

***Self-evaluation of negative symptoms in adolescent and young adult first  
psychiatric episodes***

Jasmina Mallet\*\* <sup>1, 2</sup>, MD, PhD , Sélim Benjamin Guessoum\*\* <sup>1</sup>, MD, Sarah Tebeka <sup>1, 2</sup>, MD,  
Yann Le Strat <sup>1, 2</sup>, MD, PhD, Caroline Dubertret<sup>1, 2</sup>, MD, PhD

**Affiliations**

1 AP-HP; Psychiatry Department, University Hospital Louis Mourier; Paris Diderot  
University, France.

2 University of Paris; INSERM UMR1266, Institute of Psychiatry and Neurosciences of  
Paris (IPNP), Paris, France.

*\*corresponding author: Jasmina Mallet, CHU Louis Mourier, 178 rue des Renouillers,  
92700 Colombes, tel 00 331 47 60 64 13 ; Fax : 00 331 47 60 67 40*

*\*\* : joint 1<sup>st</sup> authors : these two authors equally contributed to this work*

**Full postal address of each affiliation:**

- Department of Psychiatry, Louis Mourier Hospital, 178 rue des Renouillers,  
92700 Colombes, France
- Inserm UMR 1266, Institute of Psychiatry and Neurosciences, 102-108 rue de la  
Santé, 75014 Paris, France
- University Paris Diderot, Sorbonne Paris Cité, Faculty of Medicine, 16 rue Henri  
Huchard, 75018 Paris, France

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27 **Abstract (295 words)**

28 *Background:* Negative Symptoms (blunted affect, alogia, anhedonia, avolition, and  
29 asociality) are usually described in schizophrenia but they are also present in other  
30 psychiatric disorders. The diagnosis and prognosis relevance of negative symptoms  
31 (NS) self-assessment during a first psychiatric episode is still unknown.

32 *Aims:* To determine (i) the rate of self-assessed NS in a first psychiatric episode among  
33 adolescents and young adults compared to control subjects; and (ii), whether there is a  
34 difference in the prevalence of NS between schizophrenia and major depressive  
35 disorder first episodes.

36 *Methods:* The population included patients aged 15-25 years, with no psychiatric history  
37 and no history of medication. A dimensional evaluation was assessed during  
38 hospitalization, including depressive (Hamilton Depression Scale), psychotic symptoms  
39 (Prodromal Questionnaire, 16 items) and the self-evaluation of negative symptoms (SNS  
40 scale). Prospective categorical diagnoses were updated 6 months after hospitalization.  
41 The population included 117 individuals (58 patients and 59 healthy controls).

42 *Results:* Among healthy individuals, 47.5% reported at least one NS, the most reported  
43 being amotivation. After binary logistic regression, Negative Symptoms (SNS score)  
44 were associated with a diagnostic of psychiatric disorder at the 6-months follow-up (OR  
45 = 1.163,  $p=.001$ ), whereas depressive symptoms and psychotic experiences were not. A  
46 SNS threshold allowed to screen first episode patients and SZ patients in the general  
47 population (assessed with ROC curve). A high prevalence of self-reported NS was  
48 observed across diagnostic boundaries in first psychiatric episodes, with a mean SNS  
49 score of  $19.3 \pm 7.1$  for schizophrenic disorders and  $20.7 \pm 8.6$  for depressive disorders.

The prevalence of NS was not significantly different between depressive disorders as in schizophrenic disorders ( $p>.05$ ).

*Conclusion:* NS are an important transnosographic dimension during first psychiatric episodes among adolescents and young adults. Negative symptoms self-assessment with the SNS scale is relevant during a first psychiatric episode.

**Keywords.** negative symptoms, first episode, schizophrenia, depression, transdiagnostic, dimensional

**Declarations of interest.** None.

#### **Highlights.**

- Negative symptoms are transdiagnostic in first psychiatric episodes
- Negative symptoms self-assessment is pertinent during first psychiatric episodes
- There is a high negative symptoms prevalence during first psychiatric episodes
- Negative symptoms were as frequent in depression as in schizophrenia in our sample
- Negative symptoms differentiate patients from the general population in our study, better than depressive symptoms and psychotic experiences do

## **1. Introduction**

Negative symptoms (NS) encompass five symptoms: alogia, blunted affect, anhedonia, avolition, and asociality. At the beginning of the 20<sup>th</sup> century, Bleuler and Kraepelin considered NS as major symptoms of schizophrenia (Tandon et al. 2013; Mach and Dollfus 2016). During the second part of the 20<sup>th</sup> century, Schneider's first-rank symptoms, which are mostly positive symptoms, prevailed over NS (Tandon et al. 2013). This omission of NS could be explained by their subtle symptomatology, their difficult clinical evaluation (differential diagnosis of depression, extrapyramidal symptomatology, social withdrawal secondary to delusions, disorganization, environmental hypostimulation), the low inter-judge reliability, and the low efficacy of medications and psychosocial interventions (Mach and Dollfus 2016).

NS have long been considered as associated with several-years long and gradually deteriorating schizophrenia (Bleuler et al. 1983), whereas they are also observed at early stages (Quattrone et al. 2018). NS are transnosographic symptoms that are observed in schizophrenia and mood disorders (Guessoum et al. 2020), and have also been described in other disorders such as borderline personality disorder (Marissen, Arnold, and Franken 2012), substance use disorders (Garfield, Lubman et al. 2014; Cook et al. 2015), neurological diseases (Winograd-Gurvich et al. 2006) or even in the general population (Stefanis et al. 2002; van Os and Reininghaus 2016; Werbeloff et al. 2015). Identifying NS at an early stage of the disorders is an important prognosis challenge. An early and active management is associated with a decrease incidence of NS (Lutgens et al. 2018). Conceptual borders between symptoms of schizophrenia and depressive disorders can be unclear and NS are overlapping symptoms across diagnostic categories (Moritz et al. 2018; Guessoum et al. 2020).

NS are an important factor of disability and a public health burden. More than 50% of patients with schizophrenia have at least one NS (Sicras-Mainar et al. 2014), and more than 40% have at least two NS, which are associated with more and longer hospitalizations (Patel et al. 2015). In depressive disorders, anhedonia leads to poorer recovery among depressed patients (McMakin et al. 2012) and it is a strong predictor of psychosocial functioning (Vinckier, Gourion, and Mouchabac 2017).

At the early stage of psychiatric disorders, psychiatric assessment of NS is however limited. The Prodromal Questionnaire (PQ-16), that aims at detecting psychosis prodromes, is composed of 16 items, only 2 of which are related to NS (Ising et al. 2012). Yet, early assessment and management of NS is a challenge for patients with schizophrenia and mood disorders. The Self-evaluation of Negative Symptoms Scale (SNS) has been recently developed to fill the need of a reliable and acceptable tool to assess NS. The SNS has a good correlation with the Scale for the Assessment of Negative Symptoms (SANS) and presents good psychometric properties (Dollfus, Mach, and Morello 2016).

To date, the diagnosis and prognosis relevance of NS self-assessment during a first psychiatric episode is unclear. No study has yet examined the prevalence of NS in the general population compared to patients during a first psychiatric episode. The objectives of this prospective observational study are:

- 1) to evaluate the rate of self-reported NS in a population of adolescents and young adults with first psychiatric episodes versus the general population,
- 2) to evaluate the difference in NS self-assessment across diagnostic categories, especially between schizophrenia and depressive disorder first episodes.

## **2. Methods**

**Population:** Adolescents and young adults hospitalized for the first time in the Adolescents Unit or the Young Adults Unit of the Psychiatry Department of Louis Mourier University Hospital in Colombes (a suburb of Paris), France. The inclusion criteria were: age 15 to 25 years, no personal history of psychiatric disorder, no lifetime psychiatric medication. Inclusions were conducted from July 2016 to November 2018. The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). All data were collected anonymously. Each patient agreed to participate and gave an oral consent. The control subjects were aged 15 to 25 years and had no psychiatric history or lifetime psychiatric medication (inclusion criteria). Subjects were recruited among the friends of relatives from the entourage of the staff. The study was approved by the local ethics committee (Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) Paris Nord : N°2019-032) .

**Assessment:** Patients were assessed at their arrival in the unity. The diagnoses were established at the end of hospitalizations and updated 6 months later. The NS were assessed using the SNS scale (Dollfus, Mach, et al. 2016), a 20-item Likert scale evaluating the five dimensions of NS. For each of the five NS dimensions, patients answer "Strongly agree" (2 points), "Somewhat agree" (1 point) or "Strongly disagree" (0 points), to 4 items such as: "1: I prefer to be alone in my corner" or " 6: There are many happy or sad things in life but I don't feel concerned by them". The total score is a continuous score from 0 to 40. For each NS dimension, we calculated a continuous subscore from 0 to 8.

The psychiatric diagnosis was discussed by two different senior psychiatrists and recorded at the end of hospitalization (diagnoses of the International Classification

of Diseases 10 (World Health Organization and WHO 1992)). The prospective diagnosis was updated 6 months later by contacting each patient's psychiatrist. The prospective diagnosis was used to determine the subgroups of patients: schizophrenia disorder (SZ) and depressive disorder (DEP).

Psychotic symptoms were assessed with the Prodromal Questionnaire (PQ16), a 16-item self-assessment questionnaire (Ising et al. 2012). As no French validation of the PQ16 was available at the time of inclusion, we translated and retrotranslated this questionnaire with the help of a bilingual speaker. It was initially designed to identify young patients at risk of psychosis. A score with positive responses to 6 or more items is assumed to identify patients at a higher risk of psychosis. Depressive symptoms were assessed with a hetero-evaluation, using the Hamilton Depression Scale (HAMD17) (Hamilton 1960).

In the control population, depression was assessed with the Beck Depression Inventory (Beck, Steer, et al. 1996; Beck, Steer, et al. 1988) and maniac symptoms with the Mood Disorder Questionnaire (Hirschfeld et al. 2000; Weber Rouget et al. 2005).

Other parameters were included: family psychiatric history, treatment at the end of hospitalization, substance use, place of residence, and school or academic level.

**Statistics:** Sociodemographic and clinical characteristics are presented using means and standard deviations for continuous data and distribution frequencies for categorical variables. The normality of the distributions was verified with Shapiro-Wilk tests. In Tables 1 and 2, univariate associations between demographic and clinical characteristics across subject groups were made using a Chi-2 test for categorical variables, and continuous variables were analyzed with Student t-tests for data with a normal distribution. Non-parametric tests were used when necessary. For the total

population, a binary logistic regression was performed using Odds Ratio and their 95% confidence intervals.

The prevalence of individuals with at least one NS was calculated, according cut-offs within the SNS subscores that rate from 0 to 8 for each NS dimension (alogia, blunted affect, anhedonia, avolition, and asociality). To determine the discriminant performances of the SNS, Area Under Receiver Operating Characteristic Curve (AUROC) analysis were performed. Sensitivity (Se) and specificity (Sp) of SNS thresholds for discriminating patients with psychiatric disorders and with SZ were calculated (Supplementary material). All p-values were two sided and  $p < 0.05$  was considered statistically significant. Statistics were conducted using the Statistical Pack for Social Sciences Software (SPSS-22).

### **3. Results**

#### **3.1 Socio-demographic and clinical characteristics**

The total population of 117 subjects was composed of 58 patients and 59 control subjects. The patients' group included 19 subjects with schizophrenia disorder (SZ), 22 with depressive disorder (DEP), 3 with bipolar disorder (BD) and 15 with other psychiatric disorders (personality disorder, adjustment disorder or anxiety disorder). Socio-demographic and clinical characteristics of patients and control subjects are presented in **Table 1**. NS differed significantly between patients and control subjects, for the total SNS score as well as for each of the five subscores that assess alogia, blunted affect, anhedonia, amotivation and asociality ( $p < .001$ ). The Pearson correlation coefficient of the SNS score with the PQ-16 score was 0.521 ( $p < .001$ ). A binary logistic



regression showed that NS measured with SNS score was significantly associated with any psychiatric disorder in the total population, whereas depressive symptoms (HAMD17) and psychotic experiences (PQ-16) were not (**Table 2**). Age was also associated with any psychiatric disorder, as expected in the univariate analyse.

In patients group, due to small numbers in subgroups, patients with a diagnosis of BD, personality disorder and adjustment disorder were excluded from the analysis of the population of patients. SZ (N= 19) and DEP (N= 22) patients were compared in **Table 3**. SNS, HAMD17 and PQ16 scores were normally distributed for SZ and DEP patients. No significant difference in NS was observed between SZ and DEP patients, including analyses of the five subscores for the five dimensions of NS (all  $p > .05$ ). There was no significant difference between SZ and DEP patients for the PQ-16 score. There was no correlation between the SNS and HAMD17 scores (Pearson's coefficient = 0.180,  $p = 0.261$ ) and between the SNS and PQ16 scores (Pearson's coefficient = 0.110,  $p = 0.493$ ). There was a high correlation ( $p < 0.001$ ) between total SNS score and the negative item of the PQ16 (item 1), as expected.

**Table 1. Socio-demographic and clinical characteristics of the total population (n = 117)**

	Controls (n = 59)	Patients (n = 58)	Statistics	p
Ratio Female/Male	37/22	33/25	$\chi^2 = 0.41$	.521
Age (mean $\pm$ SD)	20.4 $\pm$ 2,8	18.1 $\pm$ 2.6	t = -4.73	<b>&lt;.001</b>
Educational level (mean $\pm$ SD)	14.5 $\pm$ 2.2	11.7 $\pm$ 1.7	t = -7.71	<b>&lt;.001</b>
1st degree psychiatric history (%)	10 (17)	24 (41)	$\chi^2 = 8.47$	<b>.004</b>
2nd degree psychiatric history (%)	9 (15)	10 (17)	$\chi^2 = 0.09$	.771
Cannabis use (%)	16 (27)	20 (34)	$\chi^2 = 0.745$	.388
<b>Negative symptoms (mean <math>\pm</math> SD)</b>				
Total SNS score	8.9 $\pm$ 5.5	19.3 $\pm$ 8.1	t = 8.186	<b>&lt;.001</b>
Alogia	1.6 $\pm$ 1.8	4.2 $\pm$ 2.4	t = 6.509	<b>&lt;.001</b>
Blunted Affect	1.8 $\pm$ 1.7	3.8 $\pm$ 2.2	t = 5.531	<b>&lt;.001</b>
Avolition	3.3 $\pm$ 2.2	4.7 $\pm$ 2.4	t = 3.198	<b>.002</b>
Anhedonia	0.7 $\pm$ 1.1	3.2 $\pm$ 2.2	t = 7,685	<b>&lt;.001</b>
Asociality	1.5 $\pm$ 1.4	3.5 $\pm$ 2.1	t = 6,061	<b>&lt;.001</b>
<b>Positive symptoms</b>				
PQ16 number of positive items (mean $\pm$ SD)	3.8 $\pm$ 2.8	7.3 $\pm$ 3.8	t = 5.73	<b>&lt;.001</b>
<b>Depressive symptoms</b>				
Moderate or severe depression (%)	8 (14)	34 (59)	$\chi^2 = 25.809$	<b>&lt;.001</b>

AUDIT: Alcohol Use Disorders Identification Test, CUDIT: Cannabis Use Disorders Identification Test, SNS: Self-Evaluation of Negative Symptoms scale, PQ16: Prodromal Questionnaire 16 items,  $\chi^2$ : Chi2 test, t: t-test, SD: standard deviation, p<0.05 in **bold**

**Table 2. Binary logistic regression showing odd ratios for the dimensions of symptoms comparing the patients and the controls groups (n = 117)**

	Coefficient	SD	Wald	p value	OR	IC 95%
<b>Age</b>	-.298	.096	9.557	<b>0.002</b>	0.742	0.615-0.897
<b>Negative symptoms</b>	0.151	.044	11.632	<b>0.001</b>	1.163	1.066-1.268
<i>SNS score</i>						
<b>Positive symptoms</b>	0.136	.089	2.336	0.126	1.146	0.962-1.364
<i>Number PQ16 positive items</i>						
<b>Depressive symptoms</b>	-1.127	.628	3.221	0.073	0.324	0.095-1.109
<i>Moderate or severe depression</i>						
Constant	3.607	2.043	3.119	0.077	36.871	

SNS: Self-evaluation of Negative Symptoms scale, PQ16: Prodromal questionnaire, Wald: wald statistic, SD: standard deviation, OR: odd ratio, IC 95%: confidence interval 95 %, Significant value (p<0.05) in **bold**

**Table 3. Socio-demographic and clinical characteristics of patients with schizophrenia (SZ), depressive disorder (DEP)**

	SZ (= 19)	DEP (n = 22)	Statistics	p value
Ratio Female/Male	7/12	13/9	$\chi^2 = 2.020$	.155

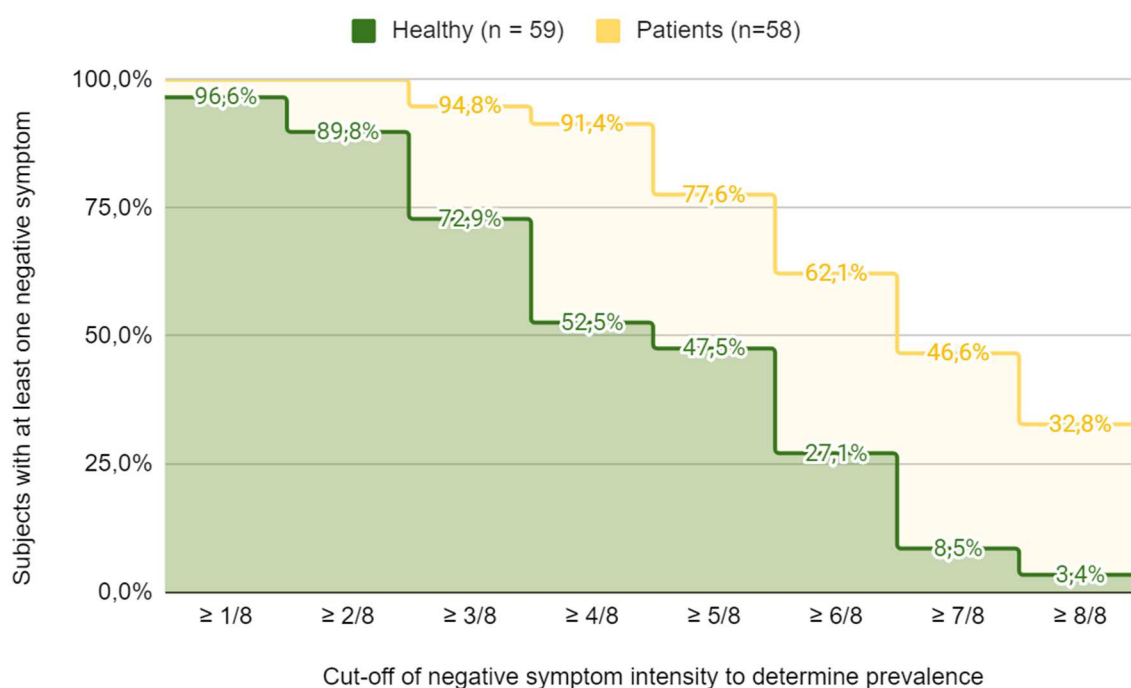
Age (mean ± SD)	19.4 ± 3.0	18.0 ± 2.0	t = 2.21	<b>.033</b>
Educational level(mean ± SD)	12.1 ± 2.0	11.4 ± 1.5	t = 1.27	.214
1st degree psychiatric history (n, %)	9 (47)	9 (41)	χ <sup>2</sup> = 0.173	.678
2nd degree psychiatric history (n, %)	4 (21)	4 (18)	χ <sup>2</sup> = 0.054	.817
Cannabis use (n, %)	8 (42)	6 (27)	χ <sup>2</sup> = 0.997	.318
<b>Negative symptoms</b> (mean ± SD)				
Total SNS score	19.3 ± 7.1	20.7 ± 8.6	t = - 0.566	.575
Alogia	4.4 ± 2.2	4.5 ± 2.8	t = - 0.10	.921
Blunted Affect	3.8 ± 2.1	3.7 ± 2.4	t = 0.15	.881
Avolition	4.7 ± 2.5	4.9 ± 2.2	t = -0.23	.817
Anhedonia	2.9 ± 1.7	3.5 ± 2.4	t = - 0.84	.404
Asociality	3.5 ± 2.0	4.2 ± 2.3	t = - 1.05	.302
<b>Positive symptoms</b>				
PQ16 number of positive items (mean ± SD)	8.5 ± 4.1	7.5 ± 3.3	t = 0.879	.385
<b>Depressive symptoms</b>				
Hamilton Depression Scale				
Hamilton score (mean ± SD)	13.2 ± 6.7	19.0 ± 6.6	t = -2.797	<b>.008</b>

Significant value (p<0.05) in **bold**; AUDIT: Alcohol Use Disorders Identification Test, CUDIT: Cannabis Use Disorders Identification Test, SNS: Self-Evaluation of Negative Symptoms scale, PQ16: Prodromal Questionnaire 16 items, χ<sup>2</sup>: Chi2 test, t: t-test, SD: standard deviation

### **3.2 Prevalence of Negative Symptoms**

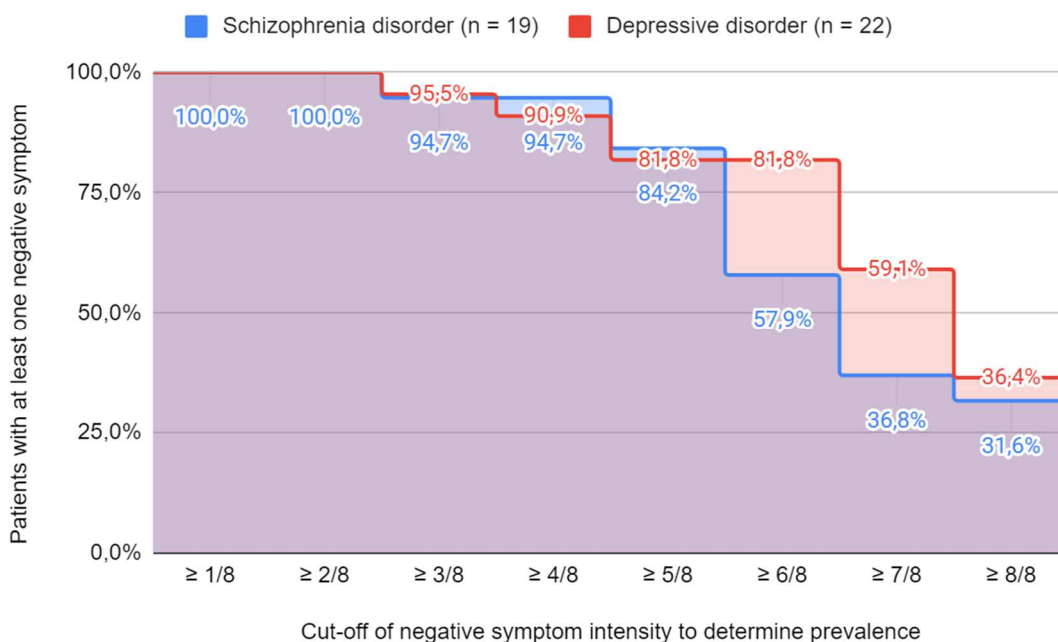
The prevalence of individuals with at least one NS, depending on various cut-off scores within the continuous NS subscores of the SNS, are presented in **Figures 1a and 1b**. A cut-off score > 4/8 was proposed to establish NS prevalence, as it seemed clinically relevant (**Table 4**). Indeed, for each NS dimension, a NS 4-item subscore > 4/8 can be achieved answering at least: (i) “somewhat agree” to 3 items and “strongly agree” to 1 item, or (ii) “strongly agree” to 2 items and “somewhat agree” to 1 item. In patient population, 77.8% present at least one NS in comparison to 47.5% in the healthy controls (HC) group. According to this cut-off score, NS prevalences are relatively similar in the two groups of patients (84.2% in the SZ group versus 81.8% in the DEP group).

252 **Figure 1a. Prevalence of individuals with at least one negative symptom in the total population**



253 The Self-Evaluation of Negative Symptoms scale is a 20-item scale with a continuous score (0-40), with 4 items for each of the 5  
 254 Negative Symptom dimension, thus a continuous score from 0 to 8. This figure presents the percentage of patients with at least 1  
 255 Negative Symptom, depending on the cut-off, from 1 to 8, chosen to determine the existence of a Negative Symptom.  
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257  
 258 **Figure 1b. Prevalence of individuals with at least one negative symptom within the patients' population**  
 259  
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261 The Self-Evaluation of Negative Symptoms scale is a 20-item scale with a continuous score (0-40), with 4 items for each of the 5  
 262 Negative Symptom dimension, thus a continuous score from 0 to 8. This figure presents the percentage of patients with at least 1  
 263 Negative Symptom, depending on the cut-off, from 1 to 8, chosen to determine the existence of a Negative Symptom.  
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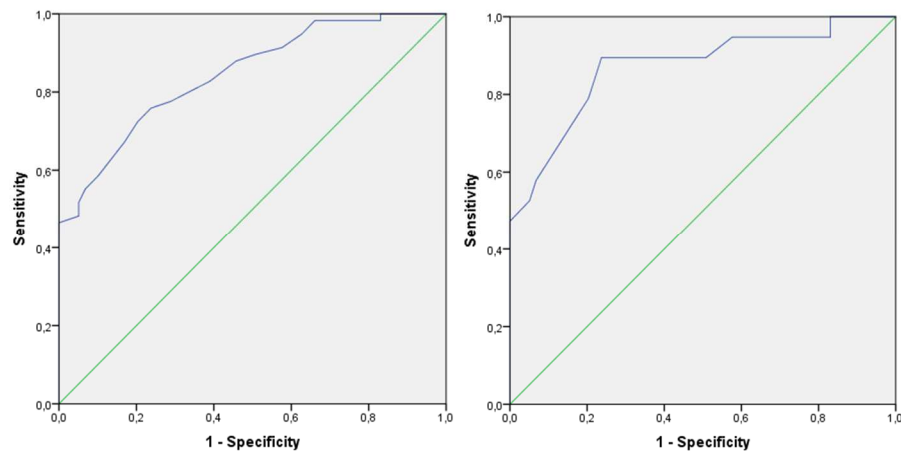
**Table 4. Prevalence of negative symptoms according to the SNS (score > 4/8 for at least one negative symptom)**

Negative symptom (%)	Total population		Patients	
	Healthy (n = 59)	Patients (n=58)	Schizophrenia disorder (n = 19)	Depressive disorder (n = 22)
Alogia	10.2	48.3	52.6	59.1
Blunted affect	10.2	37.9	36.8	40.9
Anhedonia	0	24.1	15.8	31.8
Avolition	32.2	50.0	52.6	50.0
Asociality	5.1	37.9	36.8	54.5
Individuals with at least one NS (%)	47.5	77.6	84.2	81.8

### **3.2 Screening performances of the SNS**

An AUROC analysis was performed to assess the discriminant performance of the SNS scale for screening first psychiatric episodes or SZ patients in the general population (figure 2 and 3). The SNS seems to be an appropriate screening tool for distinguishing first episode patients and HC at a threshold value of 11 (>11 versus < or =11), with an AUROC=0.845 (SE= 0.035), CI 95%= (0.776-0.914), p<.001. The sensitivity and specificity were 77.6% and 71.2% (Table S1, supplementary material). The results were similar when using a graphic method (where the threshold corresponds to the point lies at the intersection of the ROC curve and the line perpendicular to the diagonal of no discrimination). Concerning the performances to discriminate SZ patients and HC, the performances were also good (AUROC=0.872, SE=0.052, 95%CI=0.769-0.974, p<0.001). The threshold was comparable (respectively >11 versus < or = 11) with a sensitivity of 89.5% and a specificity of 77.2%.

**Figure 2. Performances of SNS scale to screen patients with (a) psychiatric first episode and (b) schizophrenic disorder in the general population ( ROC curve)**



(a) Psychiatric disorder

(b) Schizophrenic disorder

### **3. Discussion**

This study suggests (i) that NS can discriminate first psychiatric episode adolescents from healthy ones and (ii) that within the patients' group, NS are as prevalent in early SZ as in the first depressive disorder episode in adolescence. This is an important finding because the easy self-assessment of NS with the SNS scale could specifically identify young patients with psychiatric disorders in the general population. NS self-assessment would also be useful in young patients with psychiatric disorders at an early stage of the disorders, regardless of the diagnosis. Thus, whereas under-evaluated, NS are an important transdiagnostic dimension of the clinical profiles of adolescents and young adults during a first psychiatric episode. This study also suggests a threshold to screen first episode adolescents using the SNS.

#### **3.1 Negative symptoms from the general population to first psychiatric episode**

Studies evaluating NS in the general population using a self-assessment tool are scarce, in comparison to studies evaluating psychotic-like experiences and their correlates. Our results suggest that the self-assessment of NS with the SNS could identify adolescents with psychiatric disorders in the general population, which PQ16 and depressive symptoms did not in binary logistic regression in this study (Table 2). This is intriguing, as positive and depressive symptoms may seem noisier and clinically relevant. These results are based on a self-assessment, which can more easily highlight NS (compared to hetero-evaluation, when NS are evaluated, which is rare). NS could also be considered as sub-threshold and non-clinical forms of mental illness processes, as psychotic-like experiences are, in a continuum approach between healthy individuals and clinical populations.

This study reported that 47.5 % of the young healthy group had at least one NS (Figure 1, Table 4). This is relevant for dimensional studies. However, for targeting individuals with significant psychiatric disorders, it highlights the pertinence of a syndromic approach encompassing both the number and the intensity of the NS, which the SNS does, rather than a one-symptom-approach.

A study among 4,914 individuals from general population, aged 25-34 years, reported that 20.2% had at least one NS, but no specific tool for the evaluation of NS was used (Werbeloff et al. 2015). Another recent large general population study among adolescents aged 11 to 18 years old in Spain provided results close to ours, with a total mean SNS score of  $10.57 \pm 6.27$ , especially a high avolition score ( $3.23 \pm 2.12$ ), when our study reports a mean SNS score of  $8.9 \pm 5.5$  in healthy controls and a also a high avolition score ( $3.3 \pm 2.2$ )(Rodríguez-Testal et al. 2019). Interestingly, in a population of 99 healthy subjects aged  $28.8 \pm 13.2$ , a lower mean SNS score was observed ( $3.47 \pm 3.58$ ) and the avolition score was low ( $0.86 \pm 1.10$ ) (Dollfus et al. 2019). It suggests that healthy adolescents report more NS, in particular more amotivation. One explication might be the amotivational effects of chronic cannabis use, which is relatively high in young samples (27% in this study).

Concerning the psychometric properties of the SNS scale, a threshold of 7 was proposed as a screening tool for distinguishing between SZ and HC among adult populations (Dollfus et al. 2019). However, the mean score of HC seems higher in adolescent population, as shown by our results and Rodriguez-Testal et al. (Rodríguez-Testal et al. 2019). The mean SNS score in Rodriguez-Testal's study is 10,57 (SD = 6.27) among 4521 adolescents aged 14.32 (SD = 1.66, range 11–18 years). In our study and Rodriguez-Testal's study, we found higher scores than in the study of Dollfus et al., in which the 99 HC have an SNS mean score of 3.47 (SD = 3.58). This difference suggests that healthy adolescents report more NS than healthy adults. These results are consistent with a dimensional approach of NS, with symptoms from the normal to the pathological, but it also supports a longitudinal reflexion on NS throughout the development from adolescence to adult age. For psychiatric disorders, the screening threshold in an adolescent population may be higher, as our result suggest (threshold of 11). In our study, a threshold of 7 would lead to a sensitivity of 94.7% with a low specificity (57.6%), which is not far from chance (50%). In Dollfus's study, the 109 SZ patients have an SNS score of 16.39 (SD = 7.87) whereas we found SNS scores around 20 for SZ and DEP first episode adolescent patients. This suggests different SNS score interpretations depending on the population. Adolescents may report higher scores of NS, and patients may report higher scores during acute episodes. The age may be an important variable to detect NS.

In a community sample of 777 adolescents (mean age: 14.4 years), various avolition-related experiences were reported by 31 to 83% of adolescents but the prevalence decreased to 0.9 to 5.0 % regarding adolescents who reported these experiences “nearly always” (Barragan et al. 2011), similarly to our healthy sample wherein only 3.4% report at least one NS dimension of maximal intensity (all 4 items, each rated “Strongly agree”), which highlights the utility of a continuous scores to identify intense symptoms (Figure 1a).

### **3.2 Negative symptoms across diagnostic categories**



Identifying NS during a first psychiatric episode is an important issue for both dimensional diagnosis and treatment. In the patient population, we observed high levels of NS in both schizophrenia and depressive disorders. NS being transnosographic, our results suggest that the SNS may be useful across diagnostic boundaries, and not only in SZ. Patients with DEP or SZ showed significant difference on Hamilton's score but not SNS's score. In schizophrenia spectrum disorders, a study among 1452 outpatients (mean age: 40.7 years old) reported the most frequent NS are social withdrawal (45.8%), emotional withdrawal (39.1%), poor rapport (35.8%) and blunted affect (33.1%) (Bobes et al. 2010). However, these patients were treated with antipsychotic drugs. In our study, first episode patients had no history of drug medication, which avoids confusion bias with secondary NS caused by antipsychotic drugs.

The prevalence of NS in the SZ sample is relatively high (88%), in comparison to a recent study by Mucci et al (2019), who found prevalences around 55% with the BNSS (Brief Negative Symptom Scale) and the PANSS (Positive and Negative Syndrome Scale). However, this discrepancy may be due to the difference of assessment (the SNS is a self-evaluation), and to the samples differences (Mucci et al provide prevalence in chronic and stabilized patients). Among first psychiatric episodes, Lyne et al. reported that items from the Scale for the Assessment of Negative Symptoms) were more prevalent in schizophrenia spectrum disorder (87% with a score  $\geq 3$  on any SANS item) (mean age of patients:  $30.2 \pm 10.4$ ) but frequently presented major depressive disorders (68%) (mean age of patients:  $37.7 \pm 14.4$ ) and other psychiatric disorders (bipolar disorders, acute psychotic disorders, delusional disorders) (Lyne et al. 2012).

Our study shows that NS are important dimensions of first psychiatric episodes, whether it is a psychotic or a mood disorder. Our results highlight that more than 80% of the patients with schizophrenic and mood disorders reported at least one NS during

the first episode. NS were particularly studied in schizophrenia whereas there is scarce data on NS in early depressive disorders. NS may even precede a first psychotic episode (Schmidt et al. 2017). In particular, social withdrawal and anhedonia may be factors of vulnerability to schizophrenic disorders (Matheson et al. 2013; Tarbox and Pogue-Geile 2008; Kwapil 1998). NS would predict the functioning of patients with "Ultra High Risk" of psychosis (Mechelli et al. 2017) and they would be present at a very early stage of the disorders (Matheson et al. 2013; Tarbox and Pogue-Geile 2008; Schmidt et al. 2017). Transdiagnostic studies examining the prognosis value of NS would be relevant.

The results of studies comparing NS in patients with schizophrenic disorders and patients with other disorders are heterogeneous. In our study, there is no significant difference in NS between SZ and DEP groups. Some studies report more NS in schizophrenic disorders compared to mood disorders (Strauss et al. 2016; Herbener and Harrow 2001; Lewine 1990), while others do not find any difference (Gerbaldo et al. 1994; Klosterkötter et al. 1995). However, studies rarely take into account the duration or sequence of NS setup during the disorder. The results may also depend on whether or not the studies differentiate between primary and secondary NS and transient and persistent NS. In a transdiagnostic study among 76 patients, there was no difference in NS between patients with SZ and those with DEP, hospitalized for an acute episode. However, the duration of persistent NS assessed by patients and their relatives distinguished the two groups (Bottlender, Sato, et al. 2003). A transdiagnostic study among 96 outpatients (46 BD, 50 SZ, 27 control subjects) did not report any difference between the BD et SZ groups regarding anhedonia, avolition, and asociality items, but a difference regarding items related to blunted affect and alogia (Strauss et al. 2016).

However, this study hetero-evaluated NS in older patients with BD and SZ while our study regards first episode young patients with SZ and DEP.

### **3.3 Perspectives**

Each dimension of NS could have specific pathophysiological correlates that are partly common to schizophrenia and depressive disorders (Guessoum et al. 2020) and the pathophysiology of persistent NS during first psychotic episodes may be specific (Makowski et al. 2017). A study on a patient population during a first psychotic episode showed an association between low metacognitive abilities and NS (Trauelsen et al. 2016). The genetic risk for schizophrenia (according polygenic risk scores) appears to be manifest as anxiety and NS during adolescence (Jones et al 2016). SZ patients with more NS would also represent a specific subgroup with more neurodevelopmental and cognitive impairment (Mallet et al. 2017). A greater focus on these phenotypes rather than on psychotic experiences might be required for prediction of transition in at-risk samples. In a recent work (Bourgin et al. 2020), we found that the negative dimension of psychotic-like experiences was associated with various mental disorders and personality disorders (e.g adjusted Odd Ratio=2,88 IC95% (2,70–3,07) for Major Depressive Disorder). Further prospective studies are needed. If NS are associated with later risk of psychotic disorders, it raises important question about the consequences of NS themselves, even in healthy populations.

There are neurodevelopmental hypotheses suggesting interactions between neurodevelopmental cognitive deficits and neuroplasticity changes leading to NS and functional decline (Bora 2015). Adding cognitive assessments of patients with NS would help identify cognitive correlates of negative symptoms.

NS may also have an important role in the functional prognosis of patients. The early assessment of NS at an early stage of psychiatric disorders is, therefore, an important issue. After the first psychotic episode, the NS remission at 24 months follow-up would depend on the prior baseline intensity of NS in adolescents and adults (Veru et al. 2016). Significant NS during the first psychotic episode may be a predictive factor for poor social functioning recovery, whether patients are in remission or not (Gee et al. 2016). A recent study showed that NS trajectories were associated with long-term prognosis (Chang et al. 2018). In depressive disorders, anhedonia may also be a prognostic factor in resistant depressions in adolescents (McMakin et al. 2012). In a study of 178 young adults ( $22.4 \pm 4.4$  years), NS improved significantly during the first 2 years after a first psychotic episode (Lutgens et al. 2018). In this study, management included low-dose antipsychotic medication, psychological and psychosocial interventions aimed at recovery, including cognitive-behavioral therapy and family interventions. Therefore, NS should be evaluated and studied to explore early therapeutic strategies.

### **3.4 Limitations**

First, while being the first one to provide a comparison in both general sample and in first psychiatric episode patients, the whole sample is relatively small. Second, this study does not specify the duration of the NS, nor their persistence. Transient NS are different from persistent NS. Persistent NS are defined by a duration of 6 months or more. Persistent NS are reported to be more specific to schizophrenia (Bottlender, Sato, et al. 2003). In a 10-year longitudinal transdiagnostic study of 150 patients, more persistent NS were observed in individuals with schizophrenia or schizoaffective disorders, compared to patients with DEP (Herbener and Harrow 2001). However the

present study focuses on acute-stage NS during a first psychiatric episode and provides a good inventory. Third, the self-assessment of NS has not been completed by a hetero-assessment scale, which would have been complementary. Nevertheless, the SNS is a validated self-assessment scale, whose scores correlate with the SANS (Scale for the Assessment of Negative Symptoms) and are not correlated with the patients' insight level (Dollfus, Mach, and Morello 2016). Self-assessment of NS allows the patient to evaluate its own experience and it can provide information that is not provided by standard interviews (Dollfus, Mach, et al. 2016). On the contrary, hetero-evaluation of NS can be influenced by the assumed or suggested diagnosis to the evaluator. Indeed, psychiatrists use different semiological terms for the same NS depending on the suggested diagnosis of depression or schizophrenia (Moritz et al. 2018). Fourth, The HC sample is older than patients sample. It is a limit but also a strength of our study, as the subjects did not develop a psychiatric disorder during this 1.7 years difference. Finally, the follow-up was limited to 6-months to decrease drop-out. A more extended follow-up may have had an impact on categorical diagnoses (as an example, some DEP patients may correspond to BD who have not yet experienced any manic or hypomanic episode).

#### **4. Conclusions**

NS are transdiagnostic and dimensional symptoms, observed in the general population and in several psychiatric disorders. This study shows that the self-assessment of NS with the SNS scale can help to identify patients during a first psychiatric episode, regardless of diagnosis, compared to healthy controls. In our study, there was no transdiagnostic difference for the NS of adolescents and young adults during a first psychiatric episode progressing to schizophrenic or depressive disorder.

Using the SNS during first psychiatric episodes could help to measure specific symptoms that categorical diagnoses do not clearly point out. SNS threshold of 11 could identify adolescents with psychiatric disorders with good psychometric properties. This threshold is higher than the previous threshold mentioned in an adult population to distinguish SZ and HC.

These results show that NS are important transdiagnostic clinical symptoms during first psychiatric episodes among adolescent and young adult patients. Longitudinal transnosographic studies could clarify the prognostic value and the correlates of effective management of NS at early stages of psychiatric disorders.

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## **Declaration of interest**

The authors declare no conflict of interest

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