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

Schizophrenia comprises various symptom domains the two most important being positive and negative symptoms. Nevertheless, using (un)supervised machine learning techniques it was shown that a) negative symptoms are significantly interrelated with PHEM (psychosis, hostility, excitation, and mannerism) symptoms, formal thought disorders (FTD) and psychomotor retardation (PMR); and b) stable phase schizophrenia comprises two distinct classes, namely Major Neuro-Cognitive Psychosis (MNP, largely overlapping with deficit schizophrenia) and Simple NP (SNP). In this study, we recruited 120 MNP patients and 54 healthy subjects and measured the above-mentioned symptom domains. 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 additionally shows excellent internal consistency reliability, convergent validity, and predictive relevance. Confirmatory Tedrad Analysis indicates that this latent vector fits a reflective model. Soft Independent Modeling of Class Analogy (SIMCA) shows that MNP (diagnosis based on negative symptoms) is better modeled with PHEM symptoms, FTD and PMR than with negative symptoms. In conclusion, in MNP, a restricted sample of the schizophrenia population, negative and PHEM symptoms, FTD and PMR belong to one underlying latent vector reflecting general psychopathology and, therefore, may be used as an overall severity of schizophrenia (OSOS) index. The bi-dimensional concept of positive and negative symptoms and type I and II schizophrenia is revised.

Keywords: deficit schizophrenia, positive symptoms, negative symptoms, inflammation, neuro-immune

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 (Mellor, 1991; Marneros et al., 1991; Cuesta and Peralta, 1995). 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 (Burton, 2012). 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 (Burton, 2012).

Based on this distinction between positive and negative symptoms of schizophrenia patients 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 (Crow, 1985). 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 (Ahmed et al., 2015; Kirkpatrick et al., 1989). 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 (Jablensky, 2010). 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 (Jablensky, 2010). Nevertheless, it is debated whether negative symptoms increase in severity along a continuum from the healthy state to schizophrenia patients with a “fully developed

syndrome" (dimensional theory) or whether type II or deficit schizophrenia is a separate nosological class (categorical theory) (Takahashi, 2013; Kanchanatwan et al., 2018a).

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 (Kanchanatawan et al., 2018a; Kanchanatawan et al., 2018b). 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 non-deficit 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 (Kanchanatawan et al., 2018b). The non-deficit 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 neuro-immune pathways (Kanchanatwan et al., 2018b; Maes et al., 2019a). As such, we have delineated two homogeneous phenotypes of schizophrenia which allow more precise identification of clinical, neuro-cognitive and neuro-immune features.

Another major finding of our laboratory is that different symptom domains such as psychotic symptoms (hallucinations, delusions, suspiciousness), hostility (and poor impulse control and uncooperativeness), excitation (and grandiosity), mannerism (and posturing) and negative symptoms are highly significantly intercorrelated (Kanchanatawan et al., 2018a; 2018b; Maes et al., 2019a). These findings suggest that the differentiation of negative symptoms versus 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 (Sirivichayakul et al., 2019b; Maes et al., 2019a). Firstly, 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 (Bleuler, 1950; Simpson and Davis, 1985; Andreasen and Grove, 1986; Bachman and Cannon, 2012; Kircher et al., 2018). 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 (Sirivichayakul et al., 2019b). Secondly, 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 (Maes et al., 2019a). In addition, PMR is strongly associated with other symptom domains including psychosis, hostility, excitation, mannerism, and negative (PHEMN) symptoms (Maes et al., 2019a). 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 major neuro-cognitive psychosis (MNP) and 54 healthy subjects. Schizophrenia patients and healthy individuals were recruited from the same catchment area, i.e. 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 schizophrenia patients were in a stabilized phase of illness and did not suffer from acute episodes the year prior to the study. Patients were diagnosed according to DSM-IVTR criteria as "schizophrenia" and according to the Schedule of Deficit Schizophrenia (SDS) criteria as "deficit schizophrenia" (Kirkpatrick et al., 1989). Moreover, all schizophrenia patients also complied with the diagnostic criteria of MNP as published by Kanchanatawan et al. (2018b). 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. Schizophrenia patients 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 (CRP) 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.

Measurements

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 (Kirkpatrick et al., 1989), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Scale for the Assessments of Negative Symptoms (SANS) (Andreasen et al., 1989), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), and the Hamilton Depression (HAM-D) and Anxiety (HAM-A) rating scales (Hamilton, 1959; 1960). The same day a research psychologist assessed the Mini-Mental State Examination

(MMSE) (Folstein et al., 1975) in a validated Arabic translation. 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 (TUD) 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 (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 (Maes et al., 2019a; Sirivichayakul et al., 2019a; 2019b). **Table** 1 shows the different z unit-weighted composite scores used in the current study to assess the severity of symptom domains including PHEMN (psychosis, hostility, excitation, mannerism, negative) 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 (χ^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, drug state) on the 8 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,1995).

Multiple regression analysis was used to examine the significant biomarkers that predict the symptom domains using an automatic stepwise method (p-to-entry of 0.05 and p-to-remove 0.06) 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.

Single joint PCA performed on the 8 symptom domains in MNP and controls was used to visualize the distribution of both groups in a 2D space (the PC plot) whereby MNP patients and controls are differentiated by marker colors and shapes (Unscrambler, CAMO, 2019). We employed a standard deviation weighting process and a 20-fold cross-validation scheme, while outlier limits are based on 0.05% F-residuals and Hotelling's T2. Correlation loadings for each of symptom domains are displayed in a plot that comprises two ellipses, the outer ellipse indicating 100% explained variance and the inner one explaining 50% explained variance.

We used exploratory factor analysis (EFA) as a data-driven method to explore the factor structure of schizophrenia phenomenology in patients with MNP and all subjects combined (MNP and controls). EFA was performed using FACTOR, windows version 10.5.03 (Ferrando, 2013, 2017) to examine the factor structure of the dataset. Factors were extracted using the robust unweighted least squares (RULS) method and the number of bootstrap samples was 500 (Ferrando and Lorenzo-Seca, 2013; 2017; Lloret et al., 2017). The dispersion matrix was based on Pearson's correlations, and a robust analysis was carried out with bias-corrected and accelerated (BCa) bootstraps. Before performing EFA, the Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity were applied to determine the matrix' adequacy for factorization. Schwartz's Bayesian

Information Criterion (BIC), the Hull test and Parallel Analysis (Optimal Implementation) were employed as dimensionality tests and to estimate the number of factors to be retained. Model fit indices were computed in order to examine the goodness-of-fit of the model, namely the goodness-of-fit index (GFI) and the adjusted goodness-of-fit index (AGFI). The distribution of residuals is assessed with the root mean square of residuals (RMSR) with an expected mean value of RMSR for an acceptable model (Kelley's criterion) and the weighted Root Mean Square Residual (WRMR), whereby values <1.0 represent a good fit. Closeness to unidimensionality was checked employing unidimensional congruence (UNICO), explained common variance (ECV) and mean of item residual absolute loadings (MIREAL). The data should be treated as essentially unidimensional when UNICO >0.95; ECV >0.85; and MIREAL <0.300. Construct replicability was assessed using the H index (values between 0 and 1) whereby values ≥0.80 indicate good replicability of the latent vector and stability across studies. The factor determinacy index (FDI) was used to estimate the quality of factor score estimates and values >0.80 are adequate.

If EFA suggested a unidimensional structure (one latent vector) underlying the 8 symptoms domains we planned to perform Partial Least Squares (PLS) analysis. PLS path analysis using PLS-structural equation modeling algorithms (SmartPLS) (Ringle et al., 2018) was employed in order to examine a) the contribution of the symptom domains to the latent vector extracted from all symptoms domains using a hierarchical component model (HCM) (reflective – reflective model) build using the repeated indicator approach (Garson, 2019), b) the convergent validity and reliability of the main construct, c) associations of the LV with known predictors including age and the MMSE (Kanchanatwan et al., 2018c), d) association between the main LV and a general index of severity comprising the BPRS (shBPRS), PANSS general (shPANSSg) and HAM-D (shHAM-D) scores (without all item used in constructing PHEM, FTD and PMR indices) and total

HAM-A scores. The input variables were 2 single indicators (age and MMSE score) predicting the latent vector (reflective mode) extracted from the 8 symptom domains. The eight symptom domains are grouped into negative and PHEM symptoms considering reflective and formative models. We performed PLS analysis when the model fit and constructs complied with quality criteria including standardized root mean residual (SRMR) < 0.08; and adequate internal consistency reliability (construct validity) and convergent validity as indicated by composite reliability > 0.800; Cronbach alpha > 0.750; rho_A >0.800 and average variance extracted (AVE) > 0.500. Indicators are only included in the LV when the factor loadings are > 0.650 with $p < 0.01$. Discriminant validity is examined using the Fornell-Larcker criterion and the Heterotrait–Monotrait (HTMT) ratio which should be <0.9 (and more conservative < 0.85). Subsequently, we performed complete consistent PLS bootstrapping (5000 bootstraps) and computed t-values and loadings on the LVs for the outer model, and path coefficients with exact p-values for the inner model. We also performed Confirmatory Tedrad Analysis (CTA) to check possible misspecification of our LV model, namely whether the LV is reflective (our hypothesis) or formative. We also performed blindfolding to examine predictive validity using construct cross-validated communality (Q2 statistic) whereby values of $Q^2 > 0$ indicate that the model has predictive relevance and values > 0.35 indicate a large relevance.

Soft independent modeling of class analogy (SIMCA) is a supervised machine learning method which builds separate PCA models for all classes, thus one model for MNP and another model for controls (CAMO, 2018). A training set (comprising 50% of the MNP subjects and 50% of the controls) is used to construct the PCA models and a test (validation) set (the remaining 50%) is used to validate the models. The number of PCs used to build the models in the training set is determined by cross-validation after outliers are deleted as detected by sample residual vs samples

and Hotelling's T2 vs samples plots. Subjects from the test set are then classified into the group for which they display the best similarity based on critical limits for two relevant distances, namely Si, that is the subject to model distance (reflecting how far the subject is located from the target class) and Hi that is the leverage of one subject to the model center (reflecting how different the subject is from the other subjects). The test subjects are consequently projected into both PCA models whereby SIMCA allocates cases to the models by comparing the computed distances to the model subspaces at alpha=0.05. As such, subjects may be assigned to the target model (MNP class members) or the control model (alternative class members) or they can be allocated to both models (hybrids) or to none of the models (outsiders). Healthy controls that intrude into the MNP target class are identified as "aliens". In this study we used a) the model-to-model distance indicating the degree of separation between both models with a distance > 3 indicating a good separation; b) the discrimination power plot showing the contribution of all features (the symptom domains) separating both models; and c) The Si/S0 (relative distance of the subjects to the class model) vs Hi plot with critical model membership limits allowing to classify cases into the target class (authentication), alternate class members, outsiders, hybrids or aliens.

Results.

Socio-demographic data

Table 2 shows the socio-demographic and clinical data of the MNP patients 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, 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=0.652) on the 8 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<0.001), SANS (t=-3.49, p=0.001), psychosis (t=-2.64, p=0.009), hostility (t=-2.51, p=0.013), mannerism (t=-2.40, p=0.018) and FTD (t=-2.47, p=0.015). 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=0.103) or fluphenazine (F=1.76, df=8/111, p=0.092) 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<0.001 level after p correction for false discovery rate, 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 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 1** 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 2** 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 MNP patients and extracted PCs from the data set comprising SANS, PANSSnegative, PHEM symptoms, FTD and PMR. **Figure 3** shows a PC score plot, namely PC1 (explaining 87% of the variance) vs PC2 (explaining 4%), which displays the distribution of MNP patients (red dots) and controls (blue squares) in the 2D space made by both PCs. MNP patients 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 4 shows the correlation loadings of the 8 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 factor analysis performed on the 8 symptom domains. The KMO statistic of sampling adequacy was 0.899 and the significance of Bartlett's test ($\chi 2$=876.1, df=28, p<0.00001) indicated that the factorability of the correlation matrix was adequate and, thus, that 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, PA analysis based on minimum rank factor analysis and the BIC test showed that the advised number of factors was one. Table 5 shows that all 8 variables loaded highly on this first factor with 6 variables having loadings > 0.707 and 2 with loadings of 0.660 (excitation) and 0.682 (PMR). In addition, the UNICO (>0.95), ECV (>0.85) and MIREAL (<0.3) values indicated that the data should be treated as essentially unidimensional. The model fit indices (GFI and AGFI) showed an adequate fit of the model and the distribution of residuals as assessed with RMSR performed well whilst also 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, FDI) were even more adequate as compared with the factor model in MNP patients. As such, EFA showed that the data structure of the 8 clinical domains is essentially unidimensional. In order to exclude potential common method bias, we have used the correlation matrix procedure (Tehseen et al., 2017). The association matrix between the

different latent constructs showed no large associations (all r<0.90), indicating lack of common method bias.

SmartPLS

First we tested the reflective – reflective HCM described in the statistics section. This PLS analysis was performed in subjects with MNP with age and MMSE (single indicators) predicting the main higher order construct (HOC) named "overall severity of schizophrenia" (OSOS) LV (extracted from the 8 domains). The HCM model also includes two lower order constructs (LOC) with more concrete traits, namely a first LOC extracted from PHEM symptoms and a second LOC extracted from negative symptoms. Inspection of cross-loadings showed that FTD is part of the PHEM LOC and PMR is part of the negative LOC. Finally, we also examined the association between the OSOS HOC and a general psychopathology LV extracted from ShBPRS, ShPANSSg, shHAM-D, and total HAMA-A scores. The model showed a good fit with SRMR = 0.071, and all constructs showed excellent Cronbach alpha (all > 0.858), rho_A (all > 0.871), composite reliability (all > 0.862) and AVE (> 0.621) values while all loadings in the outer models were significant at p<0.001 and > 0.671. Nevertheless, the model lacks discriminant validity as indicated by the Fornell-Larcker ctiterion and HTMT ratio. The latter showed that discriminant validity was not established for many pairs including the PMEM and Negative (0.966), PHEM and General (0.992) and Negative and General (0.978) LOCs. There was a strong relationship between the OSOS LV and General LV scores (r=0.860, p<0.0001, n=120).

Table 6 shows the results of a second complete consistent PLS analysis with age and MMSE as indicators and the OSOS LV as output variable and using the factor weighting scheme on 5000 bootstrap samples. All factor scores obtained by PLS factor analysis of the symptom

domains loaded highly (all > 0.707). Moreover, composite reliability and Cronbach alpha and rho_A values were all very high (all > 0.9) while AVE was 0.682 (indicating good internal consistency reliability and convergent validity). The results of CTA support a reflective model which is in agreement with our hypothesis. Blindfolding shows a construct cross-validated communality of Q^2=0.614, indicating good predictive relevance. Consequently, we have performed the same analyses in all subjects combined. Table 6 shows that all symptom domains loaded highly on the LV and that this LV has excellent internal consistency reliability and convergent validity. In the total study group, CTA supports a reflective model, while blindfolding shows a construct cross-validated communality of Q^2=0.774, indicating a very good predictive relevance.

SIMCA

Using the 8 symptom domains as input variables to build PCA models we did not find any indication of outliers in the control and MNP PCA models and therefore no subjects were omitted from the models. MNP was modeled using 6 PCs, while controls were modeled using 3 PCs. All input variables showed significant modeling power in both classes (all > 0.7404) while also the discriminant power was significant, in decreasing order of power: hostility (352.2469), PMR (83.8985), excitation (48.3529), mannerism (35.7912), SANS (23.9502), FTD (17.2292), PANSSnegative (13.21411) and psychosis (11.6959). We found that the model-to-model distance was 565.73 indicating a huge separation of both classes. **Figure 5** shows the Si/S0 vs Hi plot and the distances of all subjects allocated to the test set to the critical limits of the control class, as well as their leverage to the same class. All MNP and control subjects were correctly authenticated as belonging to their target class while no aliens could be detected (e.g. MNP subjects intruding the

critical limits of the control class). In addition, no outsiders were detected and also the classification table showed that all cases were correctly classified yielding an accuracy of 100%. We performed a second SIMCA whereby the MNP class (training set) was modeled with hostility, PMR, excitation, mannerism, and psychosis and projected the test set into this SIMCA model. We found that 57 MNP patients were correctly authenticated as belonging to the MNP class while 3 cases fell outside the critical limits, one with an increased distance to the model and 2 who showed increased leverage. Since no outsiders were detected and no aliens (controls intruding the MNP class) the sensitivity of these symptom domains for MNP was 95% and specificity 100%. We performed a third SIMCA analysis whereby the SANS negative symptom subdomains (flattening, alogia, apathy, anhedonia, and attention) were used to model MNP. Projecting the subjects of the test set into the target class showed that 51 MNP cases were authenticated as belonging to the target class while 8 cases showed an increased distance to the MNP model and one an increased leverage. Since there were no aliens (controls intruding the MNP class), the sensitivity is 85% with a specificity of 100%.

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 schizophrenia patients and controls the same symptom domains may be conceptualized under an overall single trait (Maes et al., 2019a; Sirivichayakul et al., 2019b). Nevertheless, in the current study, performed on Iraq patients, 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 (Wiberg and Sundstrom, 2009; Lakes, 2013). An unrestricted sample should comprise MNP and SNP patients 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 MNP patients 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. Firstly, the obtained AVE value (0.682) showed that the model converged to an adequate result and, therefore, has good convergent validity. Secondly, the high Cronbach alpha and rho values (both > 0.9) indicate good internal consistency reliability or composite reliability. Thirdly, other statistics showed an adequate construct cross-validated communality indicating good predictive relevance and construct replicability. Fourth, the latent construct 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 reflective 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 (Jablensky, 2010). Crow also made a quite similar two-dimensional concept that distinguishes between positive and

negative symptoms (Crow, 1985). The NHS and NINH classify schizophrenia symptoms as positive and negative (NHS, 2019; NIMH, 2019). Roy and Devriendt (1994) 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 (Sirivichayakul et al., 2019a; 2019b), 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 (Maes et al., 2019a). Roy and Devriendt (1994) also discussed that not all data supported Crow's model (1985) 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 (Maes et al., 2019a). Moreover, we reported that FTD, as another hallmark of schizophrenia, was significantly associated with memory impairments while in the current study FTD belongs more to the PHEM than to the negative symptom domain (Sirivichayakul et al., 2019a; 2019b). In addition, a strong association among the negative domain and either depression or physio-somatic symptom domains was established (Kanchanatawan et al., 2017; Kanchanatawan et al., 2018c).

The results of the present study showed that the latent phenomenon OSOS is reflectively measured through 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. (2019a) 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 domain 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 reflecting PHEM (but not positive symptom) construct. Moreover, neuro-immune biomarkers often predict the PHEM symptoms but not the positive PANSS subdomain score (Maes et al., 2019b), further indicating that the latter is not a valid construct.

There is evidence that schizophrenia is a neuro-immune disorder (Smith and Maes, 1995; Anderson and Maes, 2013; Davis et al., 2014; 2016) and that most neuro-immune biomarkers are significantly associated with both negative and PHEM symptoms, including indices of immune activation, increased levels of CCL-11 (eotaxin), breakdown of the paracellular gut pathway, and bacterial translocation (Maes et al., 2019a; 2019b; 2019c; Al-Hakeim et al., 2019). Nevertheless, we also observed that some neuro-immune biomarkers were differently associated with both domains. For example, IgM-mediated autoimmune responses to oxidative specific epitopes (OSEs) including malondialdehyde (MDA) and azelaic acid, and IgM responses to tryptophan catabolites (TRYCATs) are rather specifically associated with negative symptoms, whereas IgA responses to TRYCATs are more associated with positive symptoms (Kanchanatawan et al., 2018d; 2018e; Maes et al., 2019a). Decreases in paraoxonase 1 (PON1) activity are significantly and

inversely related to negative symptoms but not to the PHEM symptoms (Moreira et al., to be submitted). The results that some biomarkers may be preferentially associated with one of the clinical domains 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. Firstly, neuro-immune pathways do not act alone but work in networks (Maes et al., 2016). For example, lowered levels of natural IgM responses to OSEs, indicating lowered anti-oxidant and anti-inflammatory potential (Maes et al., 2019a), are preferentially associated with negative symptoms and may cause increased immune and TRYCAT pathway activation, which are more associated with PHEM symptoms (Sirivichayakul et al., 2019a). Secondly, neuro-immune pathways may cause neuroprogressive processes in different neuronal circuits (Anderson et al., 2013; Davis et al., 2014; 2016), which in turn determine symptom domains. These different neuronal circuits are integrated with a neuronal network, which mediates the effects of the neuro-immune network leading to OSOS and its manifestations. Moreover, the effects of neuro-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 (Sirivichayakul et al., 2019a; 2019b; Maes et al., 2019a). It is safe to hypothesize that one neuro-immune pathway may cause aberrations in specific neuronal circuits, e.g. left superior temporal gyrus and its prefrontal connectivity, thereby determining negative symptoms (Li et al., 2018). Nevertheless, immune-induced changes in one neuronal circuit will likely aggravate downstream aberrations in other neuronal circuits and the overall neuronal network and therefore in the OSOS.

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 non-deficit schizophrenia with great accuracy (Kanchanatwan et al., 2018a; 2018b). These findings are at odds with Crow's theory and with the conclusion of Roy and Devriendt (1994) that "it appears to be more productive to conceive negative symptoms as distinct dimensions rather than distinct diseases". Firstly, in the current study, we have shown that negative symptoms are not distinct dimensions, and secondly, MNP or deficit schizophrenia is a distinct nosological entity (Kanchanatwan et al., 2018a; 2018b) albeit it is better modeled by the PHEM, PMR and FTD symptom domains 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 neuro-immune and cognitive features model discriminate MNP from SNP and controls (Kanchanatwan et al., 2018a; 2018b). As such, stable-phase schizophrenia comprises two qualitatively distinct nosological classes whereby MNP is the full-blown phenotype and SNP is a less-well-developed phenotype, while the symptom areas are intertwined and shape MNP (deficit schizophrenia) as a qualitatively distinct class.

The current study should be interpreted with regard to its possible limitations. Firstly, 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 domains in acute episodes of schizophrenia. Secondly, this is a case-control study and thus no 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 conclusion: 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 domains 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 8 symptom domains and represents a reliable and replicable index of overall severity of schizophrenia (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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Conflict of interest

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Conflict of interest

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Author’s contributions

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

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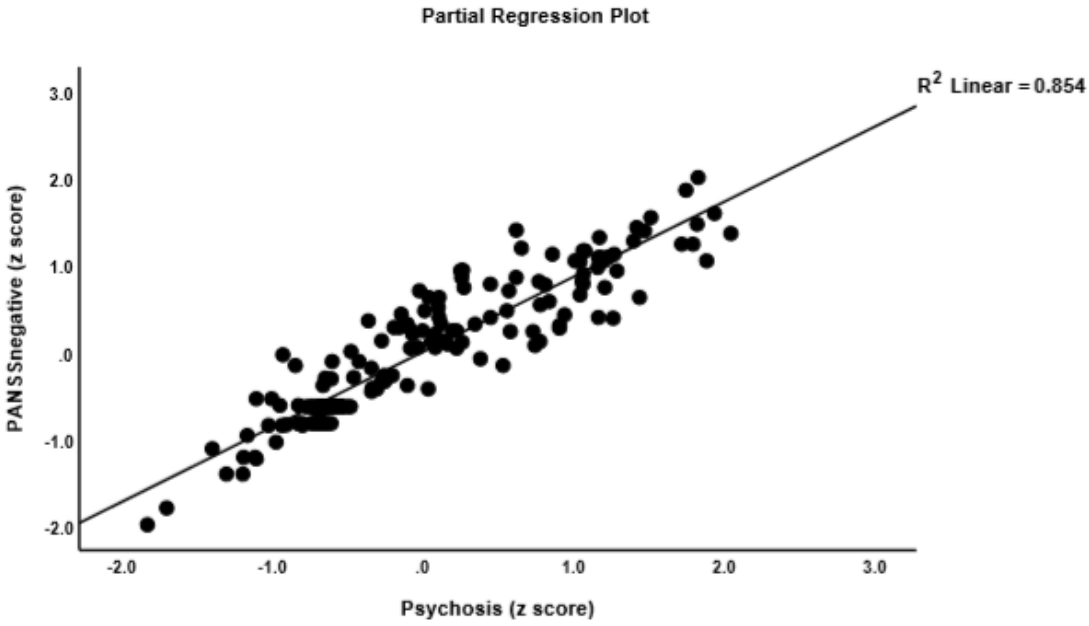

Figure 1. Partial regression plot between the PANSS negative subscale score and psychosis domain score in controls and patients with major neuro-cognitive psychosis or deficit schizophrenia (data were adjusted for education, sex and hostility).

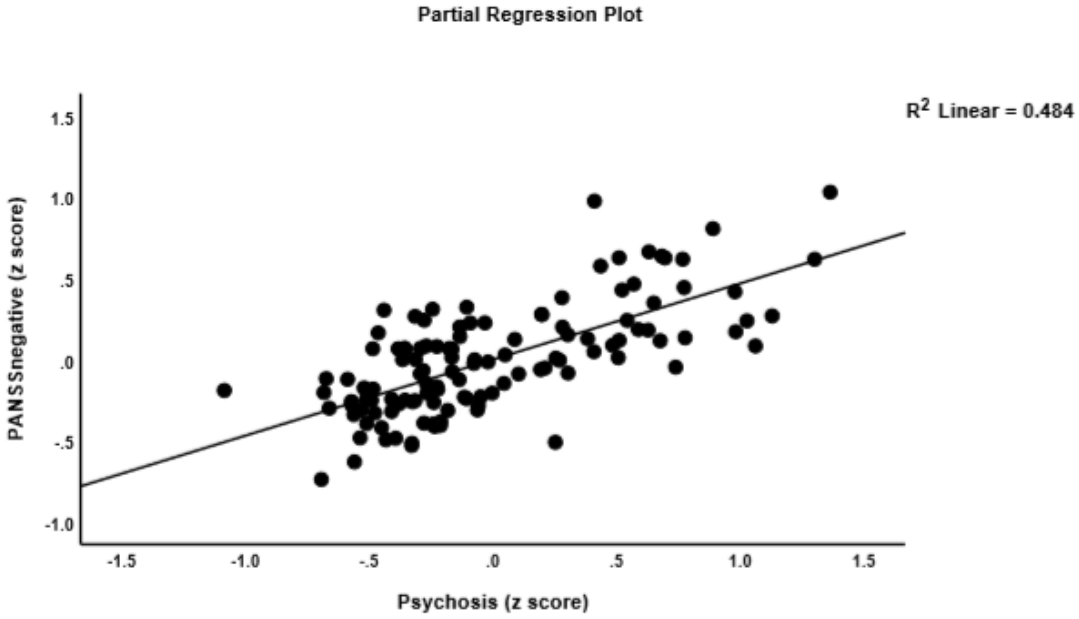

Figure 2. Partial regression plot between the PANSS negative subscale score and psychosis domain score in the restricted sample of patients major neuro-cognitive psychosis or deficit schizophrenia (data were adjusted for education, sex and hostility).

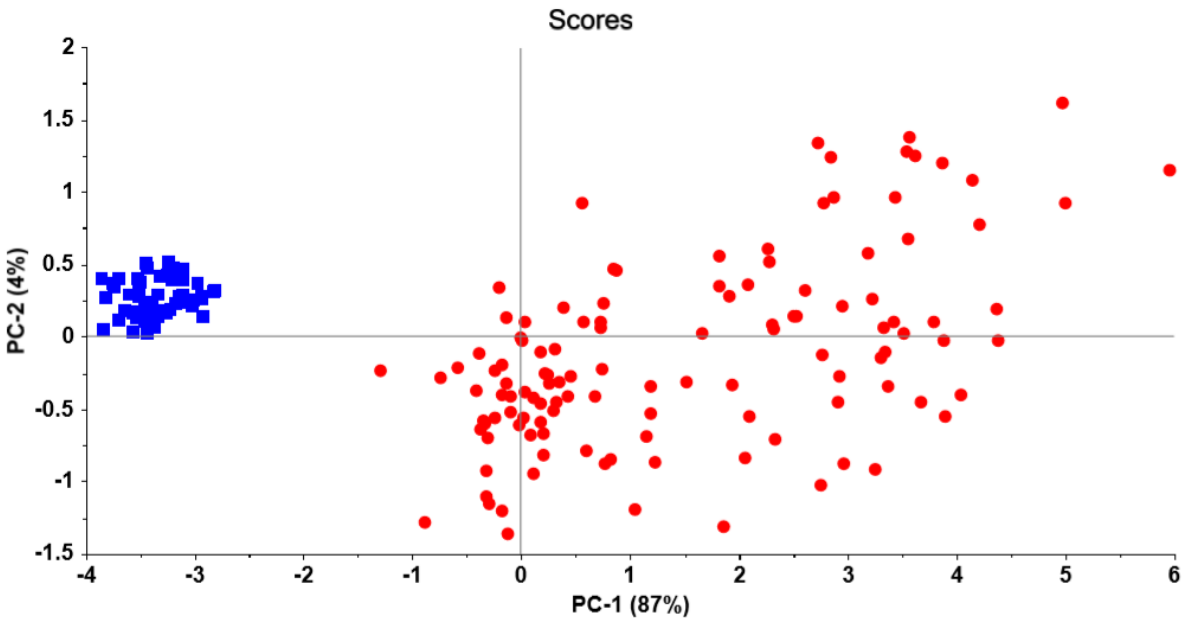

Figure 3. Principal Component (PC) plot, namely PC1 (explaining 87% of the variance) vs PC2 (explaining 4%) performed on 8 symptom domains, namely hostility, psychomotor retardation, excitation, mannerism, SANS total score, formal thought disorders, PANSS negative subscale score and psychosis. This plot displays the distribution of patients with major neuro-cognitive psychosis or deficit schizophrenia (red dots) and healthy controls (blue squares).

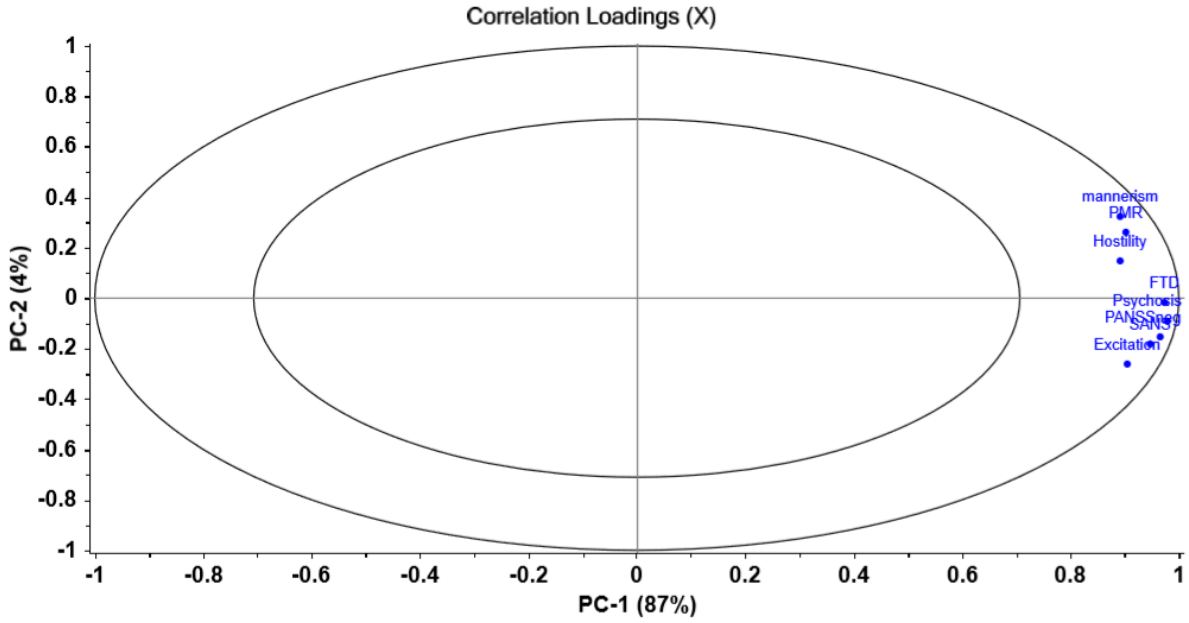

Figure 4. Correlation loading plot. The plot shows the correlation loadings of the 8 symptom domains used to perform principal component analysis (PCA) as shown in figure 3. All variables are located between both ellipses and group together.

PMR: psychomotor retardation

FTD: formal thought disorders

PANSSneg: total score on the PANSS negative subscale score

SANS: total score on the SANS

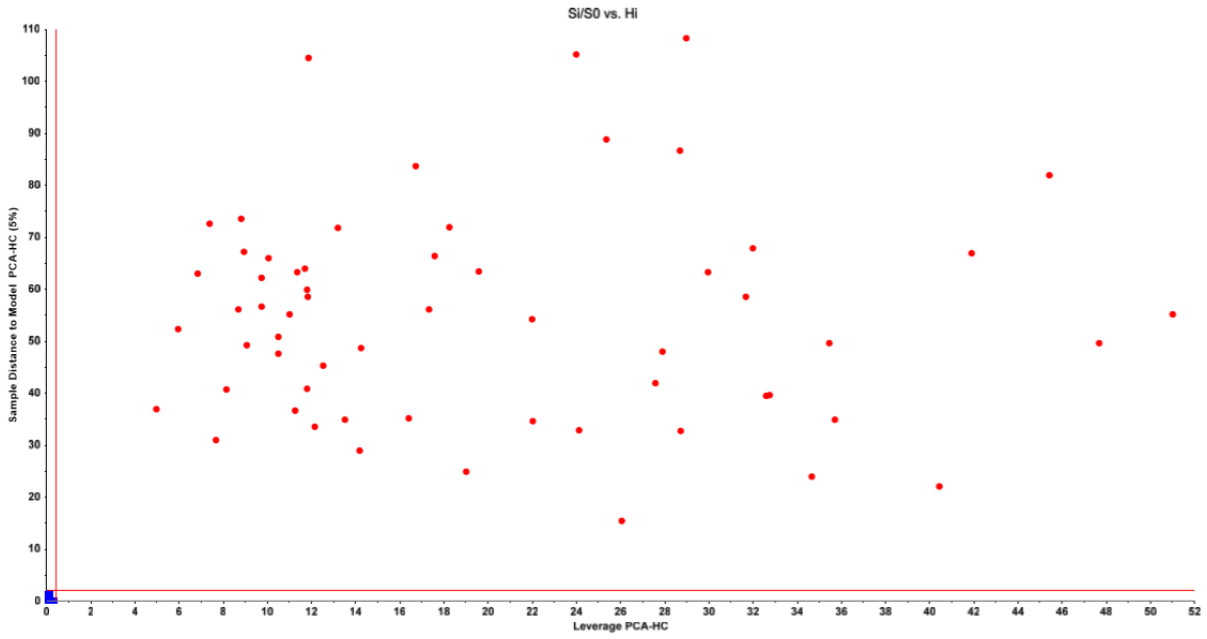

Figure 5. Si/S0 vs Hi plot obtained by SIMCA. SIMCA was performed with 8 symptom domains as modeling/discriminatory variables, namely hostility, psychomotor retardation, excitation, mannerism, SANS total score, formal thought disorders, PANSS negative subscale score and psychosis.

This plot shows the distances of all subjects allocated to the test set to the critical limits of the control class (blue squares) as well as their leverage to the same class. All healthy control subjects were correctly authenticated as belonging to the control target class while no patients with major neuro-cognitive psychosis or deficit schizophrenia intruded into the critical limits of the control class. All patients showed very large distances and leverages toward the class model and centre, respectively.

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) *plus* zPANSSP3 (hallucinations) + zPANNSP6 (suspiciousness) *plus* z score of item 11 of the BPRS (zBPRS11: suspiciousness) *plus* zBPRS12 (hallucinatory behavior) *plus* zBPRS15 (unusual thought content).
Hostility	sum of zPANSSP7 (hostility) *plus* z-score of item 14 on the general psychopathology scale of the PANSS (zPANSSG14: poor impulse control) *plus* zBPRS10 (hostility) *plus* zBPRS14 (uncooperativeness).
Excitement	zPANNSP4 (excitement) *plus* zPANNSP5 (grandiosity) *plus* zBPRS8 (grandiosity) *plus* zBPRS17 (excitement).
Mannerism	zPANNSG5 *plus* zBPRS7 (both mannerism and posturing)
Formal thought disorders	zPANNSP2 (conceptual disorganization) *plus* item 5 of the PANNS negative subscale (PANNSN5: difficulty in abstract thinking) *plus* 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) *plus* zPANSSG7 (reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli and reduced body tone) *plus* 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

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

Table 2. Demographic and clinical data in normal controls and deficit schizophrenia patients

Variables	Controls	Deficit schizophrenia	F/Ψ/X^2	df	ρ
Age (years)	37.9 (10.3)	41.0 (9.6)	3.56	1/172	0.061
Sex (F/M)	18/36	48/72	0.70	1	0.402
Single/Married	23/31	53/65	0.08	1	0.776
Rural/Urban	2/52	16/104	3.73	1	0.054
BMI (kg/m^2)	26.9 (3.8)	26.7 (4.8)	0.07	1/172	0.789
Education (years)	2.85 (0.45)	1.38 (0.9)	133.12	1/172	<0.001
Employment (N/Y)	4/50	98/22	84.66	1	<0.001
Nicotine dependence (N/Y)	37/17	78/42	0.21	1	0.650
SANS total score	1.0 (0.6)	91.1 (16.6)	MWU	-	<0.001
PANSS positive subscale score	7.0 (0.0)	15.3 (6.9)	MWU	-	<0.001
PANSS negative subscale score	7.0 (0.0)	27.8 (7.4)	MWU	-	<0.001
BPRS	18.0 0.0	63.7 14.0	MWU	-	<0.001
HAMA	0.7 (1.3)	23.1 (3.9)	MWU	-	<0.001
HAMD	0.0	29.1 (8.1)	MWU	-	<0.001
Psychosis (z score)	-1.242 (0.083)	0.559 (0.660)	MWU	-	<0.001

Hostility (z score)	-1.027 (0.123)	0.462 (0.868)	MWU	-	<0.001
Excitation (z score)	-1.164 (0.096)	0.524 (0.747)	MWU	-	<0.001
Mannerism (z score)	-1.003 (0.036)	0.451 (0.890)	MWU	-	<0.001
FTD (z score)	-1.200 (0.076)	0.540 (0.710)	MWU	-	<0.001
PMR (z score)	-0.992 (0.127)	0.447 (0.893)	MWU	-	<0.001

All results are shown as mean (SD)

^{A,B,C}: pairwise comparisons among the three subgroups (tested at $p<0.05$)

MWU: Results of Mann-Whitney U test

BMI: body mass index

SANS: Scale for the Assessment of Negative Symptoms; PANSS: the Positive and Negative Syndrome Scale; BPRS: Brief Psychiatric Rating Scale; HAMA/HAMD: Hamilton Depression Anxiety and Depression Rating Scale.

FTD: formal thought disorders; PMR: psychomotor retardation (see table 1 for computation).

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, education.

All significant at $p<0.001$

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	<0.001
	Psychosis	0.789 (0.050)*	15.80	<0.001				
	Hostility	0.450 (0.090)	2.00	0.047				
	Education	-0.620 (0.090)	-5.46	<0.001				
	Sex	0.090 (0.048)	-3.75	<0.001				
2#. PANSSnegative in MNP only	Model				0.710	94.59	3 / 116	<0.001
	Psychosis	0.469 (0.045)	10.44	<0.001				
	Hostility	0.104 (0.034)	3.06	0.003				
	Sex	-0.138 (0.046)	-3.04	0.003				
#3. PANSSpositive in MNP only	Model				0.940	354.60	5 / 114	<0.001
	Psychosis	0.513 (0.063)	8.10	<0.001				
	Excitation	0.243 (0.028)	8.77	<0.001				
	FTD	0.249 (0.050)	4.99	<0.001				
	Age	0.085 (0.017)	4.93	<0.001				
	Hostility	0.124 (0.035)	3.54	0.001				

MNP: Major Neuro-Cognitive Psychosis

HC: healthy controls

FTD: Formal Thought Disorders

PANSS+: positive subscale of the Positive and Negative Syndrome Scale

PANSS-: negative subscales of the Positive and Negative Syndrome Scale

Shown are heteroscedascticity-consistent or robust standard errors (SE) estimated using the HC3 method

Table 5. Results of Exploratory Factor Analysis (EFA)

	MNP + HC	**MNP**
Variables	**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)
	MNP + HC	**MNP**
	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 Kelley's criterion	0.0272 (0.018-0.033) <0.0758	0.0541 (0.038-0.066) <0.0913
Weighted Root mean Square Residual	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 patients with Major Neuro-Cognitive Psychosis (MNP) and one in all subjects combined, that is MNP and healthy controls (HC)

Significant Loadings (>0.5) are shown in bold

CI: confidence intervals

Table 6. Results of Partial Least Squares 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)
Reliability data	**MNP + HC**	**MNP only**
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 (>0.707) are shown in bold