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PREDICTORS OF NEGATIVE SYMPTOM DOMAINS IN OUTPATIENTS WITH SCHIZOPHRENIA: A CROSS-SECTIONAL STUDY

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Abstract

Background: Current research suggests that negative symptoms may not be a unitary construct. Factor analytic studies typically found evidence for a two-factor solution of the negative symptom domain: the expressive and the volitional deficit. This study aimed to investigate whether the two-factor solution of negative symptoms is supported across different instruments of evaluation: PANSS and NSA-16 in outpatients with schizophrenia and to explore the relationship between these domains and sociodemographic, clinical, and metabolic outcomes, routinely assessed in daily practice.Another aim was to determine clinical predictors of negative symptoms domains among these variables.

Materials and methods: 107 patients with schizophrenia were included in this cross-sectional study. The Principal Component Analysis was used to identify negative symptom domains and Spearman's rank correlation coefficient and multiple regression analyses were used to assess the relationship between the negative symptom domains and clinical variables.

Results: PCA indicated a two-component solution explaining 85.2% of the variance for the NSA-16 subscales, reflecting an expressive deficit and an experiential deficit component. Age of onset of the disease and the cognitive deficit were significant predictors of the expressive deficit , body mass index and the number of admissions in the hospital for the experiential deficit.

Conclusions: The current findings indicate that the expressive deficit and the experiential deficit should be considered as distinct domains of the psychopathology and should be rated separately.

Keywords: expressive deficit, experiential deficit, negative symptoms, predictive factors, schizophrenia

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Introduction

Negative symptoms of schizophrenia are recognized as a core feature of the disease and are associated with poor functioning outcomes and a more significant impact on quality of life than other symptoms (Rocca et al., 2014). In the last decade, there has been a growing interest in this category of symptoms because the currently available treatments control the positive symptoms, but the negative symptoms remain an unmet therapeutic target (Remington et al., 2016, Correll et al., 2020, Capatina et al., 2021).

Several studies have made a distinction between primary and secondary negative symptoms. The primary negative symptoms are considered to be the manifestation of the underlying pathophysiology of the disease itself, and the secondary to be the display of another underlying cause. Potential factors determining secondary negative symptoms are positive (e.g., active social avoidance), depressive, extrapyramidal symptoms, social deprivation, drug abuse or substimulation (Kirkpatrick et al., 2017, Bucci & Galderisi, 2017). The distinction between these categories has important implications regarding the treatment since the underlying cause of the secondary negative symptoms might be responsive to available treatments (Foussias et al., 2014, Galderisi et al., 2018, Kirkpatrick, 2014, Kirschner et al., 2017).

An accumulating body of research suggests that negative symptoms may not be a unitary construct. Factor analytic studies typically found evidence for a two-factor solution of the negative symptom domain, one factor representing the expressive deficit and the other one reflecting the volitional deficit (Kaiser et al., 2017, Blanchard et al., 2006). The expressive deficit or diminished expression (DE) consists of blunted affect, alogia, and the volitional deficit or avolition-apathy factor (AA) includes avolition, asociality, and anhedonia. This factorial solution emerged from factor analytic studies, but it is unclear whether these symptoms can be fully reduced to this solution because the genetic, cognitive and neural bases are not fully understood (Galderisi et al., 2013, Liemburg et al., 2013, Strauss et al., 2013, Savill et al., 2016, Xavier et al., 2017, İnce & Üçok, 2018). Findings from neuroimaging studies support different etiologies for the two domains. Dysfunctions in the reward system are common mechanisms for all symptoms in the avolition-apathy domain, but mechanisms underlying each symptom may also be present (Foussian et al., 2008, Kaiser et al., 2017).

On the other hand, no common mechanisms have been described for the diminished expression domain, but for each symptom, functional and structural brain modifications have been found (Kring & Barch, 2014, Mucci et al., 2017). Several studies have tried to identify the clinical implications of this factorial structure which derives from mathematical models (Savill et al., 2016, Kaiser et al., 2017, Ahmed et al., 2018). Literature suggests that the AA domain is associated with worse functional outcomes such as unemployment, a greater number of hospitalizations,

more unsatisfactory instrumental role performance, and family functioning than the DE domain (Vaskinn et al., 2015, Messinger et al., 2011, Galderisi et al., 2018). The DE factor has been associated with impaired neurocognition (Farreny et al., 2013, Chang et al., 2013, Kaiser at al., 2017). Investigating whether the two domains of the negative symptoms relate differently to sociodemographic or clinical variables, level of functioning, or quality of life, can guide the development of future treatment strategies to more specific targets (Strauss et al., 2019, Fervaha et al, 2014, Strauss et al., 2013, Kring & Brach, 2014). Many clinical trials use total negative symptom scores, which could be driven only by one factor, and the responsiveness or unresponsiveness to treatment can be mainly driven by one subdomain (Krynicki et al., 2021, Schooler et al., 2015, Harvey, 2013).

The factorial structure of the negative symptoms has been tested in several studies. However, only a few studies tested these models in patients with primary negative symptoms (Galderisi et al., 2018, Bègue et al., 2020). Given the substantial burden of this category of symptoms regarding functioning and quality of life and the different associations of the two domains of the negative symptoms, we think it is meaningful to investigate the factors predicting each of these domains separately. In our study, we chose as predictors clinical variables commonly assessed in daily practice: baseline characteristics such as age, age of onset, duration of illness, number of admissions in the hospital, dose equivalents of antipsychotics, metabolic outcomes such as body weight, cholesterol, triglycerides, drug-induced extrapyramidal side-effects, and psychiatric symptoms. The reason for choosing these indicators is based on previous studies which indicated some unique associations that are true only for one of the domains. For example, the DE domain has been strongly associated with the neurocognitive deficit, an association that is not sustained for the AA domain. Moreover, the experiential deficit has been associated with more severe psychopathology: longer duration of the disease, younger age of onset, longer duration of untreated psychosis, higher doses of treatment. Also, higher doses of antipsychotic treatment are correlated with a higher rate of metabolic syndrome.

This study aimed to investigate whether the two-factor solution of negative symptoms is supported consistently across the different instruments of evaluation, namely the PANSS negative factor and the NSA-16 in outpatients with schizophrenia with minimal secondary negative symptoms. Furthermore, another aim of the study was to investigate the relationship between negative symptom domains and sociodemographic, clinical, and metabolic outcomes routinely assessed in daily practice and to determine clinical predictors of negative symptoms domains among these variables.

Method

Participants

One hundred seven patients meeting the ICD-10 criteria for schizophrenia were included in this cross-sectional study. The patients were recruited from the Cluj-Napoca Outpatients Psychiatric Clinic and were included in the study after signing the informed consent. The study was approved by the Iuliu Hatieganu University Of Medicine and Pharmacy Cluj-Napoca ethics committee.

Variables

For all participants, data were obtained on the following variables: age, years of education, age of onset and duration of illness, morphometric measures (weight, height, BMI= weight (kg)/height²(m²)), the plasma level of total cholesterol, triglycerides, the dosage of antipsychotic converted into chlorpromazine according to defined daily dose methods (DDD) (Leucht et al. 2016).

Assessment scales

The severity of psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS), the Wallwork five-factor model (Cognitive factor: P2, N5, G11; Positive factor: P1, P3, P5, G9, Excitement factor: P4, P7, G8, G14: Depression factor G2, G3, G6 and Negative factor: N1, N2, N3, N4, N6, G7), Negative Symptoms Assessment Scale-16 (NSA-16), for depression Calgary Depression Scale for Schizophrenia (CDSS) was used and for extrapyramidal symptoms Simpson Angus Scale (SAS) (Wallwork et al., 2012).

For this study, we used both the PANSS and NSA-16 for the measurement of negative symptoms. Because the PANSS negative subscale contains two items (N5 and N7) which are now considered cognitive, we shifted from the classical approach (sum of items N1 to N7) to the five-factor model approach proposed by Wallwork et al., based on prior studies and factorial analysis, which captures more accurately the negative domain (Wallwork et al., 2012). The 16 NSA items load into a 5-factor model represented by: Alogia, Blunted affect, Avolition/Anhedonia, Social withdrawal, and Motor retardation (Axelrod et al.,1993). These factors were used for the purpose of this study.

Inclusion and exclusion criteria

The inclusion criteria for the recruited participants were:

- age between 18 and 60 years
- Schizophrenia diagnosis according to ICD-10 criteria
- clinically stable (defined as those patients who did not require any change in their treatment in the prior three months)

- predominant negative symptoms (the presence of at least 2 negative symptoms of moderate-intensity or at least 1 of moderately severe intensity of the seven negative PANSS subscale items and a restricted severity of symptoms which may contribute to secondary negative symptoms – positive symptoms PANSS positive subscale<19, depression CDSS<6, extrapyramidal symptoms SAS<4) (Rabinowitz et al., 2013).

The participants were excluded if they had comorbidities like substance use disorder, mental retardation, dementia, brain injury, or chronic terminal diseases.

Statistical analyses

The statistical analysis was performed using SPSS 23.0 Windows version. The Principal Component Analysis (PCA) was used to identify negative symptom domains in the broad area defined as negative symptoms. We performed the PCA with varimax rotation and Kaiser normalization for the PANSS items included in the negative factor (N1.N2, N3, N4, N6, G7) and the five domains' scores evaluated by the NSA-16. The five global scores for each domain were selected for the analysis, rather than the 16 items because these domains emerged from previous factorial analyses and met the recommendation regarding the number of subjects and number of factors that enter the analysis. The eigenvalue >1 criterion was used for identifying the number of components extracted. Afterward, individual component scores were calculated and saved for each subject.

Spearman's rank correlation coefficient was calculated between the scores of components of the negative symptomatology, for the PANSS and the NSA-16, and age, years of education, age of onset and duration of illness, BMI, the plasma level of total cholesterol, triglycerides, the dosage of antipsychotic converted into chlorpromazine, PANSS five-factor Wallwork model scores (positive, cognitive, depressive, excitement factors). Statistical significance was considered at $p<0.05$, with Bonferroni correction for multiple correlations. Since 15 variables were assessed, we used the Bonferroni p-value 0.05/15=0.003.

In the next stage, multiple linear regression analyses were run with negative symptom components derived from the PCA of the PANSS negative factor and NSA-16 as dependent variables, and the clinical variables were used as independent variables. The level of significance for the multiple regression analyses was considered 0.05.

Results

One hundred seven consecutive outpatients who met the inclusion criteria were included in the study. The sample was on average 41.1 years old, with a mean

of 12.5 years of education and an average duration of the disease of 13.1 years. Mean BMI of the sample was 26.13 kg/m2, treatment mean dose, in equivalents of Chlorpromazine, was 345.11 and mean PANSS Total score was 70.80 and mean NSA-16 score was 3.46. Patient detailed sociodemographic and clinical characteristics are presented in Table 1.

Table 1. Socio-demographic and clinical data characteristics of the sample (n=107)

Characteristics	Mean values (standard deviations)
Gender, *n* (%) Female	83 (77,58%)
Age, years	41.18(10.30)
Years of education, years	12.54 (4.05)
Age of onset, years	28.14 (3.16)
No. of admissions in the hospital	5.61 (4.07)
Duration of the disease, years	13.12(7.40)
Treatment, equivalents of Chlorpromazine	345.11(145.07)
BMI (kg/m2)	26.13(5.06)
Negative symptoms (NSA-16)	3.46 (0.84)
Alogia (NSA-16)	3.21(0.75)
Blunt affect (NSA-16)	3.56(0.78)
Social withdrawal (NSA-16)	3.34(0.81)
Anhedonia/Avolition (NSA-16)	3.86(1.07)
Motor retardation (NSA-16)	3.35(0.77)
PANSS total (PANSS)	70.80(8.92)
Negative symptoms (PANSS)	3.60 (0.91)
Positive symptoms (PANSS)	15.79 (2.64)
Cognitive symptoms (PANSS)	7.44 (2.22)
Disorganization symptoms (PANSS)	7.41 (1.77)
Depressive symptoms (CDSS)	4.38 (1.07)
Extrapyramidal symptoms (SAS)	2.89 (0.91)

Note: BMI-body mass index, NSA-16 – Negative Symptom Assessment Scale-16, PANSS – Positive and negative syndrome scale, CDSS-Calgary Depression Scale for Schizophrenia, SAS – Simpson-Angus Scale

For the PANSS negative factor, the PCA indicated a two-component solution explaining 70.8% of the variance. The components are represented by Diminished expression (DE) and Avolition/Apathy (AA). DE consists of blunted affect, poor rapport, lack of spontaneity and flow in conversation, and motor retardation. AA consists of emotional withdrawal and passive/apathetic social withdrawal. None of these items loaded highly (>.45) on more than one component (Table 2).

PCA indicated a two-component solution explaining 85.2% of the variance for the NSA-16 subscales, reflecting a DE and an AA component. The DE component includes alogia, blunted affect, and motor retardation, and AA includes social withdrawal and avolition/anhedonia subscales. None of these subscales loaded highly (>.45) on more than one component (Table 2).

Table 2. Component loadings for negative symptom severity scores on the PANSS and on the NSA-16

	Diminished expression	Avolition/Apathy
PANSS		
Blunted affect	**.836**	-.178
Emotional withdrawal	.127	**.900**
Poor Rapport	**.695**	.377
Passive/apathetic social withdrawal	-.275	**.808**
Lack of spontaneity and low of conversation	**.849**	-.011
Motor retardation	**.723**	-.090
Eigenvalues	2.51	1.73
% of variance	41.9%	28.9%
NSA-16		
Alogia	**.748**	.436
Blunted affect	**.783**	.351
Social withdrawal	-.561	**.790**
Avolition/anhedonia	-.631	**.730**
Motor retardation	**.874**	.296
Eigenvalues	2.64	1.61
% of variance	52.9%	32.2%

Note: NSA-16 – Negative Symptom Assessment Scale-16, PANSS – Positive and Negative Syndrome Scale.

No correlation was found between the PANSS components AA and DE and the sociodemographic and clinical measures, as shown in Table 3. For the NSA-DE component, a significant positive correlation was found with the PANSS-Cognitive factor (r=.254, p=.003). The NSA-AA component score had a positive correlation with the number of admissions in the hospital (r=.313, p=.001) and PANSS-Excitement factor (r=.255, p=.003) and a negative correlation with BMI (r=-.299, p=.002). The results of the correlation analyses are presented in Table 3.

Table 3. Correlation between PANSS and NSA-16 factors and socio-demographic and clinical characteristics

Characteristics	**PANSS-DE**	**PANSS-AA**	**NSA-DE**	**NSA-AA**
Age	-.021	-.004	.131	-.083
Years of education	-.235	-.081	-.227	-.190
BMI	.046	-.226	.255	**-.299***
Concentration of serum cholesterol	-.120	-.081	.075	-.054
Concentration of serum triglyceride	-.093	.024	-.093	.011
Age of onset of the disease	.063	-.019	.114	-.154
Duration of the disease	-.087	-.018	.017	.065
No. of admissions in the hospital	.009	.247	-.067	**.313***
Treatment mg/zi Chlorpromazine Equivalents	.098	-.017	.090	.067
PANSS Positive symptoms	-.140	-.035	-.062	-.162
PANSS Cognitive symptoms	.193	.013	**.254***	.061
PANSS Excitement	.087	.233	.073	**.255***
PANSS Depression	-.102	.151	-.197	.192
CDSS score	-.156	.165	-.114	.029
SAS score	-.006	.147	.263	.039

Note*: p*-values are presented in their raw, uncorrected form but statistical significance was considered after Bonferroni correction for multiple correlation and since 15 variables were assessed we used the Bonferroni *p* value

0.05/15=0.003; NSA-16 – Negative Symptom Assessment Scale-16, PANSS – Positive and Negative Syndrome Scale, AA – Avolition/Apathy, DE – Diminished Expression

The multiple regression analyses using the PANSS-DE and for PANSS-AA component scores as dependent variables, and age, years of education, BMI, Cholesterol (mg/dl), Triglyceride (mg/dl), age of onset, duration of the disease, No. of hospitalizations, treatment, PANSS positive, PANSS cognitive, PANSS excitement, PANSS depression, and SAS score, as independent variables resulted in nonsignificant models (PANSS-DE: R^2=.138, *df*=14, F=1.050, *p*=.413; PANSS-AA: R^2=.134, *df*=14, F=1.016, *p*=.445).

The multiple regression analysis using NSA-DE component score, as dependent variable, and as independent variables, the same variables as above, resulted in a significant model that accounted for 26% of the variance (adjusted R^2=.264, *df*=14, F=2.361, *p*<.008). Age of onset of the disease and PANSS-Cognitive factor were significant predictors of the diminished expression dimension, as assessed by the NSA-16.

We used the same regression model as above for the NSA-AA component score. The model was statistically significant and explained 31% of the variance of the Avolition/Apathy dimension (adjusted R^2=.312, *df*=14, F=2.986, *p*<.001). In this model, significant predictors were the BMI and the number of admissions in the hospital. The results of the regression analyses are presented in Table 4.

Table 4. Multiple regression analysis for the NSA-DE and NSA-AA component scores

	Dependent variable NSA-16-DE		**Dependent variable NSA-16-AA**	
Independent variable	**Adjusted R^2**	**Standardized coefficients β**	**Adjusted R^2**	**Standardized coefficients β**
Age	.264	.289	.312	-.128
Years of education		-.091		-.054
BMI		.287		-.320**
Cholesterol (mg/dl)		.065		-.020
Triglyceride (mg/dl)		-.145		-.024
Age of onset		-.316*		.004
Duration of the disease		-.225		-.210
No. of hospitalizations		-.332		.552**
Treatment		-.088		-.003
PANSS positive		-.151		-.103
PANSS cognitive		.303*		-.036
PANSS excitement		-.033		.180
PANSS depression		-.140		.058
SAS		.157		.057

*p<0.05
**p<0.001
Note: BMI-body mass index, NSA-16 – Negative Symptom Assessment Scale-16, PANSS – Positive and negative syndrome scale, SAS – Simpson-Angus Scale, AA – Avolition/Apathy, DE – Diminished Expression.

Discussion

The results of our study complied with previous studies regarding the factorial structure of the negative symptoms (Blanchard et al., 2006, Kaiser et al., 2017, Bègue et al., 2020). The experiential deficit and the emotional deficit were the two dimensions to which the components of negative symptoms were reduced through the principal component analysis. Blunted affect, alogia and motor retardation represent the emotional deficit, and avolition and social withdrawal are included in the experiential deficit (Messinger et al.,2011, Galdarisi et al.,2013, Strauss et al.,2013, Rocca et al.,2014, Galdarisi et al., 2018). Regardless of the scale used for measuring negative symptoms PANSS or NSA-16, both factorial analyses indicated the same structure with two dimensions: AA and DE. The importance of the result that the factorial structure holds across instruments is given by the fact that the PANSS is a widely used instrument in clinical trials and clinical practice, even though it is not a specific scale for negative symptoms. Several authors who reported the same factorial structure concluded that the current use of atypical antipsychotics makes this structure more visible through the low level of extrapyramidal symptoms, while in the past the wide use of classical neuroleptics made this dichotomy imperceptible (Marder et al., 2004, Van Oord et al., 2006, Edgar et al., 2014).

The factorial structure of the negative symptoms could represent a starting point for changing the paradigm for evaluating the response to antipsychotic treatment targeting negative symptoms. Our point of view stands for separate evaluations of the two domains, representing a more accurate assessment. Negative symptoms seen as a unitary construct could lead to missing the improvement in one domain or the other.

We tried to establish if this factorial structure, which is derived from mathematical models, has a clinical importance by correlating the negative symptom domains with clinical variables commonly assessed in daily practice. Our study included patients with a minimal level of secondary negative symptoms to exclude this potential cause of primary negative symptoms and had the primal focus on primary negative symptoms. In our study we have observed a correlation between the expressive deficit and the cognitive deficit, which is an association reported by other authors as well, and not valid for the experiential deficit (Van den Oord et al., 2006, Strauss et al., 2013, Stiekema et al., 2018). As for the experiential deficit, we found a relationship with a high number of admissions in the hospital and with a low BMI. Several studies have reported an association between the experiential deficit and a younger age of onset of the disease, a high number of admissions in the hospital, poor functioning and low quality of life (Kirkpatrick et al., 2014, Galderisi et al., 2018). Contradictory to our results several studies reported an association between a higher BMI and negative symptoms and the proposed explanation for this association derived from the fact that the motivational deficit leads to a lack of

physical activity (Koga et al., 2005). On the other hand we found two previous studies which reported an inverse association between BMI and negative symptoms, but none of them investigated the relationship of BMI with the negative symptom domains (Chen et al., 2014, Mezquida et al., 2018). Reward system dysfunctions have been incriminated for this association. (Kring et al., 2014). We have to mention that a big limitation of our results is the heterogeneity of the antipsychotic treatments, which we couldn't control for. Typical and atypical antipsychotics are the drugs used in the maintenance therapy of schizophrenia. No difference has been reported concerning the incidence of negative symptoms regardless of the class of antipsychotics. However, unfortunately, they come with various side-effects: metabolic syndrome, cardiovascular events, extrapyramidal side-effects, sexual dysfunctions, sedation, and weight gain is frequently reported. (Rocca et al., 2009, Bobes et al., 2010).

Finally, we used regression models to explain the emotional and the experiential deficit. Age of onset of the disease and the cognitive deficit were found to predict the diminished expression dimension and the number of admissions in the hospital and BMI explained 31% of the variance in the apathy/avolition dimension. To our knowledge this is the first study aiming to identify predictive factors of negative symptoms dimensions separately. Previous studies have reported a young age of onset, early onset of illness, cognitive symptoms, general psychopathology as predictors of the broad domain of negative symptoms (Fujimaki et al., 2018, Cuesta et al., 2020, Musket et al., 2020).

Several limitations of our study have to be pointed out. Firstly, the study sample consisted preponderantly of female patients limiting the power to detect gender differences. Secondly the heterogeneity of the treatment was not accounted for restricting our capacity to make a distinction between the efficacy of various treatments. And, finally, we have to mention the small sample size and the restrictive inclusion criteria, which will not permit us to generalize our conclusions to all patients diagnosed with schizophrenia.

Conclusion

The current findings, along with previous research results, indicate that the expressive deficit and the experiential deficit should be considered as distinct domains of negative symptoms and of psychopathology and should be rated separately. The severity of negative symptom domains was found to be predicted by different factors. Increasing our understanding of the variables associated with negative symptom domains may contribute to a valuable rethinking of the approach to therapy for specific symptoms. By combining these two domains the efficacy of treatments might not be visible, since treatments might be targeting only one domain.

Conflict of interest

The authors have no conflict of interest to disclose.

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