ARE NEGATIVE SYMPTOMS IN SCHIZOPHRENIA A DISTINCT THERAPEUTIC TARGET?

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Abstract

Background and aims. The relationship between negative symptoms and cognition in schizophrenia is not clear, inconsistent findings have been reported by multiple authors and meta analyses. The aim of this study was to investigate the relationship between cognition and primary negative symptoms.

Methods. 67 outpatients diagnosed with schizophrenia were evaluated using PANSS and the NSA-16 scale. Correlation and regression analyses were used in the present study to investigate the relationship between the primary negative symptoms and cognition.

Results. No relationship was found between the PANSS Cognitive factor and Negative factor, but when investigating the relationship of the Cognitive PANSS factor with the negative symptoms evaluated with the NSA-16 scale, it was shown that there is a significant association between cognition and motor retardation.

Conclusions. Our study reveals the relative independence of cognitive factor from the global negative domain of the psychopathology, even though the association with motor retardation was clear. These findings also support the need of using appropriate assessment tools in order to gain a more refined understanding of the phenomenology of schizophrenia.

Keywords: schizophrenia, psychopathology, diminished expression, avolition-apathy, cognition

Background and aims

The negative symptoms of schizophrenia have been long recognized to be a central feature of the disorder. Several studies link this feature to the poor outcome of the disease. Also, no effective treatment has been found until now for these particular signs of the disease [1,2,3]. Pharmacological therapies, psychosocial interventions, other biological therapies have been designed for this category of symptoms, some of them with promising results in some small studies, but those results have only been partially replicated in a large cohort of patients [4,5,6]. We address methodological issues for this lack of consistency in the findings. First because of the heterogeneity of the negative symptoms and second because of the overlapping definitions of negative and cognitive symptoms which in fact leads us to the poorly designed measuring tools. Negative symptoms are characterized by a marked reduction in expressivity and goal-directed activities. At present, there is a consensus regarding the factors which constitute the negative symptoms construct and they are represented by flat affect, alogia, anhedonia, social withdrawal and avolition. Also, there are two recognized dimensions of this construct: the expressive deficit and the experiential deficit. Affect flattening and alogia are standing for expressive deficit while anhedonia, social withdrawal, and avolition are components of the experiential deficit dimension [7,8,9]. Another important distinction is made between primary and secondary negative symptoms. Secondary negative symptoms appear due to factors not intrinsically linked to the disease, such as depression and anxiety, social deprivation and drug-related extrapyramidal symptoms, or secondary to positive symptoms like suspiciousness [10,11,12].

Several authors studied the relationship between negative symptoms and cognitive performance with inconsistent findings. Some individual studies reported an association between negative symptoms and cognitive performance, while others not at all; meta-analyses show a small correlation between the two types of symptoms [13,14,15,16,17,18,19]. The variability of the results can be accounted to several factors. Some of them are related to the patient or the disease, like age of onset, the stage of the disease, comorbidities (premorbid personality disorders, substance abuse related disorders) and the others are related to the definitions and measurement scales used to assess these symptoms or inclusion criteria in the trials (distinction between primary and secondary negative symptoms) [20,21]. The most widely used scale to assess symptoms of schizophrenia is the Positive and Negative Syndrome Scale (PANSS), which in its original form has three constitutive factors: positive, negative and general, but some of the items from the negative subscale are actually markers for cognitive performance, as they are assessing abstract thinking deficit, poverty of speech and stereotyped thinking [22]. This is why the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) conferences recommend the use of the five-factor Wallwork model which includes a Cognitive factor as well as a Negative one [23].

The aim of our study is to investigate the relationship between psychopathology assessed with the five-factor PANSS model and primary negative symptoms subdomains using the Negative Symptoms Assessment Scale -16 (NSA-16) in outpatients with schizophrenia. Our hypothesis is that primary negative symptoms subdomains will be associated with the PANSS Negative factor, but there will be no association with the Cognitive factor.

Methods
Participants
The present study is a cross-sectional study and it has been conducted at the Department of Neuroscience, Psychiatric Section, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca. The participants were recruited from the Outpatient Psychiatric Clinic, a sample of 67 consecutive subjects treated here: men and women, who met the criteria for schizophrenia according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), were included in the study. The sampling technique used was the nonprobability total enumerative sampling, in which every subject meeting the criteria of inclusion was selected until the required sample size was achieved.
Measures
The Positive and Negative Syndrome Scale (PANSS)
The general psychopathology was assessed using the PANSS. In the present study, we used the 5-factor

model proposed by the National Institute of Mental Health (NIMH) in the MATRICS consensus Wallwork et al. (2012). This model comprises a Positive Factor composed by P1, P3,P5, G9, a Negative Factor composed by N1, N2, N3, N4, N6, G7, a Cognitive Factor composed by P2, N5, G11, a Depressed factor: G2, G3, G6 and an Excited factor composed by P4, P7, G8 and G14 [23].

16-Item Negative Symptom Assessment (NSA-16)
The NSA-16 was used to assess negative symptoms. This scale uses a 5-factor model to describe these symptoms: 1. Communication, 2. Emotion/Affect, 3. Social involvement 4. Motivation and 5. Motor Retardation. In order to address only primary negative symptoms and to exclude the secondary negative symptoms, this scale was used in conjunction with the PANSS for the positive rating scale, with Calgary Depression Scale for Schizophrenia (CDSS) for the depressive symptoms and with the Simpson-Angus Scale (SAS) for the extrapyramidal symptoms.

Inclusion criteria:
- age between 18-65 years
- outpatients diagnosed with schizophrenia according to ICD-10 Diagnostic Manual
- the patients were stable for at least 3 months from the point of view of the symptoms
- mid-level educational status or above (i.e. successful completion of at least the 8th grade)
- the PANSS Negative scale score higher than the Positive scale score
- the CDSS score lower than 6 (to exclude the depressive symptoms)
- the SAS score lower than 4 (to exclude the extrapyramidal symptoms)

Exclusion criteria:
- Psychiatric comorbidities: mental retardation, dementia, substance abuse related disorders
- History of head trauma
- Chronic disabling diseases like renal, cardiac or hepatic failure, cancer.

The study was approved by the Iuliu Hatieganu University of Medicine and Pharmacy ethics committee and informed consent was obtained from each patient.

Data analysis
The statistical package IBM SPSS v.23 for Windows was used for data management in the present study. Patient characteristics: baseline demographics and clinical characteristics were described using mean and standard deviation for continuous data and percentages for categorical data. The Kolmogorov-Smirnov test was used to check if the data were normally distributed. We used the Pearson's correlation to investigate the relationship between the 5 PANSS factors and the 5 NSA-16 factors, checking for potential confounding effects of gender, age, the age of onset of the disease, the number of admissions in the hospital and treatment dose (equivalents of Chlorpromazine). Multiple regressions models were used

for the significant correlations which were found in the previous stage, in order to further explore the relationship between the variables. The regression analysis was performed using the PANSS factors as dependent variables and the NSA-16 factors as independent variables.

Results

Clinical and sociodemographic characteristics of the study group are presented in Table I.

Results of the correlation analyses between the NAS-16 5 factors and composite score and PANSS 5 factor and composite score are presented in Table II. Bivariate analyses of correlations exhibited a significant association between PANSS Negative factor and NSA-16 Alogia (r=0.722, p=0.000), NSA-16 Blunted Affect (r=0.466, p=0.000), NSA-16 Motor Retardation (r=0.657, p=0.000), NSA-16 Social Withdrawal (r=0.516, p=0.000), NSA-16

composite score (r=0.742, p=0.000) and no association with NSA-16 Anhedonia(r=0.118, p=0.341).

However, the PANSS Cognitive factor was found to have only a marginally significant association with the NSA-16 Motor Retardation factor (r=0.304, p=0.012) and with the NSA-16 Composite score (r=0.264, p=0.031) and was not found to correlate with any other NSA-16 factors.

Negative significant correlation were found between NSA-16 factors and the other PANSS factors: between the PANSS Positive factor and NAS-16 NSA-16 Anhedonia (r=-0.343, p=0.005), NSA-16 Social Withdrawal(r=-0.497, p=0.000), NSA-16 Composite Score (r=-0.308, p=0.011); and between the PANSS Depressed factor and NSA-16 Blunted Affect (r=-0.663, p=0.000), NSA-16 Motor Retardation (r=-0.433, p=0.000), NSA-16 Composite Score(r=-0.554, p0.000); PANSS Excited factor and NSA-16 Anhedonia (r=-0.327, p=0.007).

Table I. Sociodemographic and clinical characteristics of the patients (n= 67).

Sociodemographic and clinical characteristics of the sample (n = 67)	
Gender, (n %)	
Male	16 (23.9)
Female	51 (76.1)
Age, years, mean (SD)	39.78 (12.71)
Education, years, mean (SD)	14.21 (2.20)
Employment status, n (%)	
Employed	18 (26.9)
Unemployed	49 (73.1)
Marital status, single/married, yes/no, n (%)	
Single or divorced/separated	50 (25.4)
Married/stable partner	17 (74.6)
Age of onset of the disease, mean (SD)	25.82(6.87)
Number of admissions in the hospital, mean, (SD)	5.88 (3.55)
Treatment, equivalents of Chlorpromazine, mean (SD)	303.84 (187.82)
Psychopathology	
PANSS, mean (SD)	67.90 (7.96)
PANSS Positive, mean (SD)	7.31 (2.69)
PANSS Negative, mean (SD)	19.91 (3.88)
PANSS Cognitive, mean (SD)	6.67 (1.98)
PANSS Depressed, mean (SD)	6.37 (2.57)
PANSS Excited, mean (SD)	5.48 (1.77)
NSA-16, mean (SD)	53.72(8.36)
NSA-16 Alogia, mean (SD)	9.67(3.03)
NSA-16 Blunted Affect, mean (SD)	10.36(3.27)
NSA-16 Motor Retardation, mean (SD)	6.21(2.02)
NSA-16 Social withdrawal, mean (SD)	7.37 (1.53)
NSA-16 Anhedonia, mean (SD)	20.10 (3.62)

PANSS: Positive and Negative Syndrome Scale.

NSA-16: Negative Symptoms Assessment Scale.

The simple linear regression with PANSS Cognitive factor as the dependent variable and NSA-16 composite score as independent variable confirmed the results of the correlation model (beta-0.264, p=0.31) (Table III). But after introducing in the model the NSA-16 Motor Retardation factor as a second independent variable we noticed that there was no significant association between PANSS Cognitive factor and NSA-16 composite score (beta=0.114, p=0.468) (Table IV) and that the regression coefficient decreased by 43.1%, leading to the fact that the NSA-16 Motor Retardation factor is a confounding factor, which can explain the association between PANSS Cognitive factor and NSA-16 composite score.

The simple linear regression with PANSS Cognitive factor as the dependent variable and NSA-16 Motor Retardation factor as independent variable confirmed the results of the correlation model and of the previous regression model with significant relationship (beta=0.304, p=0.012) (Table V). And when we introduced in the model the patient's age, the age of onset, the number of admissions in the hospital and treatment (equivalents of Chlorpromazine) as covariates we noticed that the association still remained significant (beta=0.254, p=0.033) even though the magnitude of the association was lower after controlling for confounding factors (0.304 vs. 0.255) (Table VI). The regression coefficient decreases by 11.9%. Given the fact that the change in the coefficient is more than 10% we meet the criteria for confounding, so part of the association between PANSS cognitive factor and NSA-16 Motor Retardation factor is explained by treatment (beta=0.268, p=0.05).

Table II. Partial correlations between NSA-16 factors score and PANSS five-factor model scores.

	PANSS Positive		PANSS Negative		PANSS Cognitive		PANSS Depressed		PANSS Excited		PANSS Composite score	
	r	p	r	p	r	p	r	p	r	p	r	p
NSA-16 Alogia	-.167	.178	.722**	.000	.183	137.	-.184	.137	.117	.346	.372**	.002
NSA-16 Blunted Affect	-.071	.567	.446**	.000	.215	.081	-.663**	.000	-.189	.125	-.222	.071
NSA-16 Motor Retardation	.085	.495	.657**	.000	.304*	.012	-.433**	.000	-.037	.768	.198	.107
NSA-16 Anhedonia	-.343**	.005	.118	.341	.191	.122	-.207	.092	-.327**	.007	-.103	.409
NSA-16 Social withdrawal	-.497**	.000	.516**	.000	-.233	.058	-.223	.070	-.177	.151	-.071	.568
NSA-16 Composite Score	-.308*	.011	.742**	.000	.264*	.031	-.554**	.000	-.223	.069	.039	.755

PANSS: Positive and Negative Syndrome Scale.
NSA-16: Negative Symptoms Assessment Scale.
**. Correlation is significant at the 0.01 level (2-tailed), (p<0.01).
*. Correlation is significant at the 0.05 level (2-tailed), (p<0.05).
r- Pearson's partial correlation coefficient.

Table III. Simple linear regression model with PANSS Cognitive factor as dependent variable and NSA-16 composite score as independent variable.

Independent variable	Regression Coefficients	p
	Beta	
(Constant)		.035
NSA-16 Composite Score	.264	.031

NSA-16: Negative Symptoms Assessment Scale.
Beta: linear regression coefficient.
Dependent Variable: PANSS Cognitive.

Table IV. Multiple linear regression models with PANSS Cognitive factor as dependent variable and NSA-16 composite score and NSA-16 Motor Retardation score as independent variables.

Independent variables	Regression Coefficients	P
	Beta	
(Constant)		.017
NSA-16 Composite Score	.114	.468
NSA-16 Motor Retardation	.230	.147

NSA-16: Negative Symptoms Assessment Scale.
Beta: linear regression coefficient.
Dependent Variable: PANSS Cognitive.

Table V. Simple linear regression model with PANSS Cognitive factor as dependent variable and
NSA-16 Motor Retardation score as independent variable.

Independent variable	Regression Coefficients	P
	Beta	
(Constant)		.000
NSA-16 Motor Retardation	.304	.012

NSA-16: Negative Symptoms Assessment Scale.
Beta: linear regression coefficient.
Dependent Variable: PANSS Cognitive.

Table VI. Simple linear regression model with PANSS Cognitive factor as dependent variable and NSA-16 Motor Retardation score as independent variable and age, age of onset of the disease, number of admissions in the hospital and treatment as covariates.

Independent variable	Regression Coefficients	P
	Beta	
(Constant)		.023
NSA-16 Motor Retardation	.255	.033
Age	.120	.590
Age of Onset	-.042	.833
No. of Admissions	.165	.316
Treatment	.268	.050

NSA-16: Negative Symptoms Assessment Scale
Treatment: equivalents of Chlorpromazine
Beta: linear regression coefficient
Dependent Variable: PANSS Cognitive

Discussion

Our results have revealed that negative symptomatology as assessed by the NSA-16 scale has a significant relationship only with the PANSS Negative factor using the Wallwork 5 factor model. We conducted the analysis using this 5-factor model in order to avoid the overlapping of cognitive symptoms and negative symptomatology because in the original PANSS factor model described by Kay at al. (1987) the negative PANSS factor included neurocognitive items such as stereotype thinking and abstract thinking [22,23]. All factors of the NSA-16 alogia, blunted affect, motor retardation, social withdrawal, with the exception of anhedonia, show significant relationships with the negative PANSS factor. The lack of association between the anhedonia NSA-16 factor and the PANSS negative factor which comprises blunted affect, emotional withdrawal, poor rapport, passive apathetic social withdrawal, lack of spontaneity and flow

of conversation and motor retardation, can be explained by fact that only one of the items in the PANSS Negative factor address this symptom, emotional withdrawal. By its definition in the PANSS scale this item is overlapping passive social withdrawal and alogia and is not addressing directly specific areas of interest in the patient's life, but more his general interest and involvement [23].

The small magnitude relationship between the PANSS cognitive factor and the negative symptomatology as assessed by the NSA-16 composite score appears to be explained by the NSA-16 Motor Retardation factor and not by any of the other negative symptoms. This is not entirely surprising given the fact that the items which compose the PANSS cognitive factor are difficulty in abstract thinking, poor attention and conceptual disorganization [23]. Also, the treatment explains part of the variance in the regression model, and it seems plausible that the treatment and its side effects such as sedation, dizziness, drowsiness can be at least partly responsible for a decreased neurocognitive performance [23,24,25].

Our study proves the relative independence of the negative symptomatology from the cognitive performance and from the other aspects of the pathology. Of course in our study there are several methodological caveats that should be mentioned: the sampling technique and size of the sample. The non-probability approach used was more suitable for the purpose of our study in which the focus was to understand the complex relationship between primary negative symptoms and cognitive performance and given the inclusion criteria our results are applicable only to a subpopulation of patients with schizophrenia with predominant primary negative symptoms. Also, only stable patients were evaluated from the point of view of the symptomatology for at least three months, which could imply that our results are not applicable to acute patients. The heterogeneity of the sample from the point of view of the age, education, age of onset of the disease, duration of the illness, heterogeneity of the treatments (type of medication and dose) and potential side effects of each treatment are other limitations of our study.

The strength of this study is the assessment of negative symptomatology with a comprehensive scale NSA-16, which unlike the PANSS covers all the domains of the negative symptomatology: alogia, diminished expressivity, social withdrawal and anhedonia-avolition, the exclusion of the secondary negative symptoms by using the CDSS scale for depressive symptoms, SAS for extrapyramidal and the assessment of the general pathology by using the five-factor PANSS model. But the main limitation of the study is actually the cognitive assessment because the PANSS cognitive factor does not cover the whole range of domains which are impaired in patients with schizophrenia, so the neurocognitive assessment should be widened to include learning and processing speed, attention, working memory. The inconsistency of the results of previous studies

regarding the relationship between negative symptoms and cognitive performance can be explained by the different measuring tools used to assess these symptoms and by the overlapping definition of these constructs. The novel scales for negative symptoms have solved a number of these issues, in particular making a clearer distinction between cognitive performance, disorganization, social functioning and negative symptoms.[25,26] Up to present the research for effective treatments for this particular category of symptoms has not yielded efficient therapies [27,28]. Although there have been some promising results in small trials, the results have not been replicated in large cohorts. The failure to replicate the results could arise from several issues: one concerning the heterogeneity of the negative symptoms and another form using different definitions and measuring tools [29,30].

Conclusions

In conclusion, our study supports the evidence of the relative independence of the negative symptom construct in patients with schizophrenia and also for the need of using appropriate definitions and measuring tools for this dimension of the pathology. First, we need to disentangle whether primary or secondary negative symptoms are addressed and in a similar manner, and there is a need to tailor the interventions specific for the central dimensions of the negative symptoms: expressive deficits and avolition-apathy. Also, the sharpening of the distinction in definition and measurement of this domain of the pathology could further help us elucidate the mechanisms that underlie the formation and the maintenance of these constructs.

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