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Specificity and sensitivity of the Self-assessment of Negative Symptoms (SNS) in patients with schizophrenia☆

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ABSTRACT

Objectives: Negative symptoms can be present at any stage of schizophrenia but their evaluation remains challenging. Self-evaluations may be particularly useful in screening negative symptoms quickly and effectively. The purpose of this study was to determine the sensitivity, the specificity, and the threshold beyond which the negative symptoms are considered pathological in a comparative study between patients with schizophrenia and healthy subjects using the Self-assessment of Negative Symptoms (SNS).

Methods: One hundred and nine patients with schizophrenia and schizoaffective disorders (DSM-5) and 99 healthy controls were included and evaluated with the SNS. AUROC analyses were performed to assess the discriminant performance of the SNS scale for screening negative symptoms in the whole sample of patients but also in 2 patient sub-samples without high scores of depression or negative symptoms.

Results: The SNS (AUROC = 0.942 ± 0.046; $p < 0.001$) appears to be an appropriate screening tool for distinguishing between SZ and HC with a threshold value of 7, and the sensitivity and specificity were 92.7% (95CI = [86.1–96.8]) and 85.9% (95CI = [77.4–92.1]) respectively. A threshold at 7 was also observed in the samples without patients with high level of depressive or negative symptoms.

Conclusion: These results indicate that SNS might be a valuable tool for screening negative symptoms in clinical practice regardless the level of depressive and negative symptoms. Further studies using SNS in subjects at high risk for psychosis or with a first psychotic episode would be useful in the detection of negative symptoms.

1. Introduction

Negative symptoms are found in patients with schizophrenia at any stage. They can be the first symptoms during the prodromal phase (Piskulic et al., 2012), they can be observed during a first episode of schizophrenia (Galderisi et al., 2013) or during the late stage of illness, they can persist despite the improvement of positive symptoms, and they are often responsible for impaired social functioning and quality of life (Moller et al., 2000; Delamillieure et al., 2005). The detection and evaluation of negative symptoms remains challenging despite their frequency, at all stages of illness. Recent tools including the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al., 2011) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) have improved the evaluation of negative symptoms. However these scales are based on observer ratings and aim to quantify the severity of negative symptoms thanks to a semi-structured interview with prompts and queries. Therefore, these scales do not allow patients self-assessing their feelings and experiences even if ratings of internal experiences regarding asociality and avolition are however considered. Analysis of the scales highlights the predominance of hetero-assessments over self-assessments and a consensus supports five negative symptom dimensions (affective flattening, alogia, anhedonia, social withdrawal and avolition) (Lincoln et al., 2016; Kirkpatrick et al., 2006; Strauss et al., 2018a). Recently, two scales have been developed to

☆ SNS is available in French, Arabic, Chinese (Beijing), Czech, Danish, English US, German, Italian, Hebrew, Hungarian, Luthuanian, Norwegian, Polish, Russian, Spanish, Turkish at the time of the publication, and can be obtained from the corresponding author by emailing to dollfus-s@chu-caen.fr. The corresponding author is also available to validate a back translation from any languages.

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specifically evaluate negative symptoms by self-rating. One is the Motivation and Pleasure Scale–Self-Report (MAPSR), an 18-item self-report version of the CAINS Motivation and Pleasure subscale (Llerena et al., 2013). Another one is the Self-assessment of Negative Symptoms (SNS) for which patients with schizophrenia have demonstrated the ability to complete its reliably and consistently (Dollfus et al., 2016; Hervochon et al., 2018). The SNS has several advantages. It is a short 20 item scale with short and easily understandable sentences, and the three response choices allow a fast self-evaluation in under five minutes. The five negative symptom dimensions are self-evaluated and one strength of the scale is that patients are able to express their deficits in motivation and pleasure as well as their loss of emotion independently of depressed mood (Dollfus et al., 2016). Moreover, the first validation study for the SNS revealed a good test-retest reliability, good internal consistency, tight convergent and divergent validities. A factor analysis on the 5 sub-scores revealed 2 factors, 'motivation' and 'emotion' ones in accordance with the literature (Dollfus et al., 2016) although the hierarchical model reported by Strauss (Strauss et al., 2018b) with the five subscales representing separate dimensions influenced by two higher-order factors (motivation and emotion) was not tested. A second study in another French population confirmed these good psychometric properties (Hervochon et al., 2018).

The purpose of this study was to evaluate the sensitivity and specificity of the SNS in order to determine the suitability of SNS as a screening measure. We hypothesize that some negative symptoms can be revealed by the SNS in healthy subjects and so their comparison with patients can allow us to determine the threshold beyond which the symptoms are considered as pathological in patients with schizophrenia. Consequently, we used the SNS to conduct a comparative study between patients with schizophrenia and healthy subjects.

2. Materiel and methods

2.1. Population

Ninety nine healthy controls (HC) with no history of psychiatric disorders or substance abuse and with a Beck Depression Inventory (BDI) score (Beck et al., 1996) under 4 were included along with 109 patients diagnosed with schizophrenia or schizoaffective disorders (SZ) based on the DSM-5 (Diagnostic and Statistical of Manual Disorder 5th edition) with no history of substance abuse. Forty-nine patients were recruited from the university hospital (Caen, France) and 60 came from the clinic affiliated with the University of Medicine of Rouen (France), both groups participated in previous validation studies of the SNS after providing informed consent (Dollfus et al., 2016; Hervochon et al., 2018). So, both data from both studies were gathered and reanalyzed in the present study.

2.2. Symptom assessments

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) is a 18-item clinician-rated measure that assesses clinical psychiatric symptoms. Items are rated on a 7-point Likert scale, ranging from 1 (not present) to 7 (extremely severe). The total score reflects symptom severity, while the subscores reflect the positive (conceptual disorganization, hallucinations, unusual thought content) and negative components (emotional withdrawal, motor retardation, and blunted affect).

The Scale of Assessment of Negative Symptoms (SANS) (Andreasen, 1989) had 25 items divided into five subscales (Affective Flattening or Blunting, Alogia, Avolition–Apathy, Anhedonia–Asociality, and Attention) for which global severity is rated from 0 to 5, with higher scores for the more severe dimension.

The SNS is a self-assessment of 20 items, allowing patients to evaluate themselves on the five dimensions of negative symptoms (Dollfus et al., 2016). Each item is scored as either 2 (strongly agree), 1 (somewhat agree), or 0 (strongly disagree). The number of responses was voluntarily limited to 3 in order to simplify completion and to avoid random responses when score ranges are too broad. The total score is the sum of the 20 items, ranging from 0 (no negative symptoms) to 40 (severe negative symptoms). Five subscores can also be computed, corresponding to the 5 negative dimensions (social withdrawal, emotional range, alogia, avolition, and anhedonia).

The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) is a 9 item semi-structured interview that assesses depressive symptoms in schizophrenia. Each item is rated on a 4-point scale ranging from 0 (absent) to 3 (severe). The CDSS was used to take into account potential depression in the patients since overlap of negative and depressive symptoms has been observed (Dollfus et al., 2016).

2.3. Data analyses

Continuous data were expressed as mean ± standard deviation (mean ± SD). HC and SZ groups were compared by Student's *t*-test following verification of homoscedasticity with Levene's test. Categorical variables were presented as percentages and compared using Chi-square or Fisher's exact tests as appropriate.

Receiver Operating Characteristic (ROC) curves were established for discriminating SZ and HC participants by assigning the best threshold as determined by sensitivity (Se) and specificity (Sp). The threshold corresponds to the point lies at the intersection of the ROC curve and the line perpendicular to the diagonal of no discrimination. This threshold is optimal since it minimizes the difference between sensitivity (Se) and specificity (Sp). The area under the ROC curve (AUROC) and the diagnostic odds ratio were used to evaluate the diagnostic performance of the SNS scale. Diagnostic parameters are given with their 95% confidence intervals (95% CI).

Positive and negative predictive values (PPV and NPV) were also calculated. Since these values depend on the rate of illness (RoI) in the sample studied (here RoI = 52%), these values were also computed at a lower rate (RoI = 10%) with the pretest odds (pretOdds = RoI/1-RoI), the positive and negative posttest odds (Pos_posttOdds = pretOdds X LR+ and Neg_posttOdds = ptOdds × LR−; LR+ and LR− being the positive and negative Likelihood Ratio (LR+ = sensitivity / (1-specificity) and LR− = (1-sensitivity) / specificity)). PPV is equal to Pos_posttOdds/1 + Pos_posttOdds and NPV to 1 – (Neg_posttOdds/1 + Neg_posttOdds).

In order to make sure that depression or severity of negative symptoms did not influence the results, the number of patients with a CDSS score above 8 or with a negative sub-score BPRS above 1 DS of the mean were identified and two analyses were done without these patients.

The diagnostic odds ratio (DOR) is a measure of the effectiveness of a diagnostic test and is defined as the ratio of the likelihoods ratios (LR+/LR−). The rationale for the diagnostic odds ratio is that it is a single indicator of test performance and independent of prevalence (unlike accuracy), and is presented as an odds ratio (Glas et al., 2003).

All p-values were two sided and $p < 0.05$ was considered statistically significant. All statistical analyses were conducting using IBM®-SPSS® 22.0 software.

3. Results

3.1. Descriptive statistics

The characteristics of the 109 patients with schizophrenia and 99 controls are summarized in Table 1. The patients with SZ were significantly older ($p < 0.001$) than healthy subjects but no correlation was found between age and total SNS scores in patients ($r = 0.16$, $P = 0.08$). As expected SNS scores and subscores were significantly higher in SZ patients than in HC (Table 1). Patients had a significant lower level of school education than that in healthy subjects but SNS total scores did not differ ($P = 0.5$) in subgroups of patients characterized

Table 1
Participant characteristics.

Variables		Patients with schizophrenia (N = 109)	Healthy controls (N = 99)	p
Age		38.9 ± 11.3	28.8 ± 13.2	<0.001
Bacchalaureate	or more (%)	50.5	98.1	<0.001
SNS	Social withdrawal	3.13 ± 2.52	0.48 ± 0.80	<0.001
	Diminished emotional range	3.52 ± 1.95	1.10 ± 1.37	<0.001
	Alogia	3.56 ± 2.27	0.84 ± 1.35	<0.001
	Avolition	3.74 ± 2.39	0.86 ± 1.10	<0.001
	Anhedonia	2.62 ± 2.25	0.19 ± 0.67	<0.001
	Total score	16.39 ± 7.87	3.47 ± 3.58	<0.001
SANS	global total score	15.05 ± 4.41		
BPRS	Positive symptoms	8.36 ± 4.55	–	–
	Negative symptoms	10.67 ± 3.79	–	–
	Total score	43.80 ± 12.35	–	–
	Patients with negative symptoms >14 (%)	14.7		
BDI	Total score		1.85 ± 1.85	–
CDSS	Total score	4.02 ± 4.76	–	–
	Patients with CDSS score > 8 (%)	16.5		

SNS: Self-assessment of Negative symptoms; BPRS: Brief Psychiatric Rating Scale; BDI: Beck Depression Inventory; CDSS: Calgary Depression Syndrome Scale; SANS: Scale for the Assessment of Negative Symptoms.

by higher level (N = 55; 15.92 ± 7.54) or lower level than bacchalaureate (*N* = 54; 16.85 ± 8.22).

The DOR was equal to 72.8, 95% CI = [29.1–181.8].

The PPV and NPV were 87.8% and 91.4% respectively (Table 2) meaning that 87.8% is the probability to present the disease in a subject with SNS score above 7 and 91.4% is the probability to be healthy with SNS score under 7. When the rate of illness in the sample was lowered at 10%, the PPV and NPV were 42.1% and 99.0% respectively.

3.2. ROC curve

An AUROC analysis was performed in order to assess the discriminant performance of the SNS scale for screening (Fig. 1). The SNS (AUROC = 0.942 ± 0.046; p < 0.001) appears to be an appropriate screening tool for distinguishing SZ and HC at a threshold value of 7 (<7 vs ≥ 7). The sensitivity and specificity were 92.7% (95% CI = [86.1–96.8]) and 85.9% (95CI = [77.4–92.1]) respectively. Various thresholds according to the sensitivity and specificity are displayed on Table 3.

Table 2
Accuracy of SNS scale's screening parameters for the schizophrenic and control subjects detection - SNS 's threshold value = 7 (Schizophrenic patient: ≥7 - Control subject: <7).

Screening characteristics	Value: % (n/N)	95CI: [lower bound – upper bound]
Sensitivity (Se)	92.7 (101/109)	[86.1–96.8]
Specificity (Sp)	85.9 (85/99)	[77.4–92.1]
Positive predictive value (PPV)	87.8 (101/115)	[81.6–92.2]
Negative predictive value (NPV)	91.4 (85/93)	[84.4–95.4]
Accuracy	89.4 (186/208)	[84.4–93.3]
Positive likelihood ratio (LR +)	6.55	[4.02–10.68]
Negative likelihood ratio (LR −)	0.09	[0.04–0.17]

95% CI: 95% confidence interval is given in brackets.

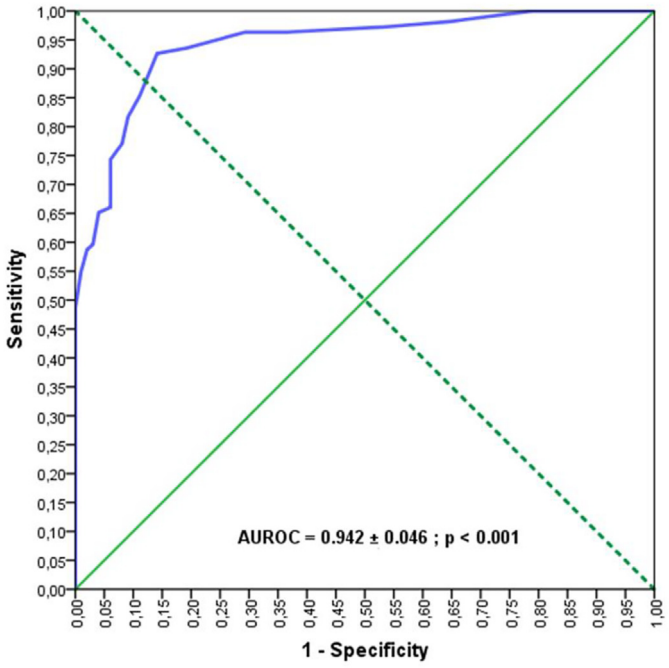

Fig. 1. Screening performances of SNS scale – Area Under Receiver Operating Characteristic curve (AUROC). The threshold corresponds to the point lies at the intersection of the ROC curve and the line perpendicular (discontinuous line) to the diagonal of no discrimination (continuous line).

AUROC analyses in the population after removing the patients with a CDSS score > 8 (N = 18; 16.5%) or a negative BPRS subscore >14 (N = 16; 14.7%) showed similar results with the same thresholds at 7 with AUC at 0.933 ± 0.018 (p < 0.001) and 0.934 ± 0.018 (P < 0.001) respectively.

4. Discussion

This is the first study highlighting a scale threshold for the identification of the negative dimension of schizophrenia with good sensitivity and specificity.

The results demonstrate that healthy subjects can report negative symptoms without any relationship with schizophrenia. Moreover, the SNS allows thresholding the intensity of negative symptoms beyond which it can be related to the negative dimension of schizophrenia. The sensitivity and specificity were 92.7% (95% CI = [86.1–96.8] %) and 85.9% (95% CI = [77.4–92.1] %) respectively at the optimal threshold, classifying subjects with SNS scores ≥7 as patients with schizophrenia. The positive and negative likelihood ratios (LR+ and LR−) were independent of illness prevalence. The DOR was equal to 72.8, 95% CI = [29.1–181.8]. This value is much greater than one, indicating that the test is correctly discriminant. The DOR is a measure of test performance. It combines the strengths of sensitivity and specificity, as prevalence independent indicators, with the advantage of accuracy as a single indicator. The DOR at 72.8 means that the probability of having negative

Table 3
Sensitivity and specificity of SNS for different threshold values.

Threshold	Sensitivity	Specificity
5,0	0,963	0,707
6,0	0,936	0,808
7,0	0,927	0,859
8,0	0,853	0,889
9,0	0,817	0,909
10,0	0,771	0,919
11,0	0,743	0,939

symptoms beyond 7 in patients is 72 times higher than that in healthy subjects.

Contrarily to the DOR, the PPV and NPV depend on the rate of illness. This rate is high in the present sample (52%) that could explain the high PPV (87.8%) and NPV (91.4%). However, PPV and NPV were still high (42.1% and 99.0% respectively) when the rate was artificially lowered at 10% underlining the interest of using SNS in psychiatric population.

As SNS can be used for screening negative symptoms in clinical practice and research in schizophrenia, the important point is to avoid missing true positives and so a highly sensitive test is required to respond to this (Rothman et al., 2012).

The good discriminant properties of the SNS including high values for sensitivity, specificity, and DOR might support its use for the identification of negative symptoms as pathological. Indeed, a total SNS score >7 is associated with an 87.8% probability that negative symptoms are related to the negative dimension of schizophrenia. In contrast, a total SNS score <7 is associated with a 91.4% probability that the symptoms are not pathological negative symptoms related to schizophrenia. This result suggests that under the SNS threshold of 7, the level of severity of symptoms reported with SNS might be considered as no pathological in healthy subjects or as very mild in patients with schizophrenia. In the same vein, we could consider that 7 is an SNS minimal score for a patient to be included in a trial targeting negative symptoms. After excluding the 16 patients with high level of negative symptoms, same results were obtained with the same threshold at 7 supporting the fact that the severity of negative symptoms did not impact on the threshold observed. However, further studies would be necessary in a larger group of patients with and without negative symptoms to confirm that this SNS threshold can discriminate both groups of patients with schizophrenia.

In the present study, SNS was used in patients with an advanced stage of illness. Consequently, we cannot extrapolate the pathological threshold found here in a younger population and particularly in patients at an early stage of illness. Further studies are needed in this specific population. Indeed, primary negative symptoms are observed in up to a quarter of patients with first episode schizophrenia (Galderisi et al., 2013; Chang et al., 2011). Negative symptoms are often the first to appear at the beginning of illness prior to the emergence of positive symptoms and are often retrospectively related to the prodromal stage (HÄfner, 2000). Eighty two percent of subjects with a high risk of psychosis scored at moderate or above on at least one negative symptom, and negative symptoms significantly predicted the likelihood of conversion to psychosis (Piskulic et al., 2012). However, negative symptoms are difficult to evaluate and recent standardized scales like the BNSS (Kirkpatrick et al., 2011) or CAINS (Kring et al., 2013) are based essentially on observer ratings. If internal experiences for avolition and asociality are also rated in these scales, they are based on semistructured interview and cannot be considered as self-assessments of subjective experiences. However, a self-assessment from CAINS was developed. In a first version, poor reliability and validity of the expression items were reported (Park et al., 2012) leading to a revised version, the Motivation And Pleasure Scale Self-report (MAPSR) (Llerena et al., 2013) that focused exclusively on self-reported deficits in motivation and pleasure. Consequently, MAPSR only covers 2 negative dimensions instead of the 5 ones recommended (Kirkpatrick et al., 2006) (Strauss et al., 2018a; Ahmed et al., 2018). Compared to hetero-evaluations, self-evaluation like SNS provides clinical information not necessarily detected by caregivers or medical staff in a standard interview and can provide information on the symptoms as recognized by the patients themselves (Lindstrom et al., 2001). Consequently, the SNS might be a valuable tool to help clinicians who guide the cognitive or social therapy based on the patient's answers. Whether self-reports have previously been developed to evaluate psychotic symptoms in schizophrenia (Niv et al., 2007) and prodromal psychotic symptoms (Kobayashi et al., 2008; Kelleher et al., 2011), they do not allow screening negative symptoms. The recent scales, BNSS and CAINS were adapted for assessing negative symptoms in clinical high-risk population but are still based on interviews (Strauss and Chapman, 2018; Gur et al., 2015). Consequently, the SNS based on self-assessment might be a valuable and complementary tool for detecting negative symptoms at an early stage of illness.

Despite the excellent sensitivity and specificity shown by SNS in the identification of negative symptoms, the study has some limitations. The absence of a cross validation in other samples prevent us to confirm the efficiency of the identified cutting score and to demonstrate its stability and generalization in other populations.

The fact that patients presented a low level of depressive symptoms assessed with CDSS and the exclusion of healthy subjects with depressive symptoms did not allow to evaluate the overlap of depressive and negative symptoms or to address the discrimination of primary and negative symptoms secondary to depression. However, after removing the 18 patients with high scores of depression, same results were obtained with the same thresholds supporting the fact that the severity of depressive symptoms did not impact on the threshold observed. Other limitations are that assessments of insight, clinical functioning and cognitive functions were not included. Regarding insight, the previous study did not reveal any relationship between the severity of insight and the level of negative symptoms assessed by SNS (Dollfus et al., 2016). However, further studies are needed to explore the relationship between the level of negative symptoms and the level of functioning and cognitive deficit since several studies have reported some relationships (Gur et al., 2015). Another limitation regards the demographic characteristics since healthy subjects were younger and with better school levels than patients, that might contribute to varying the threshold of SNS. However, we did not find any correlation between age and total SNS scores and any difference of total SNS scores according the level of education in patients.

In conclusion, the excellent sensitivity and specificity of the SNS makes it a valuable tool for the screening of negative symptoms in clinical practice. Further studies on the detection of negative symptoms with the SNS in subjects at high risk for psychosis or with a first psychotic episode would be of great interest.

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Declaration of Competing Interest

S. Dollfus received honoraria as expert/consultant by Fabre, Gedeon, Roche and Takeda; invited Conferences: Lundbeck, Otsuka, Janssen, and has contracts with Prophase MedAvances and NeuroCogTrials.

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Contributors

Sonia Dollfus designed, coordinated, supervised the study and wrote the article with Camille Delouche. Camille Delouche included and evaluated the healthy subjects; Camille Delouche, Cyril Mach, Maxime Tréhout, Anaïs Vandevelde included and evaluated the patients with schizophrenia in Caen; Cécile Hervochon, Valérie Bourgeois and Maud Rotharmel included and evaluated the patients with schizophrenia in Rouen. Olivier Guillin supervised the study in Rouen; Rémy Morello did the statistical analyses; All authors revised the manuscript.

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