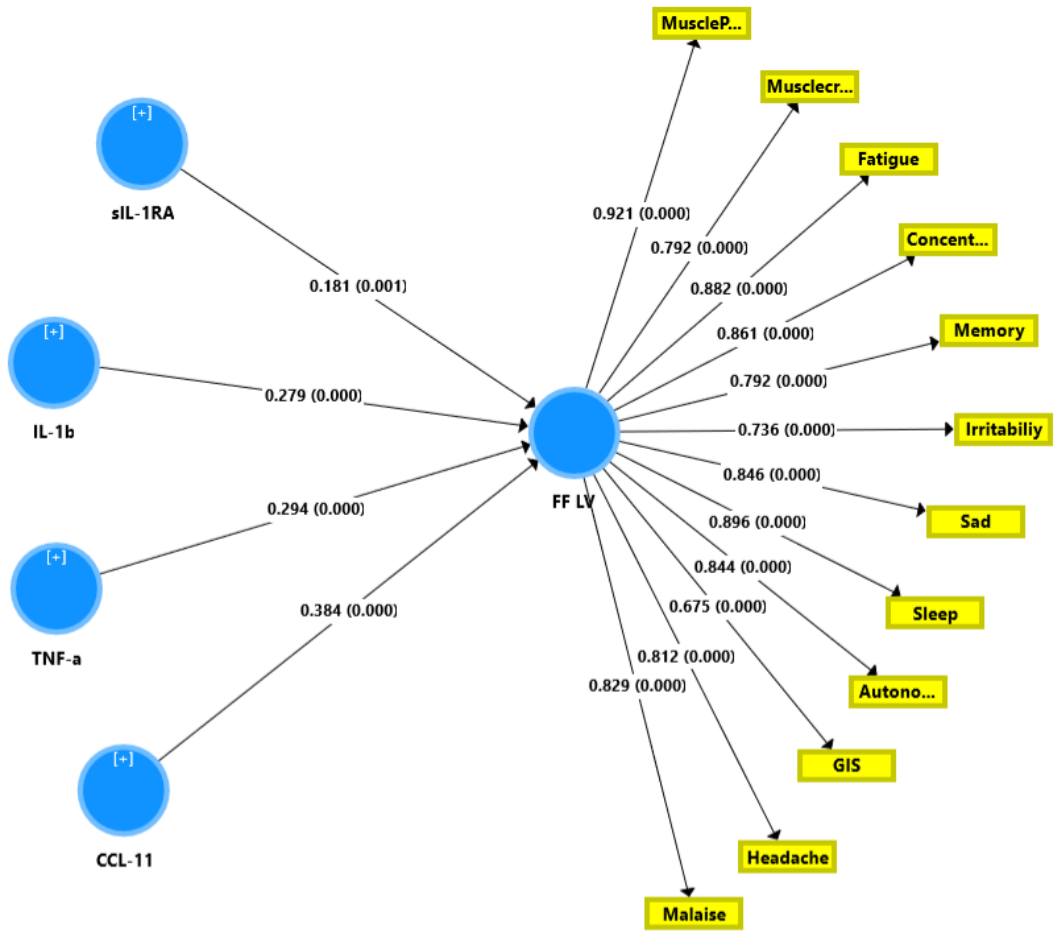
ESF Figure 5 Results of Partial Least Squares analysis with the 12 FibroFatigue items as output variables and biomarkers as input variables. 66.8% of the variance in the latent vector extracted from the 12 FibroFatigue items (FF LV) was explained by the regression on 4 biomarkers, namely soluble interleukin (IL)-1 receptor (sIL-1RA), IL-1β, tumor necrosis factor (TNF)-α and CCL-11 (eotaxin).



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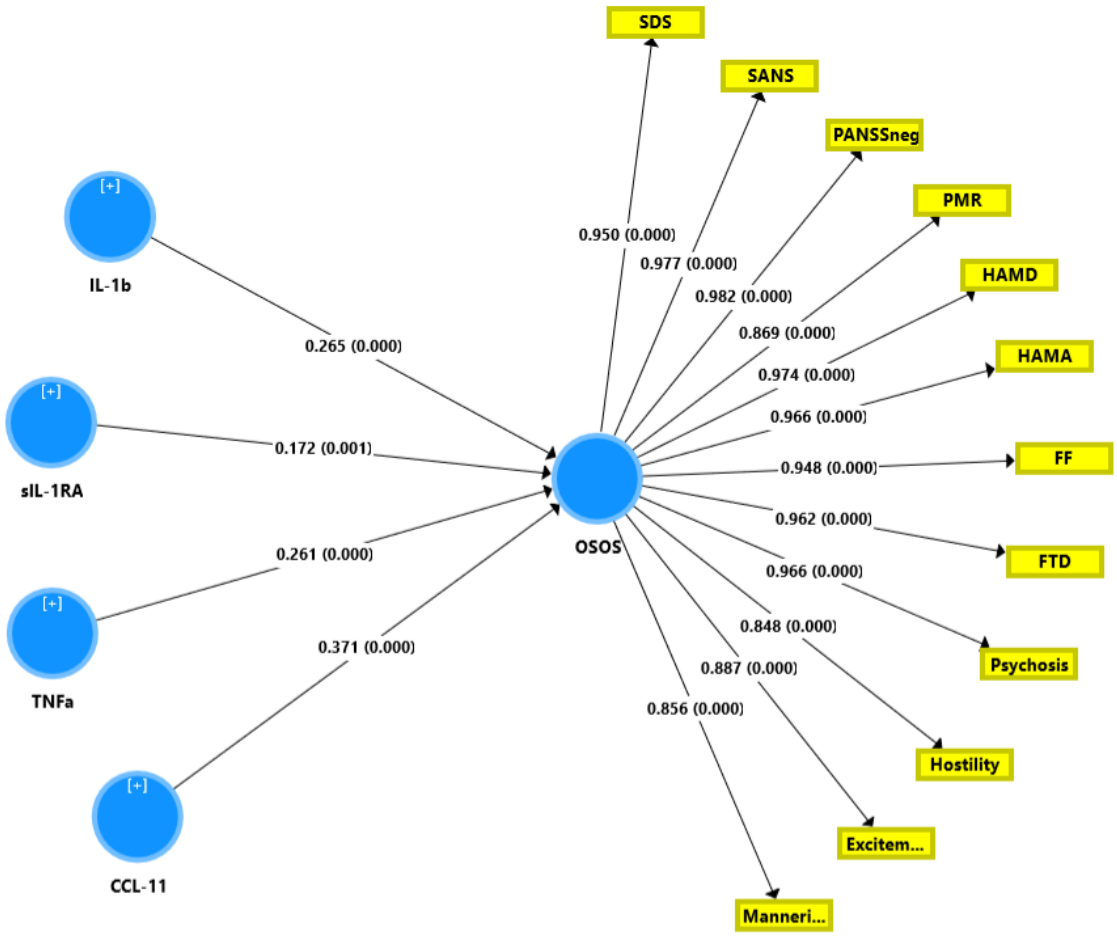
ESF Figure 6 Results of Partial Least Squares analysis with the 12 symptom domains as output variables and biomarkers as input variables. 59.4% of the variance in the overall seveity of illness (OSOS) latent vector (LV) was explained by soluble interleukin (IL)-1 receptor (sIL-1RA), IL-1β, tumor necrosis factor (TNF)-α and CCL-11 (eotaxin).

SDS: Schedule for the deficit syndrome; SANS: Scale for the Assessment of Negative Symptoms; PANSSneg: Negative subscale of the Positive and Negative Syndrome Scale; PMR: Psychomotor retardation; HAM-A, HAM-D: Hamilton Anxiety and Depression Rating Scale score; FF: FibroFatigue score; FTD: Formal thought disorders; Excitem: Excitement; Manneri: Mannerism



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ESF Figure 7 Results of neural network analysis. Relevance chart showing the (normalized) importances of all input variables predicting the total FibroFatigue scale score entered as output variable.

SDS: Schedule for the deficit syndrome; HAMA: Hamilton Anxiety Rating Scale score; SANS: Scale for the Assessment of Negative Symptoms; sIL-1RA: soluble interleukin-1 receptor;

sTNFR: soluble tumor necrosis factor; PMR: Psychomotor retardation; PC cognition: First principal component extracted from neurocognitive test scores; HAMD: Hamilton Depression Rating Scale; MCP: monocyte chemoattractant protein; PANSSneg: Negative subscale of the Positive and Negative Syndrome Scale; FTD: Formal thought disorders

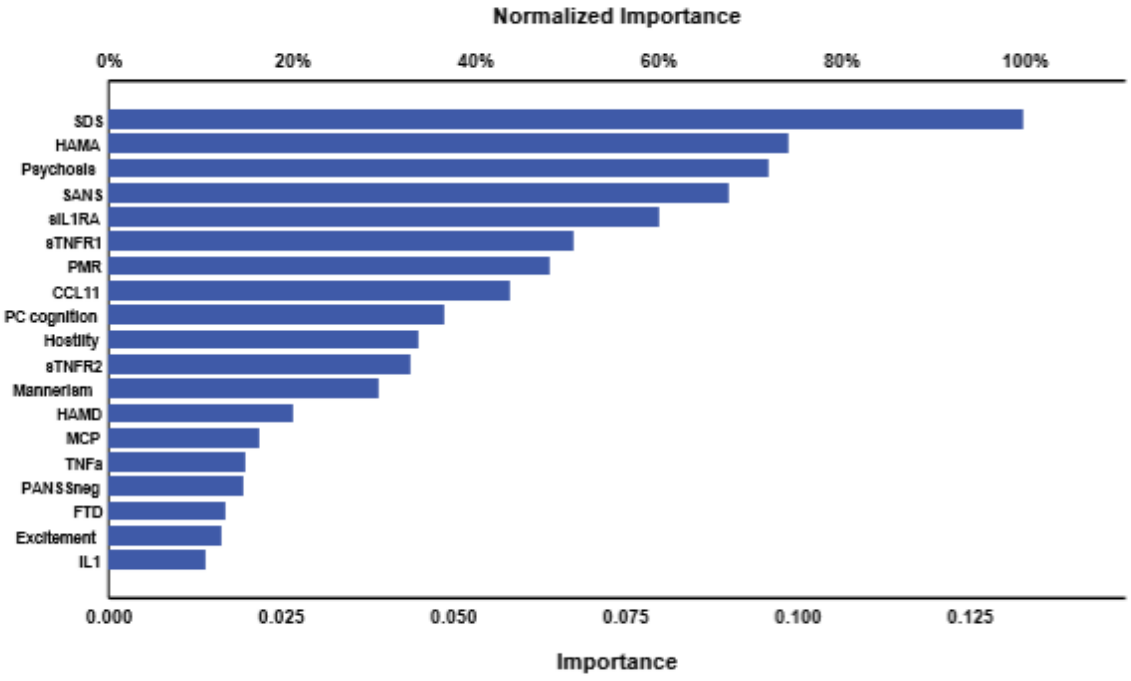

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Table 1: Socio-demographic, clinical and biomarker data in healthy controls (HC) and deficit schizophrenia (SCZ) patients divided into those with and without an increased FibroFatigue (FF) score.

Variables	HC [A] n=54	SCZ (FF<23.5) [B] n=63	SCZ (FF≥23.5) n=57	F/χ^2/KW	df	p
Age (Years)	37.9(10.3)	42.0(9.1)	39.9(10.2)	2.51	2/171	0.085
Sex (Female/Male)	18/36	26/37	22/35	0.79	2	0.672
BMI (kg/m^2)	26.9(3.8)	26.7(52)	26.7(4.3)	0.04	2/171	0.962
Age of onset (Years)	-	30.6(8.6)	30.0(10.9)	0.11	1/118	0.737
Education (0,1,2,3)	2.85(0.45)^{B,C}	1.41(0.84) ^{A}	1.33(0.95)^{A}	KW	-	<0.001
Marital state (Y/N)	23/31	29/33	24/32	0.26	2	0.876
TUD (N/Y)	37/17	39/24	39/18	0.77	2	0.680
Rural/Urban	2/52	6/57	10/47	5.80	2	0.055
Employment (N\Y)*	4/50^{B,C}	50/13 ^{A}	48/9 ^{A}	84.95	2	<0.001
MMSE*	28.4(0.7)^{B,C}	15.7(0.6)^{A}	15.6(0.6)^{A}	94.73	2/168	<0.001
List learning*	56.7(1.5)^{B,C}	26.2(1.2)^{A}	25.9(1.3)^{A}	120.98	2/168	<0.001
Digit sequencing task*	16.9(0.6)^{B,C}	4.5(0.5)^{A}	4.4(0.5)^{A}	138.72	2/168	<0.001
Category instances *	67.2(2.6)^{B,C}	33.4(2.0)^{A}	33.7(2.1)^{A}	51.53	2/168	<0.001
Control oral word association*	32.5(0.6)^{B,C}	7.1(0.5)^{A}	6.0(0.5)^{A}	495.71	2/168	<0.001
Symbol coding*	78.6(2.3)^{B,C}	18.8(1.8)^{A}	19.4(1.9)^{A}	215.14	2/168	<0.001
Tower of London *	18.2(0.6)^{B,C}	7.4(0.5)^{A}	6.3(0.5)^{A}	94.02	2/168	<0.001
Psychosis	-1.24(0.0)^{B,C}	0.23(0.55)^{A,C}	0.92(0.60)^{A,B}	KW	-	<0.001
Hostility	-1.00(0)^{B,C}	0.21(0.70)^{A,C}	0.72(1.00)^{A,B}	KW	-	<0.001
Excitation	-1.11(0.0)^{B,C}	0.19(0.68)^{A,C}	0.84(0.79)^{A,B}	KW	-	<0.001
Mannerism	-1.00(0.0)^{B,C}	0.05(0.67)^{A,C}	0.89(0.90)^{A,B}	KW	-	<0.001
FTD	-1.22(0.0)^{B,C}	0.21(0.62)^{A,C}	0.92(0.56)^{A,B}	KW	-	<0.001
PMR	-0.99(0)^{B,C}	0.11(0.78)^{A,C}	0.82(0.87)^{A,B}	KW	-	<0.001
FF score	1.1(0.0)^{B,C}	20.7(2.0)^{A,C}	27.5(3.1)^{A,B}	KW	-	<0.001

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SANS	1.0(0.6)^{B,C}	82.8(15.1)^{A,C}	100.2(13.2)^{A,B}	KW	-	<0.001
SDS	0.0(0.0)^{B,C}	37.6(4.4)^{A,C}	42.2(3.2)^{A,B}	KW	-	<0.001
PANSS Neg.	7.0(0.0)^{B,C}	30.7(5.3)^{A,C}	35.8(5.2)^{A,B}	KW	-	<0.001
HAM-D	0.0(0.0)^{B,C}	24.8(6.4)^{A,C}	33.8(7.1)^{A,B}	KW	-	<0.001
HAM-A	0.7(1.3)^{B,C}	21.4(3.3)^{A,C}	25.0(3.6)^{A,B}	KW	-	<0.001
IL-1β (pg/ml)**	3.68(0.70)^{B,C}	9.30(0.54)^{A}	10.32(0.59)^{A}	25.18	2/166	<0.001
sIL-1RA (pg/ml)**	282.8(44.2)^{B,C}	564.8(34.3)^{A}	566.6(37.1)^{A}	12.09	2/166	<0.001
TNF-α (pg/ml)**	39.0(2.6)^{B,C}	59.2(2.0)^{A}	60.8(2.1)^{A}	21.71	2/166	<0.001
sTNFR1 (pg/ml)**	961.3(134.1)^{B,C}	1508.6(104.1)^{A}	1505.1(112.5)^{A}	8.55	2/166	<0.001
sTNFR2 (pg/ml)**	739.9(141.0)^{B,C}	1316.6(109.4)^{A}	1267.5(118.3)^{A}	12.43	2/166	<0.001
CCL-11 (pg/ml)**	126.9(13.0)^{B,C}	288.9(10.1)^{A}	275.8(10.9)^{A}	57.45	2/166	<0.001
MCP-1 (pg/ml)**	202.4(30.0)^{B,C}	320.5(23.0)^{A}	331.2(24.9)^{A}	10.21	2/166	<0.001

All analysis of contingency tables (χ^2), analysis of variance (F), or Kruskal-Wallis test (KW),
***All values of univariate GLM analyses adjusted for age, sex, and education.*
****All values of univariate GLM analyses adjusted for age, sex, BMI, TUD, and education. These data are processed in Ln or square root transformation*
Education (0,1,2,3): 0: Illiterate, 1: Primary school, 2: Secondary school, 3: Diploma-BSc.

BMI: Body mass index; SDS: Schedule for the deficit syndrome; SANS: Scale for the Assessment of Negative Symptoms; PANSSneg: Negative subscale of the Positive and Negative Syndrome Scale; BPRS: Brief Psychiatric Rating Scale; FF score: FibroFatigue scale; FTD: Formal thought disorders; PMR: Psychomotor retardation; MMSE: Mini Mental State Examination; HAM-A, HAM-D: Hamilton Anxiety and Depression Rating Scale score;

IL: interleukin; IL-1RA: IL-1 receptor antagonist; TNF: tumor necrosis factor; sTNFR: soluble TNF receptor; MCP: monocyte chemoattractant protein; CCL-11 or eotaxin

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Table 2: Results of explanatory factor analysis (EFA) expressed as Bias Corrected Factor loadings with 95% confidence intervals (CI) in patients with schizophrenia (SCZ) and in the combined group pf patients and controls.

Variables	**SCZ+Controls**	**SCZ**
Psychosis	0.969 (0.957-0.978)	0.900 (0.857-0.927)
Hostility	0.836 (0.787-0.865)	0.717 (0.607-0.789)
Excitation	0.878 (0.844-0.912)	0.702 (0.607-0.774)
Mannerism	0.845 (0.801-0.876)	0.661 (0.677-0.819)
FTD	0.964 (0.949-0.974)	0.906 (0.873-0.928)
PMR	0.860 (0.823-0.889)	0.821 (0.747-0.861)
FF	0.937 (0.915-0.953)	0.629 (0.484-0.718)
HAM-A	0.960 (0.941-0.970)	0.789 (0.701-0.851)
HAM-D	0.973 (0.962-0.982)	0.850 (0.797-0.893)
SANS	0.974 (0.965-0.982)	0.885 (0.818-0.919)
SDS	0.938 (0.917-0.952)	0.691 (0.585-0.771)
PANSS neg	0.982 (0.973-0.988)	0.893 (0.847-0.924)
Characteristics (bootstrapped)	**SCZ+Controls**	**SCZ**
% variance	0.8658	0.66834
KMO	0.951 (0.953-0.958)	0.932 (0.930-0.939)
Root mean square of residuals	0.0406 (0.032-0.050)	0.060 (0.042-0.074)
Kelly's criterion	0.0758	0.0913
Goodness of fit index (GFI)	0.998 (0.997-0.999)	0.993 (0.988-0.997)
Adjusted GFI (AGFI)	0.998 (0.996-0.999)	0.991 (0.985-0.996)
Unidimensional Congruence (UNICO)	0.998 (0.997-0.999)	0.982 (0.967-0.995)
Explained Common Variance (ECV)	0.952 (0.940-0.962)	0.910 (0.884-0.941)
Mean of Item Residual Absolute loadings (MIREAL)	0.193 (0.168-0.216)	0.202 (0.148-0.234)
Generalized H-Index	0.995 (0.992-0.998)	0.967 (0.957-0.972)
Factor determinancy Index	0.996	0.982

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SANS: Scale for the Assessment of Negative Symptoms; PANSSneg: Negative subscale of the Positive and Negative Syndrome Scale; FF score: FibroFatigue scale; FTD: Formal thought disorders; PMR: Psychomotor retardation; HAM-A, HAM-D: Hamilton Anxiety and Depression Rating Scale score;

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Table 3: Partial correlation coefficients between the FibroFatigue (FF) score and scores on all other symptom domains in patients with schizophrenia (SCZ) and in the combined group pf patients and controls.

Variables	SCZ+Controls * n=169	SCZ ** n=115
Psychosis	0.834	0.526
Hostility	0.625	0.300
Excitation	0.713	0.360
Mannerism	0.640	0.470
FTD	0.822	0.520
PMR	0.684	0.424
HAM-A	0.927	0.510
HAM-D	0.896	0.568
SANS	0.942	0.618
SDS	0.951	0.599
PANSS neg.	0.908	0.489

FTD: Formal thought disorders;

PMR: Psychomotor retardation;

HAM-A, HAM-D: Hamilton Anxiety and Depression Rating Scale score;

SANS: Scale for the Assessment of Negative Symptoms;

SDS: Schedule for the Deficit Syndrome

PANSSneg: Negative subscale of the Positive and Negative Syndrome Scale;

** All values of partial correlation coefficient with age, sex, and education as covariates.

* $p<0.0001$ (after p-correction); ** $p<0.001$ (after p-correction).

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Table 4: Results of multiple regression analysis with FibroFatigue score as dependent variable.

Explanatory variable	**B**	**SE**	**t**	**p**	**F model**	**df**	**p**	**R^2**
Model					1599.53	2/171	<0.001	0.949
SDS	0.747	0.045	16.54	<0.001				
HAM-D	0.251	0.045	5.35	<0.001				
Model					588.92	5/168	<0.001	0.946
Flattening	0.132	0.027	4.91	<0.001				
Sense of purpose	0.087	0.026	3.31	0.001				
Anhedonia	0.106	0.027	3.91	<0.001				
Poverty of speech	0.074	0.026	2.91	0.004				
Restricted affect	0.059	0.022	2.73	0.007				

SDS: Schedule for the Deficit Syndrome

HAM-D: Hamilton Depression Rating Scale score

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Table 5: Results of stepwise multiple regression analysis with FF scores as dependent variable.

Explanatory variables	B	SE	t	p	F	df	p	R^2
Model					108.89	1/172	<0.001	0.854
COWA	-0.924	0.029	-31.76	<0.001				
Model					67.33	5/168	<0.001	0.667
CCL-11	0.366	0.052	7.09	<0.001				
TNF-α	0.267	0.053	5.07	<0.001				
IL-1β	0.252	0.051	4.95	<0.001				
sIL-RA	0.175	0.098	3.67	<0.001				
sTNFR1	0.115	0.050	2.30	0.023				

COWA: Control oral word association

CCL-11 or eotaxin

TNF: tumor necrosis factor

IL: interleukin;

IL-1RA: IL-1 receptor antagonist

sTNFR: soluble TNF receptor