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# Schizophrenia phenomenology revisited: positive and negative symptoms are strongly related reflective manifestations of an underlying single trait indicating overall severity of schizophrenia

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## Abstract

**Background.** To examine whether negative symptoms, psychosis, hostility, excitation, and mannerism (PHEM symptoms), formal thought disorders (FTD) and psychomotor retardation (PMR) are interrelated phenomena in major neurocognitive psychosis (MNP) or deficit schizophrenia and whether those domains belong to an underlying latent vector reflecting general psychopathology.
**Methods.** In this study, we recruited 120 patients with MNP or deficit schizophrenia and 54 healthy subjects and measured the above-mentioned symptom domains.
**Results.** In MNP, there were significant associations between negative and PHEM symptoms, FTD and PMR. A single latent trait, which is essentially unidimensional, underlies these key domains of schizophrenia and MNP and additionally shows excellent internal consistency reliability, convergent validity, and predictive relevance. Confirmatory Tedrad Analysis indicates that this latent vector fits a reflective model. The lack of discriminant validity shows that positive (and PHEM or psychotic) and negative symptoms greatly overlap and probably measure the same latent construct. Soft independent modeling of class analogy (SIMCA) shows that MNP (diagnosis based on negative symptoms) is better modeled using PHEM symptoms, FTD, and PMR than negative symptoms.
**Conclusions.** In stable phase MNP, which is a restricted sample of the schizophrenia population, negative and PHEM symptoms, FTD and PMR belong to one underlying latent vector reflecting overall severity of schizophrenia (OSOS). The bi-dimensional concept of "positive" and "negative" symptoms cannot be validated and, therefore, future research in stable phase schizophrenia should consider that the latent phenomenon OSOS as well as its reflective manifestations are the key factors of schizophrenia phenomenology.

## Introduction

Schizophrenia is characterized by various symptom domains the two most important being positive symptoms, including delusions, hallucinations, excitation, hostility, disorganized thinking, and negative symptoms, including affective flattening, avolition, alogia, anhedonia.[1–3] Positive symptoms are considered to be new and maladaptive mental processes and behaviors that were not present before the onset of schizophrenia and that have emerged as signs of the disorder.[4] Negative symptoms, on the other hand, are conceptualized as emotions (hedonia), thought processes (logic thinking) and behaviors (social interactions) that the patient has lost as a consequence of the disorder.[4]

Based on this distinction between positive and negative symptoms of patients with schizophrenia were subdivided according to a two-syndrome concept into those with mainly positive symptoms, named type I schizophrenia, and those with mainly negative symptoms, named type II schizophrenia.[5] When present during acute psychotic exacerbations and the inter-episode, more stable phases of illness the negative symptom cluster is referred to as deficit schizophrenia.[6,7] Previously, Bleuler described schizophrenia as a psycho-organic illness comprising two syndrome clusters, namely a primary cluster characterized by loosening of associations and withdrawal (negative symptoms) and accessory symptoms including some of the positive symptoms.[8,9] Kraepelin described schizophrenia as "dementia praecox" or an early type of "dementia" characterized by deterioration in neurocognitive functions and goal-directed behaviors, which are negative symptoms.[9] Nevertheless, it is debated whether negative symptoms

increase in severity along a continuum from the healthy state to schizophrenia with a "fully developed syndrome" (dimensional theory) or whether type II or deficit schizophrenia is a separate nosological class (categorical theory).[10,11]

Nevertheless, using supervised and unsupervised machine learning techniques, we showed that within a study sample of patients with stable phase schizophrenia, there are two distinct classes of patients, namely those with deficit and nondeficit schizophrenia.[11,12] Both neurocognitive deficits and neuro-immune aberrations, as well as negative symptoms, define deficit schizophrenia as a distinct diagnostic class which is qualitatively different from nondeficit schizophrenia and controls. Moreover, unsupervised learning generated a class of patients, named major neuro-cognitive psychosis (MNP), that largely overlapped with deficit schizophrenia although the diagnostic criteria (based on negative symptoms) were more restrictive.[12] The nondeficit group named simple neuro-cognitive psychosis (SNP) shows a quantitatively distinct profile than MNP with less pronounced neuro-cognitive disorders and negative and positive symptoms, although there were qualitative distinctions with regard to neuroimmune pathways.[12,13] As such, we have delineated two homogeneous phenotypes of schizophrenia which allow more precise identification of clinical, neurocognitive, and neuroimmune features.

Another major finding of our laboratory is that different symptom domains such as psychotic symptoms (hallucinations, delusions, and suspiciousness), hostility (and poor impulse control and uncooperativeness), excitation (and grandiosity), mannerism (and posturing), and negative symptoms are highly significantly intercorrelated.[11–13] These findings suggest that the differentiation of negative symptoms vs positive symptoms (including psychosis, hostility, and excitation) is an artificial one because both domains appear to be strongly related.

Furthermore, we delineated formal thought disorders (FTD) and psychomotor retardation (PMR) as two other major clinical domains that shape the phenemenology of schizophrenia and especially MNP.[13,14] First, FTD is characterized by aberrations in abstract and concrete thinking, including disorganized, illogical, and inadequate thought processes coupled with intrusions, fluid thinking and loosened associations.[8,15–19] We detected that FTD is, in fact, a clinical symptom of the memory deficit syndrome in schizophrenia and especially MNP and that FTD together with memory disorders explain a large part of the variance (around 92%) in negative and psychosis symptoms.[14] Second, PMR is another symptom domain characterized by impairments in gross and fine motor performance, slow motor responses and slow movements that define schizophrenia and especially MNP.[13] In addition, PMR is strongly associated with other symptom domains including psychosis, hostility, excitation, mannerism, and negative (PHEMN) symptoms.[13] Nevertheless, no research has examined whether the PHEMN symptom domains and FTD and PMR are intercorrelated in subjects with MNP, a restricted subsample of the schizophrenia population, and whether these symptoms may perhaps belong to one and the same underlying construct reflecting the severity of overall psychopathology.

Hence, this study was performed to examine whether these different symptom domains are interrelated phenomena in schizophrenia and whether those domains belong to an underlying latent vector reflecting general psychopathology.

## Subjects and Methods

### Participants

In this study, we included 120 patients with deficit schizophrenia or MNP and 54 healthy subjects. Patients with schizophrenia and healthy individuals were recruited from the same catchment area, that is Baghdad city, Iraq. Patients were recruited at the Ibn-Rushd Training Hospital for Psychiatric Medicine, Baghdad, Iraq (December 2018 until February 2019). Controls were staff members or their family members or friends. All the patients with schizophrenia were in a stabilized phase of illness for at least 12 weeks. Patients were diagnosed according to DSM-IVTR criteria as "schizophrenia" and according to the schedule of deficit schizophrenia (SDS) criteria as "deficit schizophrenia."[7] Moreover, all the patients with schizophrenia also complied with the diagnostic criteria of MNP as published by Kanchanatawan et al.[12] Since the MNP diagnostic criteria are somewhat more restrictive than those of deficit schizophrenia, it is more appropriate to use the label MNP although all patients also suffer from deficit schizophrenia. Therefore, we will employ the label MNP all over the text.

Exclusion criteria for patients and controls were: (a) lifetime use of medications that interfere with immune functions including immunosuppressive drugs and glucocorticoids; (b) use of supplements with ω3-polyunsaturated fatty acids or antioxidants the month prior to the study; (c) neurodegenerative and neuroinflammatory disorders including Parkinson's disease, stroke, multiple sclerosis, and Alzheimer's disease; (d) (auto)immune illnesses including rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, and diabetes mellitus (type 1). Controls were excluded when they presented a current or lifetime diagnosis of DSM-IV-TR axis I diagnosis and additionally when they showed a family history of schizophrenia or psychosis. Patients with schizophrenia were excluded when they suffered psychotic episodes the year prior to the study or axis-1 DSM-IV-TR disorders other than schizophrenia, including bipolar disorder, major depression, schizo-affective disorder, obsessive-compulsive disorder, psycho-organic disorders, and substance use disorders. All subjects had C-reactive protein values <6 mg/L indicating that no overt inflammation was present.

The study was conducted according to Iraq and International ethics and privacy laws. Written informed consent was obtained from all participants as well as the first-degree relatives of schizophrenia participants (the legally authorized representatives are father, mother, spouse, son, or brother) prior to participation in this study. Approval for the study was obtained from the ethics committee (IRB) of the College of Science, University of Kufa, Iraq (347/2019), which is in compliance with the International Guideline for Human Research protection as required by the Declaration of Helsinki.

### Clinical assessments

A senior psychiatrist specialized in schizophrenia used a semi-structured interview to assess socio-demographic and clinical data in patients and controls. He made the diagnosis of schizophrenia employing the DSM-IV-TR diagnostic criteria using the Mini-International Neuropsychiatric Interview (M.I.N.I.), in a validated Arabic translation (Iraqi dialect). The same psychiatrist also assessed the SDS,[7] the Positive and Negative Syndrome Scale (PANSS),[19] the Scale for the Assessments of Negative Symptoms (SANS),[20] the Brief Psychiatric Rating Scale (BPRS),[21] and the Hamilton Depression (HAM-D) and Anxiety (HAM-A) rating scales.[22,23] The same day a research psychologist assessed the Mini-Mental State Examination (MMSE) in a validated Arabic translation.[24] We also assessed the drug state of the patients, 68 were treated with fluphenazine, 108 with risperidone, and 11 with olanzapine. The diagnosis of tobacco use disorder was made using the DSM-IV-TR criteria. Body mass index (BMI) was assessed the same day as the clinical interview and was scored as body weight

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**Table 1.** Indices of the Different Symptom Domains and Biomarker Composite Scores Used in the Current Study.

| Symptom Domains | z-Unit Weighted Composite Symptom Scores |
|---|---|
| Psychosis | Sum of z score of item 1 on the positive subscale of the PANSS (zPANNSP1, delusion) + zPANSSP3 (hallucinations) + zPANNSP6 (suspiciousness) + z score of item 11 of the BPRS (zBPRS11: suspiciousness) + zBPRS12 (hallucinatory behavior) + zBPRS15 (unusual thought content) |
| Hostility | Sum of zPANSSP7 (hostility) + z score of item 14 on the general psychopathology scale of the PANSS (zPANSSG14: poor impulse control) + zBPRS10 (hostility) + zBPRS14 (uncooperativeness) |
| Excitement | zPANNSP4 (excitement) + zPANNSP5 (grandiosity) + zBPRS8 (grandiosity) + zBPRS17 (excitement) |
| Mannerism | zPANNSG5 + zBPRS7 (both mannerism and posturing) |
| Formal thought disorders | zPANNSP2 (conceptual disorganization) + item 5 of the PANNS negative subscale (PANNSN5: difficulty in abstract thinking) + zBPRS4 (item 4 of the BPRS or conceptual disorganization) |
| Psychomotor retardation | z-Score of HDRS item 8 (HDRS8: psychomotor retardation: slowness of thought and speech, decreased motor activity, impaired inability to concentrate) + zPANSSG7 (reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli and reduced body tone) + zBPRS13 (reduction in energy level evidenced in slowed movements) |
| SANS | Total sum on all items of the SANS |
| PANSSnegative | Sum of all items of the PANSS negative subscale |

Abbreviations: BPRS, Brief Psychiatric Rating Scale (BPRS); HDRS, Hamilton Depression Rating Scale; PANNS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms.

(kg)/length ($m^2$). We constructed different *z*-unit weighted composite scores based on items of the BPRS, HDRS, PANSS, SANS, and HAM-D as published previously.[13,14,25] Table 1 shows the different *z*-unit-weighted composite scores used in the current study to assess the severity of symptom domains including PHEMN symptoms, and FTD and PMR.

### Statistics

One-way analysis of variance was used to assess differences in scale variables between groups, and analysis of contingency tables ($\chi^2$ tests) was used to assess associations between categorical variables. Correlations between scale variables were assessed using Pearson's product moment correlation or Spearman's rank order correlation coefficients or partial correlation coefficients (while adjusting for extraneous variables). We used multivariate GLM analysis to examine the effects of explanatory variables (age, sex, education, and drug state) on the eight symptom domains, while tests for between-subject effects were used to examine the effects of significant explanatory variables on each of the symptom domains. These multiple tests were checked for false discovery rate (FDR) using the Benjamini-Hochberg procedure.[26]

Multiple regression analysis was used to examine the significant biomarkers that predict the symptom domains using an automatic stepwise method (*P*-to-entry of .05 and *P*-to-remove .06) while checking the $R^2$ change. In addition, the analysis was checked for collinearity (using VIF and tolerance) and homoscedasticity (using the White and Breusch-Pagan tests). When the latter was rejected, we used heteroscedasticy-consistent standard error (SE) (HCSE) or robust SE estimates using the HC3 method. Moreover, analyses were bootstrapped (n = 2000) and the bootstrapped results are reported when there are differences between both approaches. Supplementary Material S1 describes the machine learning techniques used in the current study.

## Results

### Socio-demographic data

Table 2 shows the socio-demographic and clinical data of the patients with MNP and controls. There were no significant differences in age, sex, marital status, rural/urban living ratio, BMI, and nicotine dependence between the groups. Education was significantly lower in patients than in controls. All rating scale scores, as well as composite scores (PHEM, FTD, and PMR) were significantly higher in patients than in controls. Multivariate GLM analysis did not show any significant effect of smoking ($F = 0.94$, $df = 8/107$), BMI ($F = 1.97$, $df = 8/107$, $P = .652$) on the eight symptom domains. Tests for between-subjects effects did not show any effects of sex and education, while age was significantly and negatively related with PANSSnegative ($t = -5.59$, $P < .001$), SANS ($t = -3.49$, $P = .001$), psychosis ($t = -2.64$, $P = .009$), hostility ($t = -2.51$, $P = .013$), mannerism ($t = -2.40$, $P = 0.018$), and FTD ($t = -2.47$, $P = .015$). These effects of age remained significant after FDR *P*-correction. We used multivariate GLM analysis to examine the effects of the drug state on the symptom domains. Nevertheless, we could not find any significant effects of risperidone ($F = 1.72$, $df = 8/111$, $P = 0.102$), olanzapine ($F = 1.71$, $df = 8/111$, $P = .103$), or fluphenazine ($F = 1.76$, $df = 8/111$, $P = .092$) on the symptom domains.

### Associations between negative and other symptoms

Table 3 shows the results of correlation analyses (partial correlations after adjusting for sex, age, and education) between negative symptoms (SANS and PANSSnegative) and PHEM symptoms, FTD and PMR. In the combined study group as well as in MNP, there were significant associations (all at the $P < .001$ level after *P* correction for FDR) between SANS/PANSSnegative and all PHEM symptoms and FTD and PMR. We have also examined whether the drug state of the patients had any significant effects on these associations using partial correlations adjusted for use of olanzapine, risperidone, or fluphenazine. However, we found that the correlation coefficients reported in Table 3 did not change after adjusting for the drug state.

Based on these results we examined the association between negative symptoms (here we show only the results obtained with PANSSnegative values) and PHEM symptoms, FTD and PMR while allowing for the intervening effects of extraneous variables (age, sex, education, and drug state of the patients). Table 4, regression #1 shows that, in all subjects combined, 90.8% of the

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**Table 2.** Demographic and Clinical Data in Normal Controls and Patients with Deficit Schizophrenia.

| Variables | Controls | Deficit Schizophrenia | $F/\Psi/\chi^2$ | *df* | *P* |
|---|---|---|---|---|---|
| Age (years) | 37.9 (10.3) | 41.0 (9.6) | 3.56 | 1/172 | .061 |
| Sex (F/M) | 18/36 | 48/72 | 0.70 | 1 | .402 |
| Single/married | 23/31 | 53/65 | 0.08 | 1 | .776 |
| Rural/urban | 2/52 | 16/104 | 3.73 | 1 | .054 |
| BMI (kg/m$^2$) | 26.9 (3.8) | 26.7 (4.8) | 0.07 | 1/172 | .789 |
| Education (years) | 11.4 (1.8) | 8.3 (5.3) | MWU | - | <.001 |
| Employment (N/Y) | 4/50 | 98/22 | 84.66 | 1 | <.001 |
| Nicotine dependence (N/Y) | 37/17 | 78/42 | 0.21 | 1 | .650 |
| SANS total score | 1.0 (0.6) | 91.1 (16.6) | MWU | – | <.001 |
| PANSS positive subscale score | 7.0 (0.0) | 15.3 (6.9) | MWU | – | <.001 |
| PANSS negative subscale score | 7.0 (0.0) | 27.8 (7.4) | MWU | – | <.001 |
| BPRS | 18.0 (0.0) | 63.7 14.0 | MWU | – | <.001 |
| HAMA | 0.7 (1.3) | 23.1 (3.9) | MWU | – | <.001 |
| HAMD | 0.0 | 29.1 (8.1) | MWU | – | <.001 |
| Psychosis (*z* score) | −1.242 (0.083) | 0.559 (0.660) | MWU | – | <.001 |
| Hostility (*z* score) | −1.027 (0.123) | 0.462 (0.868) | MWU | – | <.001 |
| Excitation (*z* score) | −1.164 (0.096) | 0.524 (0.747) | MWU | – | <.001 |
| Mannerism (*z* score) | −1.003 (0.036) | 0.451 (0.890) | MWU | – | <.001 |
| FTD (*z* score) | −1.200 (0.076) | 0.540 (0.710) | MWU | – | <.001 |
| PMR (*z* score) | −0.992 (0.127) | 0.447 (0.893) | MWU | – | <.001 |

All results are shown as mean (SD).
Abbreviations: BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; FTD, formal thought disorders; HAMA/HAMD, Hamilton Depression Anxiety and Depression Rating Scale; MWU, Results of Mann-Whitney *U* test; PANSS, the Positive and Negative Syndrome Scale; PMR, psychomotor retardation; SANS, Scale for the Assessment of Negative Symptoms.

**Table 3.** Partial Correlation Coefficients Between Negative Symptoms and Positive Symptoms.

| | In Controls and MNP Combined | | In MNP Only | |
|---|---|---|---|---|
| Domains | SANS | PANSSnegative | SANS | PANSSnegative |
| Psychosis | 0.967 | 0.924 | 0.756 | 0.816 |
| Hostility | 0.899 | 0.762 | 0.561 | 0.638 |
| Excitation | 0.723 | 0.803 | 0.465 | 0.530 |
| Mannerism | 0.782 | 0.721 | 0.633 | 0.647 |
| FTD | 0.879 | 0.915 | 0.746 | 0.829 |
| PMR | 0.780 | 0.806 | 0.726 | 0.744 |

The correlation coefficients were adjusted for age, sex, and education.
Abbreviations: FTD, formal thought disorders; PANSS, the Positive and Negative Syndrome Scale; PMR, psychomotor retardation; SANS, Scale for the Assessment of Negative Symptoms. All significant at $P < .001$

variance in PANSSnegative scores was explained by the regression on psychosis, hostility, education, and female sex. Psychosis had by far the greatest impact and other symptoms domains were not significant. Figure S1 in Supplementary Material S2 shows the partial regression plot between PANSSnegative and psychosis in all subjects combined (thus independent from education, sex, and hostility). Table 4, regression #2 shows that, in MNP, 71.0% of the variance in PANSSnegative scores was explained by the regression on psychosis, hostility, and female sex. Psychosis had again the greatest impact, while other symptoms domains and education were not significant. Figure S2 in Supplementary Material S2 shows the partial regression plot between PANSSnegative and psychosis in MNP. We have also examined (in MNP) the association between PANSSpositive subscore and PHEM, FTD, and PMR symptoms allowing for the effects of age, sex, and education. Table 4, regression #3 shows that 94.0% of the variance in positive symptoms was explained by the regression on psychosis, excitation, hostility, FTD, and age (all positively associated). Psychosis and excitation had the most impact on the PANSSpositive score.

### PCA and exploratory factor analysis

In order to visualize the distribution of the subjects in a 2D space we performed PCA on both controls and patients with MNP and extracted PCs from the data set comprising SANS, PANSSnegative, PHEM symptoms, FTD and PMR. Figure S3 in Supplementary Material S3 shows a PC score plot, namely PC1 (explaining 87% of the variance) vs PC2 (explaining 4%), which displays the distribution of patients with MNP (red dots) and controls (blue squares) in the 2D space made by both PCs. Patients with MNP cluster at the right-hand side of the PC plot, whereas healthy controls cluster at the left-hand side and there is no overlap between the two classes with a large boundary (street) between both classes. Figure S4 in Supplementary Material S3 shows the correlation loadings of the eight symptom domains on PC1 vs PC2. All variables are located between both ellipses and additionally group close together suggesting that they all contribute to the separation of both classes and are significantly and positively intercorrelated. Table 5 shows the results of

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**Table 4.** Results of Multiple Regression Analyses with Negative or Positive Symptoms as Dependent Variables.

| Dependent Variables | Explanatory Variables | *B* (Robust SE) | *t* | *P* | Model $R^2$ | *F* | *df* | *P* |
|---|---|---|---|---|---|---|---|---|
| #1. PANSSnegative in MNP and HC | Model | | | | 0.908 | 431.02 | 4/169 | <.001 |
| | Psychosis | 0.789 (0.050)* | 15.80 | <.001 | | | | |
| | Hostility | 0.450 (0.090) | 2.00 | .047 | | | | |
| | Education | −0.620 (0.090) | −5.46 | <.001 | | | | |
| | Sex | 0.090 (0.048) | −3.75 | <.001 | | | | |
| #2. PANSSnegative in MNP only | Model | | | | 0.710 | 94.59 | 3/116 | <.001 |
| | Psychosis | 0.469 (0.045) | 10.44 | <.001 | | | | |
| | Hostility | 0.104 (0.034) | 3.06 | .003 | | | | |
| | Sex | −0.138 (0.046) | −3.04 | .003 | | | | |
| #3. PANSSpositive in MNP only | Model | | | | 0.940 | 354.60 | 5/114 | <.001 |
| | Psychosis | 0.513 (0.063) | 8.10 | <.001 | | | | |
| | Excitation | 0.243 (0.028) | 8.77 | <.001 | | | | |
| | FTD | 0.249 (0.050) | 4.99 | <.001 | | | | |
| | Age | 0.085 (0.017) | 4.93 | <.001 | | | | |
| | Hostility | 0.124 (0.035) | 3.54 | .001 | | | | |

Shown are heteroscedascticity-consistent or robust standard errors (SE) estimated using the HC3 method
Abbreviations: FTD, formal thought disorders; HC, healthy controls; MNP, major neuro-cognitive psychosis; PANSS+, positive subscale of the Positive and Negative Syndrome Scale; PANSS−, negative subscales of the Positive and Negative Syndrome Scale.

factor analysis performed on the eight symptom domains. The Keiser-Meier-Olkin (KMO) statistic of sampling adequacy was 0.899 and the significance of Bartlett's test ($X^2 = 876.1$, $df = 28$, $P < .00001$) indicated that the factorability of the correlation matrix was adequate and, thus, that exploratory factor analysis (EFA) could be applied to our dataset. Only one real-data eigenvalue was greater than 1.0, namely 5.62, while the next eigenvalue was 0.749, while the first factor explained as much as 70% of the variance. The Hull test, parallel analysis based on minimum rank factor analysis and the Bayesian interpretation criterion (BIC) test showed that the advised number of factors was one. Table 5 shows that all eight variables loaded highly on this first factor with six variables having loadings >0.707 and two with loadings of 0.660 (excitation) and 0.682 (PMR). In addition, the unidimensional congruence (UNICO) (>0.95), explained common variance (ECV) (>0.85), and mean of item residual absolute loadings (MIREAL) (<0.3) values indicated that the data should be treated as essentially unidimensional. The model fit indices (Goodness of Fit Index [GFI] and Adjusted GFI [AGFI]) showed an adequate fit of the model and the distribution of residuals as assessed with root mean square of residuals (RMSR) performed well while also weighted root mean square residual (WRMR) (<1.0) showed a good fit. Moreover, the high values of the Generalized H index showed good construct replicability and good performance across studies. The FDI values found here (>0.80) indicate the effectiveness and quality of the factor scores estimates. Table 5 shows also the results of EFA in the combined groups and shows that the data should be regarded as essentially unidimensional and that all parameters (factor scores, explained variance, model fit indices, H-index, and FDI) were even more adequate as compared with the factor model in patients with MNP. As such, EFA showed that the data structure of the eight clinical domains is essentially unidimensional. In order to exclude potential common method bias, we have used the correlation matrix procedure.[27] The association matrix between the different latent constructs showed no large associations (all $r < 0.90$), indicating lack of common method bias.

Table 6 describes the results of PLS analysis while Supplementary Material S3 describes the results of PLS and SIMCA analysis.

## Discussion

The first major finding of this study is that a single latent trait, which is essentially unidimensional, underlies the key symptom domains of schizophrenia, namely SANS and PANSS negative, PHEM symptoms, FTD and PMR. These findings extend those of a previous report showing that in a study sample of Thai patients with schizophrenia and controls the same symptom domains may be conceptualized under an overall single trait.[13,14] Nevertheless, in the current study, performed on patients from Iraq, we used a restricted study sample of patients with MNP or deficit schizophrenia, indicating that even in a restricted study sample the same latent trait could be established. In fact, restricted sample variance artificially weakens existing correlations and generalizability, and therefore, the correlation coefficients obtained in an unrestricted sample should be corrected for range restriction.[28,29] An unrestricted sample should comprise patients with MNP and SNP as well as normal controls to estimate their actual inter-correlations. Therefore, we have also computed the associations and factor loadings in the combined group of controls and patients with MNP and found, as expected, quite similar albeit somewhat higher correlation coefficients and factor loadings.

The second major finding of this study is that the latent construct extracted from the eight domains showed excellent psychometric properties. First, the obtained AVE value (0.682) showed that the model converged to an adequate result and, therefore, has good convergent validity. Second, the high Cronbach alpha and rho values (both >0.9) indicate good internal consistency reliability or composite reliability. Third, other statistics showed an adequate construct cross-validated communality indicating good predictive relevance and construct replicability. Fourth, the latent construct

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**Table 5.** Results of Exploratory Factor Analysis (EFA).

| Variables | MNP + HC | MNP |
|---|---|---|
| BCa factor loadings and 95% CI | | |
| Psychosis | **0.983** (0.969–0.990) | **0.935** (0.888–0.957) |
| Hostility | **0.865** (0.808–0.894) | **0.744** (0.642–0.816) |
| Excitation | **0.885** (0.844–0.916) | **0.660** (0.547–0.762) |
| Mannerism | **0.867** (0.825–0.897) | **0.764** (0.666–0.835) |
| Formal thought disorders | **0.978** (0.967–0.986) | **0.942** (0.916–0.964) |
| Psychomotor retardation | **0.877** (0.836–0.904) | **0.682** (0.583–0.747) |
| Scale for the assessment of negative symptoms | **0.937** (0.913–0.952) | **0.851** (0.778–0.897) |
| Negative subscale of the Positive and Negative Syndrome Scale | **0.959** (0.932–0.971) | **0.894** (0.837–0.926) |
| Parameter values (95% CI) | | |
| % variance | 86.5 | 70.3 |
| Keiser-Meier-Olkin (KMO) test | 0.91993 (0.913–0.932) | 0.89962 (0.886–0.918) |
| Root mean square of residuals (RMSR) | 0.0272 (0.018–0.033) | 0.0541 (0.038–0.066) |
| Kelley's criterion | <0.0758 | <0.0913 |
| Weighted root mean square residual (WRMR) | 0.3451 (0.242–0.481) | 0.1179 (0.075–0.152) |
| Goodness of Fit Index (GFI) | 0.999 (0.998–0.999) | 0.995 (0.992–0.998) |
| Adjusted GFI (AGFI) | 0.989 (0.982–0.994) | 0.996 (0.988–0.996) |
| Unidimensional congruence (UNICO) | 0.999 (0.999–0.999) | 0.972 (0.934–0.990) |
| Explained common variance (ECV) | 0.971 (0.962–0.978) | 0.897 (0.862–0.925) |
| Mean of item residual absolute loadings (MIREAL) | 0.137 (0.117–0.174) | 0.213 (0.169–0.251) |
| Generalized H index | 0.989 (0.982–0.994) | 0.967 (0.951–0.981) |
| Factor determinacy index | 0.994 | 0.981 |

We performed two EFAs one patient with major neuro-cognitive psychosis (MNP) and one in all subjects combined, that is MNP and healthy controls (HC). Significant loadings (>.5) are shown in bold.
Abbreviation: CI, confidence intervals.

**Table 6.** Results of Partial Least Squares (PLS) Analysis

| Reliability Data | MNP + HC | MNP Only |
|---|---|---|
| Mean (5000 bootstraps) (SD) | | |
| Psychosis | **0.966** (0.005) | **0.907** (0.018) |
| Hostility | **0.870** (0.019) | **0.777** (0.049) |
| Excitation | **0.880** (0.019) | **0.730** (0.047) |
| Mannerism | **0.877** (0.016) | **0.780** (0.039) |
| Formal thought disorders | **0.970** (0.004) | **0.899** (0.017) |
| Psychomotor retardation | **0.917** (0.011) | **0.854** (0.036) |
| Scale for the assessment of negative symptoms | **0.936** (0.008) | **0.804** (0.038) |
| Negative subscale (Positive and Negative Syndrome Scale) | **0.954** (0.006) | **0.856** (0.028) |
| Rho_A | 0.979 (0.002) | 0.947 (0.007) |
| Composite reliability | 0.978 (0.002) | 0.944 (0.006) |
| Cronbach alpha | 0.978 ((0.002) | 0.943 (0.007) |
| Average variance extracted | 0.850 (0.012) | 0.682 (0.025) |

We performed two PLS analyses: one in patients with major neuro-cognitive psychosis (MNP) and one in all subjects combined, that is MNP and healthy controls (HC). Significant loadings (>.707) are shown in bold.
Abbreviation: SD, standard deviation.

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has also good concurrent validity as established by a highly significant association with a more general index of psychopathology. As such, this single trait underpinning the eight domains represents a reliable and replicable score that indicates overall severity of schizophrenia (OSOS).

Our findings that one OSOS factor represents all eight domains contrasts with previous theories which consistently used a two-dimensional approach of schizophrenia phenomenology. Bleuler's concept of "schizophrenia" conceptualized that a distinction between basic (or negative) symptoms, and additional (positive) symptoms is the hallmark of schizophrenia.[8,9] Crow also made a quite similar two-dimensional concept that distinguishes between positive and negative symptoms.[5] The NHS and NINH classify schizophrenia symptoms as positive and negative.[30,31] Roy and Devriendt[32] summarized that the positive and negative concepts show some validity because negative symptoms are correlated with cognitive deficits and both dimensions may have different substrates. Nevertheless, not only negative, but also positive symptoms are strongly predicted by neurocognitive impairments, including in semantic and episodic memory, attention, and executive functions,[14,25] while the eight domains included in the current study coupled with neurocognitive tests are in fact manifestations of a single trait in the combined group of patients and controls.[13] Roy and Devriendt[32] also discussed that not all data supported Crow's model[5] including the existence of other symptom dimensions. In this respect, the current study established that FTD and PMR are other manifestations of the OSOS latent trait. Previously, we found that PMR, as a key symptom of schizophrenia and especially MNP, is significantly associated with the negative and PHEM domains of schizophrenia.[13] Moreover, we reported that FTD, as another hallmark of (deficit) schizophrenia, was significantly associated with memory impairments while in the current study, FTD is strongly associated with PHEM and negative symptoms.[14,25] In addition, a strong association among the negative domain and either depression or physio-somatic symptom domains was established.[33,34]

The results of the present study showed that the latent phenomenon OSOS is reflectively measured through its eight effect indicators. As a consequence, this reflective construct is the common cause of the manifestations (eight domains) and the latter is to a large extent modulated by the OSOS index. In addition, we examined second-order constructs (Hierarchical Component Models) with the repeated indicator method and observed that the lack of discriminant validity between PHEM and negative domains did not allow to build a well-fitted Hierarchical Component Model. In the current study and in the study of Sirivichayakul et al,[25] we found that the negative domain indicators could reliably be added to the positive or PHEM latent traits. Moreover, here we detected that the psychosis, PHEM and "positive" domains could reliably be added to the negative latent vector. Moreover, there are some issues with the commonly applied practice to assess "positive" symptoms using rating scales. In this respect, the current study showed that a large part of the variance in the PANSS positive subscale score could be explained by the combined effects of three "positive" areas (psychosis, hostility, excitation) and FTD, suggesting that "positive symptoms" should be dissected into those key areas to obtain adequate manifestations of the reflective PHEM (but not positive symptom) construct. Moreover, neuroimmune biomarkers often predict the PHEM symptoms but not the positive PANSS subdomain score,[35] further indicating that the latter is not a valid construct.

There is evidence that schizophrenia is a neuro-immune disorder[36–39] and that most neuroimmune biomarkers are significantly associated with both negative and PHEM symptoms, including indices of immune activation, increased levels of CCL11 (eotaxin), breakdown of the paracellular gut pathway, and bacterial translocation.[13,35,40,41] Nevertheless, we also observed that neuroimmune biomarkers may be differently associated with both areas. For example, immunoglobulin M (IgM)-mediated autoimmune responses to oxidative specific epitopes (OSEs) including malondialdehyde (MDA) and azelaic acid, and to tryptophan catabolites (TRYCATs) are more associated with negative symptoms, whereas IgA responses to TRYCATs are more associated with "positive" symptoms.[13,42,43] The results that some biomarkers may be preferentially associated with one of the clinical areas may, at first sight, be difficult to reconcile with the existence of a single reflective OSOS measurement underpinning all effect indicators. Nevertheless, such findings may be explained by a combination of factors. First, neuroimmune pathways do not act alone but work in networks.[44] For example, lowered IgM responses to OSEs are preferentially associated with negative symptoms but are also associated with immune and TRYCAT pathway activation, which, in turn, are associated with PHEM symptoms.[25] Second, neuroimmune pathways may cause neuroprogressive processes in different neuronal circuits,[37–39] which, in turn, determine symptom domains. Moreover, the neurotoxic effects of the immune networks on the neuronal circuitry are additionally mediated by effects on semantic and episodic memory, attention and executive functions, which all together determine to a large extent the OSOS index.[13,14,25]

The third major finding of this study is that MNP or deficit schizophrenia is, as a diagnostic category, better modeled (predicted) by PHEM symptoms, FTD and PMR than by negative symptoms. A combination of all eight domains provided an accuracy of 100% while the top-5 discriminatory predictors were in descending order: hostility, PMR, excitation, and mannerism followed at a distance by the negative SANS symptoms. Previously, we detected, in another study sample, that both negative and PHEM symptoms discriminate MNP or deficit schizophrenia from SNP or nondeficit schizophrenia with great accuracy.[11,12] These findings are at odds with Crow's theory[5] and with the conclusion of Roy and Devriendt[32] that "it appears to be more productive to conceive negative symptoms as distinct dimensions rather than distinct diseases." First, in the current study, we have shown that (a) negative symptoms are not a distinct dimension and (b) MNP or deficit schizophrenia is a distinct nosological entity,[11,12] which is better modeled by PHEM, PMR, and FTD symptom areas than by negative symptoms.

At first sight, it may be difficult to reconcile our findings that MNP (deficit schizophrenia) is a distinct nosological entity (categorical distinction) based on negative and PHEM domains and that the dimensional OSOS index (a continuum based on the same symptoms) underpins schizophrenia phenomenology. Nevertheless, not only symptom domains but also neuroimmune and cognitive features model and discriminate SNP from MNP and controls.[11,12] As such, stable-phase schizophrenia comprises two qualitatively distinct nosological classes, namely SNP (a less-well-developed phenotype) and MNP (the full-blown phenotype), which are both modeled by the eight symptom areas, which increase in severity along a continuum thereby shaping two qualitatively distinct classes.

The current study should be interpreted with regard to its possible limitations. First, this study was performed in patients with stable phase schizophrenia and, therefore, cannot be generalized to acute episodes of the illness. Future research should examine the associations among different symptom areas in acute episodes of schizophrenia. Second, this is a case–control study and thus no

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causal inferences can be made. Future research should examine the time-relationships between the different symptom domains from the premorbid stage to later stages. Thirdly, studies examining the association among clinical variables are prone to common method bias (CMB) although using the correlation matrix procedure no evidence for any CMB could be detected.

In this paper we used a new approach to re-validate schizophrenia symptom dimensions and nosological classifications using supervised and unsupervised machine learning techniques. Therefore, we now discuss the merits of these methods and their contributions to the field.

- We employed SIMCA as a supervised learning technique to validate deficit schizophrenia and to examine whether this class is a qualitatively distinct category with regard to PHEM symptoms, PMR and FTD, and biomarkers as well.[11,45,46] Using this method, we were able to validate deficit schizophrenia as a qualitatively distinct category with regard to PHEM symptoms, FTD and PMR indicating that those symptom domains are together with negative symptoms key features of deficit schizophrenia. Thus, the results of this supervised machine learning technique revealed that the two-syndrome conceptualization of schizophrenia into positive and negative symptom domains cannot be validated,[5,30,31] and, by inference, that there is no evidence supporting the revised dopamine theory, which posits that positive and negative symptoms may result from hyperactive vs hypoactive mesocortical dopaminergic projections, respectively.[47,48] Moreover, using SIMCA we were able to validate deficit schizophrenia as a NIBCA (neuroimmune and brain-circuit axis) pathway-class, indicating that the phenome of deficit schizophrenia (namely the presence of negative and PHEM symptoms as well as FTD and PMR) is largely predicted by NIBCA pathways.[13,35,40,46] The latter encompass effects of neuroimmune markers on brain areas including "prefrontal system and frontal lobes, primary and supplementary motor area (SMA) and preSMA cortices, and prefrontal-limbic and cortico-striatal loops that connect the prefrontal cortex with the basal ganglia, thalamus, hypothalamus, hippocampus and amygdala."[13]
- In the current paper, we also used EFA and PLS path analysis to uncover the latent construct and associations between the different symptom domains underlying deficit schizophrenia.[49-51] Most importantly, we used EFA in conjunction with the BIC dimensionality test, parallel analysis and the Hull test (procedures to determine the number of factors) and unidimensional congruence, explained common variance, and mean of item residual absolute loadings (to ascertain unidimensionality of a common factor).[49,50] Using those methods, we were able to detect that in patients from Iraq and Thailand, schizophrenia symptom domains belong to one and the same dimension, which is unidimensional and, in addition, has adequate validity and reliability.
- We employed the Fornell-Larcker Criterion and the Heterotrait-Monotrait Ratio of Correlations (HTMT) to assess discriminant validity[51] of positive (and psychotic or PHEM) vs negative symptom constructs. Using these methods, we discovered that in our Iraq and Thai study samples, these constructs lack discriminant validity and that they, additionally, cannot be discriminated from a general psychopathology index. Therefore, our machine learning-derived findings indicate that the "positive symptom" concept may not be valid and additionally that PHEM and negative symptoms as well as FTD and PMR belong to the same latent construct, which reflects OSOS.
- Finally, we used Confirmatory Tetrad Analysis to assess the correct indicant directionality of the OSOS contruct[51] in order to examine whether the latter construct should be treated as reflective rather than formative. Using this method, we found that all symptom domains are reflective manifestations of OSOS, which is, therefore, the common cause for the symptom dimensions measured here. These findings suggest that commonly used rating scales to assess severity of schizophrenia may not be adequate as they only measure one subdomain (eg, negative symptoms using the SANS) or add symptom scores to make sum-scores (eg, the BPRS and PANSS), which are thought to reflect OSOS but were not tested for the requirements that the underlying construct should be reflective and unidimensional.[52] Future research should employ the symptom domains proposed in our studies to construct new rating scales that assess OSOS more adequately.

## Conclusions

Negative symptoms (SANS and PANSS negative subscale score), psychosis, hostility, excitation, mannerism, FTD and PMR should be treated as essentially unidimensional. The latent vector extracted from those eight symptoms areas showed excellent convergent validity, internal consistency reliability, composite reliability, predictive relevance, construct replicability, and concurrent validity. The latent trait underpinning the eight domains is reflectively measured through these eight symptom areas and represents a reliable and replicable index of OSOS. The concept "positive symptoms" cannot be validated and positive symptoms should be dissected into relevant domains, namely psychosis, hostility, and excitation, while also other areas are important including PMR, FTD, and mannerism. The bi-dimensional concepts of positive and negative symptoms and type I and II (and deficit) schizophrenia should be revised.

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