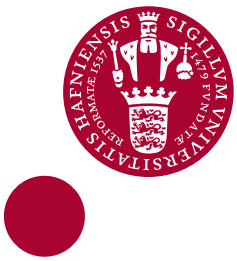

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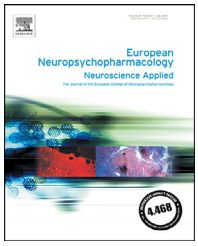

A large European, multicenter, multinational validation study of the Brief Negative Symptom Scale

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Abstract
Negative symptoms represent an unmet need of treatment in schizophrenia. Although a consensus exists on negative symptom construct, and second generation assessment instruments reflecting the consensus are available, studies still rely upon old assessment instruments, that do not reflect recent conceptualizations and might limit progress in the search for effective treatments. This is often the case in the European context, where one of the challenges encountered in designing large studies is the availability of validated instruments in the many languages of the continent. To address this challenge and promote sound research on negative symptoms in Europe, the ECNP Schizophrenia Network coordinated a large multicenter, multinational validation study of the Brief Negative Symptom Scale (BNSS). Clinically-stable subjects with schizophrenia (SCZ, $N = 249$) were recruited from 10 European Countries. Apart from BNSS, subjects were administered the Positive and Negative Syndrome Scale (PANSS) and standardized instruments for depression, extrapyramidal symptoms and psychosocial functioning. Results showed an excellent internal consistency, convergent and discriminant validity of BNSS and replicated a 5 factor-model. A larger number of subjects with predominant negative symptoms, i.e. the target population for clinical trials, was identified by using the BNSS compared to the PANSS. Regression analysis showed that BNSS-avolition, a key negative symptom poorly assessed by PANSS, explained 23.9% of psychosocial functioning, while no combination of the PANSS core negative symptoms showed the same impact on functioning. The study demonstrated that BNSS has substantial advantages with respect to PANSS for the identification of the avolition domain and subjects with predominant negative symptoms.

1. Introduction

Despite several improvements in diagnosis and treatment, deficits in real life functioning, such as independent living, social functioning and remunerative employment, persist in most people with schizophrenia (Fleischhacker et al., 2014; Velthorst et al., 2017).

Negative symptoms represent one the most important contributors to disability (Ergul and Ucok, 2015; Galderisi et al., 2014, 2017, 2018a; Marder and Galderisi, 2017; Quinlan et al., 2014; Strauss et al., 2012b; Ventura et al., 2015). Even low levels of negative symptoms were found to predict real-life functional impairment (Strassnig et al., 2018).

Primary negative symptoms seem to be resistant to most psychopharmacological treatments and rehabilitation interventions (Keshavan et al., 2017; Sarkar et al., 2015; Talpos, 2017; Veerman et al., 2017). Therefore, to date, negative symptoms in schizophrenia remain a significant unmet need (Galderisi et al., 2018a; Marder and Galderisi, 2017).

The heterogeneity of negative symptoms and the limitations in their definition and assessment might have contributed to the lack of significant progress in developing effective therapeutic interventions (Galderisi et al., 2018a).

In 2005, the National Institute of Mental Health (NIMH)-MATRICS consensus statement on negative symptoms defined the constructs to be regarded as part of the negative symptom dimension (Kirkpatrick et al., 2006; Kirkpatrick and Fischer, 2006). The consensus statement identified five main domains of the negative symptoms: anhedonia, avolition, blunted affect, alogia, and asociality (Blanchard and Cohen, 2006; Horan et al., 2011; Kirkpatrick et al., 2006, 2011; Kring et al., 2013; Millan et al., 2014). Subsequently, several factor analysis studies showed that the five constructs listed above clustered into two independent dimensions: avolition/apathy (including avolition, asociality and anhedonia) and expressive deficit (including blunted affect and alogia) (Bischof et al., 2016; Jang et al., 2016; Kimhy et al., 2006; Mucci et al., 2015; Nakaya and Ohmori, 2008; Strauss et al., 2013).

The two-factor solution has been identified in subjects with primary negative symptoms (deficit schizophrenia) and in those with a combination of primary and secondary

negative symptoms, especially after excluding items unrelated to negative symptoms, such as inattentiveness or inappropriate affect (Blanchard and Cohen, 2006; Galderisi et al., 2013a, 2018a; Kimhy et al., 2006; Kirkpatrick et al., 2011; Kring et al., 2013; Mucci et al., 2015; Nakaya and Ohmori, 2008; Strauss et al., 2013).

The two dimensions are independent of medication (Kelley et al., 1999; Tremeau et al., 2008) and have been cross-culturally validated (Bischof et al., 2016; Mane et al., 2014; Mucci et al., 2015; Strauss et al., 2012a).

However, some findings have questioned the two factors solution (Ahmed et al., 2018; Garcia-Portilla et al., 2015; Strauss et al., 2018a, 2018b) in particular, a large, multicentric study in subjects with schizophrenia, using the BNSS to assess negative symptoms, suggested that a five-domain construct might have better fit statistics (Ahmed et al., 2018; Strauss et al., 2018a, 2018b). These latter findings await independent replications.

It is widely recognized that primary negative symptoms are related to the core pathophysiology of schizophrenia and represent the true unmet need of schizophrenia treatment. Secondary negative symptoms, due to other identifiable causes such as positive symptoms, depression, extrapyramidal side effects of antipsychotic drugs or isolation, should thus be excluded in studies aiming to investigate the pathophysiology of negative symptom domains or to test new treatment effects (Carpenter et al., 1985; Galderisi et al., 2018a; Kirschner et al., 2017; Mucci et al., 2017; Treen et al., 2019).

For clinical trials targeting negative symptoms regulatory agencies require the exclusion of main confounding factors, such as high severity of positive and depressive symptoms, as well as parkinsonism (EMA, 2012; Marder et al., 2011). Two main concepts were proposed to address the issue of pseudospecific effects on negative symptoms in clinical trials (Buchanan, 2007; Mucci et al., 2017): the "predominant negative symptoms" (with negative symptoms more severe than positive ones combined with a threshold for depressive symptoms or parkinsonism), and the "persistent negative symptoms" (in which a maximum threshold for positive symptoms, depression and parkinsonism on validated scales is defined). The latter concept also requires a stability over 6 months for the negative symptoms of moderate severity.

The advantages of newly developed scales over those largely used in the past, such as the Positive and Negative Syndrome Scale (PANSS) – Negative subscale, have not been systematically investigated.

The availability of validated state of the art instruments is of crucial importance in large multicenter, multinational studies, which represent the standard context of clinical trials. The validation should also demonstrate that the new scale identifies a comparable or a larger number of subjects with negative symptoms of moderate severity in samples with and without confounding factors (i.e., severe positive symptoms, depression or parkinsonism). Finally, a larger impact on functional outcome of the negative symptoms identified by the new scale, in comparison with those identified by established scales, should be demonstrated.

The purposes of our study were: (1) to validate the BNSS within a large European multicenter, multinational and multilingual study carried out in stabilized subjects with schizophrenia, demonstrating the convergent and discriminant validity with respect to established rating scales to assess negative, positive and depressive symptoms, namely the PANSS and the Calgary Depression Rating Scale for schizophrenia (CDSS); (2) to investigate the frequency of negative symptoms in subjects with and without confounding factors; (3) to evaluate whether the new scale identifies more subjects with core negative symptoms in both groups and (4) to investigate the impact on functional outcome of core negative symptoms as identified by the BNSS or the PANSS, controlling for major confounding factors.

2. Experimental procedures

2.1. Participants

The European College of Neuropsychopharmacology (ECNP) Network on Schizophrenia Study on the Assessment of Negative Symptoms (ENSANeS) was carried out within the activities of the ECNP Schizophrenia Network.

Study participants were recruited among subjects attending the outpatient and inpatient units of the Psychiatric Departments of 12 European centers (see appendix for the list of the centers).

Recruitment was carried out from October 31, 2016 to July 15, 2017.

Inclusion criteria were a diagnosis of schizophrenia according to DSM-IV, confirmed by the Mini Neuropsychiatric Interview-Plus (MINI-Plus), and an age between 18 and 65 years.

Exclusion criteria were: (a) treatment modifications and/or hospitalization due to symptom exacerbation in the last three months; (b) a history of moderate to severe intellectual disability or of neurological diseases; (c) a history of alcohol and/or substance abuse in the last six months; (d) current pregnancy; and (e) inability to provide an informed consent.

The local Ethics Committee of the involved institutions approved the study, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

All participants signed a written informed consent to participate in the study, after receiving a detailed explanation of the study procedures and goals.

2.2. Assessment

2.2.1. Demographic and clinical information

An ad-hoc form was filled in with data on age, gender, race, education (number of years at school), paternal and maternal education (number of years at school), as well as clinical information, such as family history of schizophrenia-spectrum disorders or major mood disorders (bipolar and major depressive disorders with or without psychotic features), duration of illness, number of hospitalization, type and dosage of antipsychotic medications and concomitant medications, using all the available sources of information.

The daily antipsychotic dose was converted to olanzapine equivalents dose based on defined daily doses (DDDs), according to the World Health Organization's Collaborative Center for Drug Statistics Methodology (Leucht et al., 2016).

2.2.2. Psychopathological assessment

The Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011), developed after the MATRICS consensus initiative (Kirkpatrick et al., 2006), was used to assess negative symptom domains. The BNSS is a semi-structured interview with 13 items, organized into 5 negative symptom subscales (anhedonia, asociality, avolition, blunted affect and alogia), plus and additional subscale including

one item assessing the lack of the normal experience of distressing, unpleasant emotions, which was included to help the distinction of primary from secondary negative symptoms (Kirkpatrick et al., 2011; Mucci et al., 2015).

For all items higher scores are associated with greater impairment/presence of symptoms. A scale total score is calculated by summing up the 13 individual items; subscale scores are calculated by summing up the individual items within each subscale. The distress subscale, that quantifies the absence of distress, is treated in the same manner as the other subscales. It is not included in the core negative symptom domains (Kirkpatrick et al., 2006) and does not consistently load on the negative symptom factors (Kirkpatrick et al., 2006, 2011; Mucci et al., 2015; Ahmed et al., 2018).

All non-English versions of the BNSS were developed using the translation-backtranslation method. The translated versions were back-translated into English by a native speaker of the same language in which the scale was developed. The back-translated versions were reviewed and approved by Brian Kirkpatrick or Gregory Strauss who participated in the development of the scale (Kirkpatrick et al., 2011).

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) is one of the most widely used instruments to investigate psychopathology in schizophrenia. The scale includes a subscale for positive symptoms; a subscale for negative symptoms, that includes 2 symptoms recently excluded, i.e., difficulty in abstract thinking and stereotyped thinking, as both of them are part of the cognitive dimension; and a general psychopathology scale with 16 items. According to the five-factor model proposed by Wallwork et al. (2012), we computed the positive dimension by summing up the scores on the items "Delusions" (P1), "Hallucinatory behavior" (P3), "Grandiosity" (P5) and "Unusual thought content" (G9), and the disorganization dimension by summing up the three PANSS items: "Conceptual disorganization" (P2), "Difficulty in abstract thinking" (N5), and "Poor attention" (G11).

To compare the ability of BNSS and PANSS-negative subscale (PANSS-NEG) to identify core negative symptoms and assess the impact of identified negative symptoms on functional outcome we used the 5 subscales of BNSS (alogia, anhedonia, avolition, asociality and blunted affect) and the 5 core negative symptoms of the PANSS (blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, and lack of spontaneity and flow of conversation).

The CDSS (Addington et al., 1993) was used to assess depressive symptoms. Ratings $>$ 6 on the total score indicate clinically significant depression. Non-English versions of the CDSS are available on the official website (http://www.ucalgary.ca/cdss/).

The SHSR (Gerlach et al., 1993) was used to quantify the presence of extrapyramidal symptoms. Clinically significant parkinsonism, which might confound the assessment of negative symptoms, is defined by a "mild" (2) rating on at least three items, or a "mild" rating for tremor or rigidity plus a "mild" rating on at least another item, or a "mild-moderate" (3 or more) rating on at least one item.

Bradykinesia and reduction of facial expression have not been evaluated as confounding factors since they could be an aspect of negative symptoms (Walther and Strik, 2012).

Raters were research staff members of the participating centers. All raters had extensive prior experience in conducting clinical interviews, but the inter-rater reliability across the sites was not evaluated for the present study.

2.2.3. Functional outcome

Personal and Social Performance (PSP) scale (Morosini et al., 2000) was used to evaluate the functional outcome. The PSP is a 0-100 single-item rating scale, in which higher scores indicate better functioning.

2.3. Assessment of frequency of at least moderate severity negative symptoms

As the European Medicines Agency (EMA) guidelines on clinical trial design for negative symptoms require the inclusion of subjects with at least moderate severity negative symptoms, defined on an accepted and validated rating scale, we investigated the frequency of these symptoms using both the BNSS and the PANSS. For the BNSS a score $\geq$ 3 (moderate) was necessary on each of the 5 BNSS subscales for core negative symptoms; for PANSS a score $\geq$4 (moderate) for the following core negative symptoms: Blunted Affect (N1), Emotional Withdrawal (N2), Poor Rapport (N3), Passive social withdrawal (N4) and Lack of Spontaneity (N6).

2.4. Statistical analysis

2.4.1. Internal consistency, convergent and discriminant validity

Data distributions were examined for normality and homogeneity of variance and presence of outliers (subjects whose scores exceeded the 75th or the 25th percentile by 1.5 times the interquartile range).

The demographic and clinical characteristics of study participants were summarized as mean $\pm$ Standard Deviation (SD) and percentages where appropriate.

The construct validity of the BNSS was analyzed by assessing its internal consistency and convergent and discriminant validity, as reported in previous papers (Kirkpatrick et al., 2011; Mucci et al., 2015; Strauss et al., 2012a). Internal consistency across all items of the BNSS was assessed using the Cronbach's alpha value.

Convergent validity was evaluated by examining the association of the BNSS total score with the PANSS negative subscale score, which measures the same construct, and PANSS total score, as the latter includes the negative subscale score and thus should be at least moderately correlated with the BNSS total. Discriminant validity was assessed by examining correlations of the BNSS total score with PANSS positive subscale score and CDSS total score. The Spearman rho was used for correlations as score distributions deviated from normality for the scales. With large sample size ($N > 200$), p values are generally highly significant even for very low correlation coefficients ($r = 0.10$, $p < 0.01$); for this reason, the absolute value of the correlation coefficient is a more conservative estimation of association. Correlation coefficients (in absolute value) $<$ 0.35 are generally considered to represent low or weak correlations, those from 0.36 to 0.67 modest to moderate correlations, and those from 0.68 to 1.0 strong correlations (Evans, 1996).

2.4.2. Factor structure of the BNSS

The factor structure of the BNSS was examined using a confirmatory factor analysis (CFA), in order to evaluate the fit of 4 models of the latent structure of negative symptoms (Figs. S1-S4), according to Strauss et al. (2018a) and Ahmed et al. (2018). The first model (unidimensional model) evaluated whether all five domains (avolition, anhedonia, asociality, blunted affect and alogia) reflected a single negative symptom structure (Fig. S1); the second model (Fig. S2) considered the two negative symptom dimensions: motivation and pleasure (MAP) and expressive deficit (EXP); the third model tested the 5-factor model of negative symptoms (Fig. S3); finally the fourth model (hierarchical model) (Fig. S4) was designed with 5 first-order factors (five negative symptom domains) and 2 second-order factors (MAP and EXP). In all the CFA models the item "Lack of normal distress" was not included because it was not part of the NIMH consensus conference domains, and prior exploratory factor analysis studies reported low communalities for this item (Strauss et al. 2012a; Mucci et al., 2015).

To assess the global fit, the following indices were applied: $\chi 2$ value, the comparative fit index (CFI), the Tucker Lewis index (TLI), the root mean square error of approximation (RMSEA), the Akaike information criterion (AIC) and the sample size-adjusted Bayesian information criterion (BIC). The information criteria, AIC and BIC, are relative fit indices of model parsimony that take into account model complexity based on degrees of freedom. Lower values indicate better model fit. A good fit included a $\chi 2$ value not statistically significant, CFI and TLI values of at least 0.95, RMSEA no greater than 0.08 and lower BIC and AIC values.

2.4.3. Frequency of negative symptoms of at least moderate severity

Frequencies of at least one negative symptom of moderate severity, assessed using the PANSS and the BNSS, were calculated for each BNSS subscale assessing core negative symptoms (i.e., excluding "Distress") and PANSS five core negative symptom items in the whole SCZ sample and in male and female subgroups. Furthermore, subjects were divided in those with and without confounding factors based on the following thresholds: positive symptoms (P1, P3, P5, P6, G9) and disorganization (P2) score >4 on the PANSS, CDSS Total score >6 (Addington et al., 1993) and presence of parkinsonism evaluated with SHRS as outlined above. In these groups, the frequency of at least 1, 2 and 3 negative symptoms of moderate severity was assessed.

2.4.4. Association of core negative symptoms with functional outcome

The association of core negative symptoms with functional outcome was studied using multiple stepwise linear regression.

Separate stepwise multiple regressions were conducted for negative symptoms assessed using the 5 BNSS domains or the 5 core PANSS items as previously defined.

For each regression analysis, the PSP total score was the dependent variable, while the independent predictors were age, gender, education, duration of illness, olanzapine equivalent dose, PANSS disorganization and positive dimensions, depression, SHRS Parkinsonism, and scores on BNSS subscales (anhedonia, avolition, asociality, blunted affect and alogia) or scores on PANSS core negative items (Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive withdrawal and Lack of Spontaneity).

Statistical significance level was set at $p \leq 0.05$ for all tests.

Confirmatory factor analyses (maximum likelihood) were estimated using AMOS 21.0. All other analyses were carried out using SPSS 22 (IBM Corp, Armonk, NY).

3. Results

3.1. Sociodemographic and clinical variables

Two hundred forty-nine subjects with a DSM-IV diagnosis of schizophrenia were enrolled. Data on demographic and illness related variables are provided in Table 1. Enrolled subjects were predominantly males, with a mean age of 37 years, with a mean education level of 13 years, all in a chronic phase of the illness. Almost all subjects with schizophrenia were treated with antipsychotics (94%), mostly with second-generation antipsychotics (Table 1).

Table 1 Demographic and illness-related variables of the study sample (SCZ = 249).

	N	%
Gender § (% males)	158	63.5
Caucasian § (%)	202	81.1
Antipsychotic treatment (%)		
First generation	14	5.6
Second generation	193	77.5
Both	27	10.8
None	13	5.2
N/A	4	0.8
	N	**Mean ± SD**
Age (years)	249	37.3 ± 11.3
Education (completed years)	249	12.9 ± 3.2
Duration of illness (years)	249	12.4 ± 9.1
Olanzapine equivalent dose	232	14.75 ± 9.29
PANSS total	240	61.21 ± 17.20
PANSS positive	244	13.1 ± 5.3
PANSS negative	247	17.54 ± 16.62
PANSS disorganization	246	6.70 ± 2.83
BNSS total	246	26.5 ± 15.5
Anhedonia subscale	248	6.31 ± 4.67
Asociality subscale	249	4.20 ± 2.58
Avolition subscale	249	4.58 ± 3
Blunted affect subscale	249	6.71 ± 4.43
Alogia subscale	249	3.20 ± 3.09
CDSS total	236	3.5 ± 3.6
SHRS Parkinsonism total	248	3.78 ± 5.0
PSP total	234	57.38 ± 15.32

SCZ = subjects with schizophrenia; PANSS = Positive and Negative Syndrome Scale; CDSS = Calgary Depression Scale for Schizophrenia; SHRS = St. Hans Rating Scale; BNSS = Brief Negative Symptom Scale; PSP = Personal and Social Performance scale; § - Data not available for one of the participant centers.

3.2. BNSS internal consistency, construct validity and factor models

Two hundred thirty-six subjects with schizophrenia had a complete data set with respect to the considered measures used to assess BNSS internal consistency, construct validity and its factor structure.

Cronbach's alpha, calculated to examine internal consistency, was 0.94, indicating high internal consistency of BNSS.

BNSS total score was significantly correlated with the PANSS negative subscale score ($\rho = 0.77$) and was moderately associated with PANSS total score ($\rho = 0.57$) in the whole sample of subjects with schizophrenia. Convergent validity was assessed also in the subsample without clinically significant parkinsonism and/or depression including 164 subjects; we found a strong correlation with the PANSS negative subscale score ($\rho = 0.76$) and a moderate association with PANSS total score ($\rho = 0.61$). These correlations confirm that both scales assess a similar underlying construct of negative symptoms (Table 2).

As to the discriminant validity, the BNSS total score showed weak correlations with the PANSS positive subscale ($\rho = 0.21$) and with CDSS total score ($\rho = 0.27$) in the whole sample. In the subsample without confounding factors, the correlation was weak with the PANSS positive subscale ($\rho = 0.23$) and extremely weak with CDSS total score ($\rho = 0.13$).

Table 2 BNSS convergent and discriminant validity (rho-values) in the main sample ($n = 236$) and in the subsample without confounding factors § ($n = 136$).

	BNSS total score (main sample)	*p* value	BNSS total score (subsample without depression and extrapyramidal symptoms)	*p* value
Convergent validity				
PANSS negative subscale	0.77***	<0.0001	0.76***	<0.0001
PANSS total score	0.57**	<0.0001	0.61**	<0.0001
Discriminant validity				
PANSS positive subscale	0.21*	<0.001	0.23*	0.003
CDSS total score	0.27*	<0.0001	0.13	0.08

BNSS: Brief Negative Symptom Scale; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia.
§ Confounding factors = clinically significant levels of depression (CDSS total >6), extrapyramidal symptoms (parkinsonism on the St. Hans scale) and positive or disorganization symptoms (>4 on the PANSS).
With large sample size ($N > 200$), *p* values are highly significant even for very low correlation coefficients ($r = 0.10$, $p < 0.01$); the absolute value of the correlation coefficient is a more conservative estimation of association: *Weak correlation 0.20-0.35; **Moderate correlation 0.36-0.67; ***Strong correlation: 0.68-1.0.

Table 3 Model fit results from CFA on negative symptoms as assessed by the Brief Negative Symptom Scale (BNSS).

Model	Number of distinct parameters to be estimated	AIC	BIC	X^2value (df)	TLI	CFI	RMSEA
1 Factor	36	962.464	966.447	890.5 (54)	.531	.676	.250
2 Factor	37	490.028	494.122	416.0 (53)	.793	.859	.166
5 Factor	46	200.100	205.190	108.1 (44)	.956	.975	.077
Hierarchical	42	200.083	204.730	116.1 (48)	.957	.974	.076

CFA = confirmatory factor analysis; AIC = Akaike information criterion; BIC = Bayesian information criterion; CFI = confirmatory fit index; RMSEA = root mean square error of approximation; TLI = Tucker Lewis index.

Table 4 Frequency of negative symptoms of moderate severity in the whole study sample ($N = 249$).

A) BNSS			B) PANSS		
Negative symptoms	**Frequency**	**%**	**Negative symptoms**	**Frequency**	**%**
At least 1	147	59	**At least 1**	128	51.4
At least 2	107	43	**At least 2**	78	31.3
At least 3	73	29	**At least 3**	68	27.3
Anhedonia	79	31.7	**N/A**		
Blunted affect	90	36.1	**Blunted affect (N1)**	96	38.6
Avolition	100	40.2	**Emotional withdrawal (N2)**	62	24.9
Asociality	70	28.1	**Passive social withdrawal (N4)**	64	25.7
Alogia	60	24.1	**Lack of spontaneity (N6)**	52	20.9
N/A			**Poor rapport (N3)**	31	12.4

BNSS = Brief Negative Symptom Scale; PANSS= Positive and Negative Syndrome Scale.

Results of the CFA analyses are reported in Table 3. The 1-factor and 2-factor models provided poor fit, while the 5-factor model and the hierarchical model provided the best fit, with a small advantage of the 5-factor fit.

3.3. Frequency of negative symptoms of at least moderate severity

Frequency of at least moderate severity (≥3) negative symptoms for the five BNSS subscales in the whole sample are presented in Table 4A. One hundred and forty-seven subjects (59%) had a score ≥3 for at least one negative symptom on the BNSS scale. Frequency of the negative symptoms of moderate severity (score ≥4), evaluated using PANSS five core items is reported in the Table 4B: 128 subjects (51.4%) showed at least one negative symptom of moderate severity. The frequency of each negative symptom was systematically higher using the BNSS versus the PANSS (Table 4A and B).

The frequency of at least moderate severity negative symptoms was higher in males than in females using either the BNSS or the PANSS (Tables 5A and 5B).

The frequency of negative symptoms of moderate severity in subjects with and without confounding factors is reported in Table 6 A and B, respectively. In both subgroups, BNSS identified more subjects with at least 1 or 2 negative symptoms than the PANSS; the difference between the

Table 5A Frequency of at least moderate severity negative symptoms using the Brief Negative Symptom Scale (BNSS) in the whole study sample and in male and female subsamples.

BNSS subscale	Frequency in the whole sample: *N* (%)	Frequency in males (M) and females (F): *N* (%)
Anhedonia	79/249 (31.7)	M: 64/158 (40.5) F: 15/91 (16.5)
Asociality	70/249 (28.1)	M: 54/158 (34.2) F: 16/91 (17.6)
Avolition	100/249 (40.2)	M: 70/158 (44.3) F: 30/91 (33)
Blunted affect	90/249 (36.1)	M: 69/158 (43.7) F: 21/91 (23.1)
Alogia	60/249 (24.1)	M: 45/158 (28.5) F: 15/91 (16.5)

Table 5B Frequency of the different negative symptoms with at least moderate severity using the Positive and Negative Syndrome Scale (PANSS) in the whole study sample and male and female subsamples.

PANSS item	Frequency in the whole sample: *N* (%)	Frequency in males (M) and females (F): *N* (%)
Blunted affect (N1)	96/249 (38.6)	M: 73/158 (46.2) F: 23/91 (25.3)
Emotional withdrawal (N2)	62/249 (24.9)	M: 46/158 (29.1) F: 16/91 (17.6)
Poor rapport (N3)	31/249 (12.4)	M: 23/158 (14.6) F: 8/91 (8.8)
Passive social withdrawal (N4)	64/249 (25.7)	M: 49/158 (31) F: 15/91 (16.5)
Lack of spontaneity (N6)	52/249 (20.9)	M: 39/158 (24.7) F: 13/91 (14.3)

Table 6 Frequency of negative symptoms of moderate severity in the subgroups with and without confounding factors such as positive symptoms, disorganization, depression and extrapyramidal symptoms.

	A) Subgroup with confounding factors ($N = 113$)		B) Subgroup without confounding factors ($N = 136$)	
	BNSS *N* (%)	PANSS	BNSS *N* (%)	PANSS
At least 1 negative symptom	79 (69.9)	74 (65.5)	68 (50)	54 (39.7)
At least 2 negative symptoms	58 (51.3)	47 (41.6)	49 (36)	31 (22.8)
At least 3 negative symptoms	44 (38.9)	40 (35.4)	29 (21.3)	28 (20.6)

BNSS = Brief Negative Symptom Scale; PANSS = Positive and Negative Syndrome Scale.

scales was negligible for the identification of subjects with at least 3 negative symptoms (i.e., the most severely affected subjects).

3.4. Impact of negative symptoms on functional outcome

Table 7 illustrates the results of the multiple stepwise regression analyses on PSP total score.

When the negative symptoms assessed using the five BNSS subscales were entered among the independent predictors (Table 7A), the model was significant (adjusted $R^2 = 0.387$, $p < 0.00001$) and accounted for approximately 39% of the variance of PSP total score. Lower functional outcome was predicted by higher avolition scores ($\beta = -0.404$, $p < 0.00001$), which accounted for most of the explained PSP variance (29.3/39%), higher disorganization and positive dimension scores ($\beta = -0.193$, $p = 0.009$, $\beta = -0.154$, $p = 0.026$, respectively) and male gender ($\beta = 0.134$, $p = 0.015$). The other independent variables (age, education, duration of illness, olanzapine equivalent dose, the other negative symptoms, depression, SHRS Parkinsonism) did not enter the regression equation.

The regression model was also significant when the negative symptoms were evaluated using PANSS five core items (adjusted $R^2 = 0.378$, $p < 0.00001$) and accounted for approximately 38% of the variance of functional outcome (Table 7B). In the regression analysis, lower functional outcome was predicted by higher scores on disorganization dimension ($\beta = -0.238$, $p = 0.001$), which accounted for most of the explained PSP variance (21.4/37.8%), Passive

Table 7 Results of multiple regression analyses on Personal and Social Performance (PSP) total score in subjects with schizophrenia to investigate the impact of negative symptoms on functioning.

A) Negative symptom domains from the BNSS				
Variables entering the equation	***R* square change**	**Beta**	***T***	***P***
BNSS avolition	0.297	−0.404	−6.378	<0.00001
PANSS disorganization	0.071	−0.193	−2.628	0.009
Gender	0.017	0.134	2.449	0.015
PANSS positive	0.015	−0.154	−2.239	0.026
Variables not entering the equation	***R* square change**	**Beta**	***T***	***P***
BNSS anhedonia	NA	0.050	0.639	0.524
BNSS asociality	NA	−0.008	−0.100	0.920
BNSS blunted affect	NA	−0.115	−1.630	0.105
BNSS alogia	NA	0.022	0.325	0.746
Age	NA	0.005	0.089	0.930
Education	NA	0.087	1.515	0.131
Duration of illness	NA	0.016	0.285	0.776
Olanzapine equivalent dose	NA	−0.027	−0.480	0.632
Depression	NA	0.035	0.609	0.543
SHRS Parkinsonism	NA	−0.060	−1.049	0.295
The regression model was significant (adjusted $R^2 = 0.387$, $p < 0.00001$) and accounted for approximately 39% of the PSP total variance.				
B) Negative symptom domains from the PANSS				
Variables entering the equation	***R* square change**	**Beta**	***T***	***P***
PANSS disorganization	0.218	−0.238	−3.245	0.001
Passive social withdrawal (N4)	0.105	−0.232	−3.529	0.001
Poor rapport (N3)	0.023	−0.179	−2.722	0.007
Gender	0.017	0.134	2.398	0.017
PANSS positive	0.015	−0.156	−2.221	0.027
Variables not entering the equation	***R* square change**	**Beta**	***T***	***P***
PANSS blunted affect (N1)	NA	−0.024	−0.310	0.756
PANSS emotional withdrawal (N2)	NA	−0.099	−1.138	0.257
PANSS lack of spontaneity (N6)	NA	0.094	1.197	0.233
Age	NA	−0.052	−0.908	0.365
Education	NA	0.105	1.788	0.075
Duration of illness	NA	−0.041	−0.691	0.491
Olanzapine equivalent dose	NA	−0.057	−1.014	0.312
Depression	NA	0.021	0.351	0.726
SHRS Parkinsonism	NA	−0.075	−1.298	0.196
The regression model was significant (adjusted $R^2 = 0.378$, $p < 0.00001$) and accounted for approximately 38% of the PSP total variance.				

In A) the 5 subscales of the Brief Negative Symptom Scale (BNSS) were included as independent predictors, while in B) the 5 core negative symptom items of the Positive and Negative Syndrome Scale (PANSS) were included. The negative standardized beta for all continuous independent predictors indicates that higher severity of psychopathology is associated with lower scores on PSP (i.e., poorer functioning). Male gender was associated with lower PSP scores than female gender.

Social Withdrawal ($\beta = -0.232$, $p = 0.001$), Poor Rapport ($\beta = -0.179$, $p = 0.007$), male gender ($\beta = 0.134$, $p = 0.017$) and higher positive scores ($\beta = -0.156$, $p = 0.027$). The two negative symptoms accounted for about 12% of the PSP variance. The other independent variables (age, education, duration of illness, olanzapine equivalent dose, the other negative symptoms, depression and SHRS Parkinsonism) did not enter the regression equation.

3.5. Control analyses

As control analyses, to evaluate the comparability of BNSS across countries/languages, we assessed the presence of a center effect on: (1) the frequency of negative symptoms, as evaluated by the BNSS and PANSS; (2) the correlations of the BNSS and PANSS core negative symptom totals; (3) the correlations of the PSP total score with the BNSS and PANSS core negative symptom total scores. As reported in Table S1 of the supplemental materials, in all centers the frequency of negative symptoms of at least moderate severity was higher using the BNSS than the PANSS, except in two centers in which it was comparable. All centers showed a positive correlation between BNSS and PANSS core negative symptom totals >0.70 (Table S2). As to the correlations of the PSP total with both BNSS and PANSS core negative symptoms (Table S3), all centers showed a negative association, although in some centers the association was not significant. However, the difference between the highest and lowest correlation coefficients

was not significant ($z = 2.78/2.05$; $p > 0.05$ Bonferroni corrected).

4. Discussion

Main results of our study included: (1) the demonstration of high internal consistency, convergent and divergent validity of the BNSS in a large sample of subjects with clinically stable, chronic schizophrenia, within a multicenter, multinational, large European study; (2) the validation of the 5-factors structure of negative symptoms as assessed by the BNSS; (3) the demonstration that BNSS consistently identifies more subjects with negative symptoms compared to PANSS, in the whole sample, as well as in males and females, and in subjects with and without confounding factors; (4) the demonstration that avolition, a negative symptom domain poorly assessed by PANSS, has a larger impact on a measure of functional outcome (the PSP total score) as compared with the core negative items of the PANSS.

While the majority of the studies evaluated negative symptoms with the items of the PANSS negative subscale or with the SANS (Galderisi et al., 2013b, 2018a; Rocca et al., 2014; Lincoln et al., 2017; Strassnig et al., 2018), in our study we assessed the severity of negative symptoms with BNSS. The latter instrument has several advantages: it provides a rapid assessment of negative symptoms based on a semi-structured interview and does not include symptoms formerly regarded as part of the negative dimension but now clearly identified as aspects of other dimensions, such as the cognitive or depressive one (Bucci and Galderisi, 2017). The results of this multicenter, multinational study, in line with other studies, showed high internal consistency (Strauss et al., 2012c) and validity of the BNSS across different countries/languages (Ahmed et al., 2018). Furthermore, we confirmed the 5-factor structure of negative symptoms in agreement with Strauss et al. (2018a) and Ahmed et al. (2018).

Our results demonstrated a greater sensitivity of BNSS in the detection of negative symptoms compared to the PANSS: in particular, the PANSS has a smaller number of items to evaluate subdomains of negative symptoms and does not contain items for an adequate evaluation of anhedonia and avolition (Marder and Galderisi, 2017).

Our data confirm that the BNSS, developed specifically following the NIMH-MATRICS Consensus Development Conference on negative symptoms (Kirkpatrick et al., 2006; Kirkpatrick et al., 2011), may represent a valuable tool for a more accurate evaluation of negative symptoms, compared to the PANSS.

Our criteria for selection of the sample of subjects without confounding factors were in line with the EMA guidelines on drug approval for negative symptoms, requiring that major confounding factors, i.e. extrapyramidal symptoms and depression, have to be excluded and were also in line with the concept of "Predominant negative symptoms" (i.e., excluding positive symptoms from moderate-severe to extremely severe). In this sample, representing the ideal target of clinical trials on negative symptoms, the BNSS demonstrated advantages over the PANSS, as it identified a larger number of subjects with at least moderate severity negative symptoms. These findings are probably related to the identification of subjects with moderate severity of avolition and anhedonia, which are not assessed by the PANSS. Our results also demonstrated that the advantage of the BNSS was larger for subjects with only 1 or 2 moderate severity negative symptoms, suggesting the possibility to lower the entry cutoff for clinical trials. Of course, this implication needs further testing.

As to the impact of negative symptoms on patients' functional outcome, several studies confirmed that in particular the avolition\asociality factor (including all or some of the domains of avolition, asociality and anhedonia) is a stronger predictor than the expressive deficit factor, which includes alogia and blunted affect (Fervaha et al., 2013; Galderisi et al., 2014; Green et al., 2012; Harvey et al., 2017; Rocca et al., 2014; Ventura et al., 2015). However, the factor extracted using the PANSS often included items which are not core negative symptoms and might overlap with positive and disorganization dimensions or cognitive dysfunctions (e.g., G16-Active social avoidance that rates the avoidance of social contacts due to positive symptoms or anxiety, or G13-Avolition which rates the indecisiveness in engaging in goal-directed action due to disorganization or cognitive impairment). In our study, we decided to evaluate the impact of core negative symptom domains, assessed either by BNSS or PANSS, to investigate whether the newer scale identified one or more domains with larger functional impact. Our results showed that the avolition domain assessed by BNSS was more efficient than any combination of PANSS-assessed negative symptom domains in predicting functional outcome. The avolition domain consistently loaded on the avolition/apathy factor (Kirkpatrick et al., 2011; Mucci et al., 2015; Strauss et al., 2012a) and represents the domain with the largest impact on outcome. The two domains assessed by PANSS which entered the regression equation were Passive social withdrawal and Poor rapport. The first one, which consistently loaded on the avolition/apathy factor in previous studies, explained the largest proportion of variance (though half the proportion explained by the BNSS-assessed avolition), while the expressive-related domain, Poor rapport, only explained a small proportion of the PSP variance (about 2%).

This finding, together with the identification by BNSS of a larger number of subjects with unconfounded negative symptoms, has implications for the choice of the assessment instrument in clinical trials devoted to the development of innovative treatments for negative symptoms. Avolition is poorly defined using the PANSS: in fact, only N4-Emotional withdrawal assesses the level of interest and engagement in goal-directed activities, as inferred by the behavior of the subject. Instead, BNSS has 2 items assessing both behavior and internal experience, thus capturing the nuclear aspect of avolition that is the lack of motivation and interest for initiation and maintenance of goal-directed behavior (Galderisi et al., 2018a).

Reaching a deeper understanding of the negative symptom constructs could contribute to develop personalized treatment strategies aimed at improving functioning in subjects with schizophrenia. Until now, both pharmacological and psychotherapeutic options to treat negative symptoms have been unsatisfactory (Galderisi et al., 2018a; Keshavan et al., 2017; Sarkar et al., 2015; Talpos, 2017; Veerman et al., 2017).

The results of our study should be considered in the light of some limitations. First, we cannot make inferences on the direction of the observed effects due to the cross-sectional design; second, we cannot disentangle the role of neurocognitive deficits on functioning, a relationship that is widely reported in the literature (Galderisi et al., 2014, 2018a, 2018b; Leifker et al., 2009), due to the lack of a neurocognitive assessment; third, the experimental sample consisted of chronic and clinically stable subjects with schizophrenia and did not include patients in the acute phase or earlier in the course of the illness, thus preventing the generalizability of our findings.

The inter-rater reliability across-centers was not assessed for this study. However, as reported in the Supplementary materials, all centers involved in this study showed comparable data and results concerning the frequency of negative symptoms of at least moderate severity, the correlations between BNSS and PANSS, and the correlations of the PSP total with both BNSS and PANSS, thus suggesting a high reproducibility and reliability of the assessments.

In conclusion, our study supports the validity of the BNSS, within a large European multicenter, multinational, multilingual study. The results show that BNSS, with respect to the core PANSS negative symptoms, identifies a larger number of subjects with at least one or with at least two negative symptoms of moderate severity, particularly in subjects without confounding factors. Finally, avolition, as identified by BNSS, has a stronger association with functional outcome, with respect to any combination of core negative symptoms identified by PANSS. Our findings support the use of the BNSS in future clinical trials focusing on negative symptoms.

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CRediT authorship contribution statement

Armida Mucci: Conceptualization, Data curation, Supervision, Validation. **Annarita Vignapiano:** Conceptualization, Data curation, Supervision, Validation. **István Bitter:** Conceptualization, Data curation, Supervision, Validation. **Stephen F. Austin:** Conceptualization, Data curation, Supervision, Validation. **Camille Delouche:** Conceptualization, Data curation, Supervision, Validation. **Sonia Dollfus:** Conceptualization, Data curation, Supervision, Validation. **Andreas Erfurth:** Conceptualization, Data curation, Supervision, Validation. **W. Wolfgang Fleischhacker:** Conceptualization, Data curation, Supervision, Validation. **Giulia M. Giordano:** Conceptualization, Data curation, Supervision, Validation. **Igor Gladyshev:** Conceptualization, Data curation, Supervision, Validation. **Birte Glenthøj:** Conceptualization, Data curation, Supervision, Validation. **Karoline Gütter:** Conceptualization, Data curation, Supervision, Validation. **Alex Hofer:** Conceptualization, Data curation, Supervision, Validation. **Jan Hubeňák:** Conceptualization, Data curation, Supervision, Validation. **Stefan Kaiser:** Conceptualization, Data curation, Supervision, Validation. **Jan Libiger:** Conceptualization, Data curation, Supervision, Validation. **Ingrid Melle:** Conceptualization, Data curation, Supervision, Validation. **Mette Ø. Nielsen:** Conceptualization, Data curation, Supervision, Validation. **Oleg Papsuev:** Conceptualization, Data curation, Supervision, Validation. **Janusz K. Rybakowski:** Conceptualization, Data curation, Supervision, Validation. **Gabriele Sachs:** Conceptualization, Data curation, Supervision, Validation. **Alp Üçok:** Conceptualization, Data curation, Supervision, Validation. **Pawel Wojciak:** Conceptualization, Data curation, Supervision, Validation. **Silvana Galderisi:** Conceptualization, Data curation, Supervision, Validation.

Conflict of interest

S. F. Austin reported no conflicts of interest. I. Bitter has been, in the last 5 years, advisory board member/consultant/lecturer or received research support from Angelini, Eli Lilly, EGRIS, Janssen, Lundbeck, Pierre –Fabre, Richter and Servier. C. Delouche reported no conflicts of interest. S. Dollfus received honoraria as expert/consultant by Fabre, Gedeon; invited Conferences: Lundbeck, Otsuka, Janssen, and has contracts with Prophase MedAvances and NeuroCogTrials. A. Erfurth received consulting fees and/or honoraria for speeches within the last three years from Angelini, AOP Orphan, AstraZeneca, Eli Lilly, Ferrer, Germania, GlaxoSmithKline, Janssen, Krka, Lundbeck, Neuraxpharm, and Pfizer. W. W. Fleischhacker received grants and personal fees from Janssen, Lundbeck, Boehriger-Ingelheim, and Otsuka and personal fees from Teva, Dianippon-Sumitomo, Allergan, Gedeon Richter, and Recordati. S. Galderisi received honoraria, advisory board or consulting fees from the following companies: Gedeon-Richter, Janssen Pharmaceuticals, Janssen-Cilag Polska Sp. z o.o, Otsuka, Pierre Fabre and Sunovion Pharmarmaceuticals. I. Gladyshev received honoraria from Organica. G.M Giordano reported no conflicts of interest. B. Glenthøj is the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), which is partially financed by an independent grant from the Lundbeck Foundation, based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. Her group has also received a research grant from Lundbeck A/S for another independent investigator-initiated study. All grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them. K. Gütter reported no conflicts of interest. A. Hofer received consulting fees by AOP Orphan, Janssen-Cilag, Lundbeck and reimbursements for travel and meeting expenses by Janssen-Cilag, Lundbeck, Pfizer. He has contracts with Boehringer-Ingelheim and NeuroCogTrials. J. Hubeňák received.travel and meeting reimbursement from Lundbeck, Servier and Angelini and also received honoraria for speeches from Angelini and Servier within the last two years. S. Kaiser has received speaker honoraria from Recordati and Lundbeck as well as royalties for cognitive training software from Schuhfried. J. Libiger received travel grant from Gedeon Richter. I. Melle reported no conflicts of in-

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The following researchers collaborated to the study:

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Appendix. List of the centers included in the study

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- Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland.
- Department of Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland.
- Department of Socio-clinical and Biological Research of Psychotic spectrum disorders, Moscow Research Institute of Psychiatry, Moscow, Russia.
- Istanbul Faculty of Medicine, Istanbul University, Psychotic Disorders Research Program, Istanbul, Turkey.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.05.006.

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