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Original article

Amendment of traditional assessment measures for the negative symptoms of schizophrenia

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ABSTRACT

Schizophrenia research based on traditional assessment measures for negative symptoms appears to be, to some extent, unreliable. The limitations of the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) have been extensively acknowledged and should be taken into account. The aim of this study is to show how the PANSS and the SANS conflate negative symptoms and cognition and to offer alternatives for the limitations found.

Methods: A sample of 117 participants with schizophrenia from two independent studies was retrospectively investigated. Linear regression models were computed to explore the effect of negative symptoms and illness duration as predictors of cognitive performance.

Results: For the PANSS, the item "abstract thinking" accounted for the association between negative symptoms and cognition. For the SANS, the "attention" subscale predicted the performance in verbal memory, but illness duration emerged as a stronger predictor than negative symptoms for outcomes of processing speed, verbal and working memory.

Conclusion: Utilizing alternative models to the traditional PANSS and SANS formats, and accounting for illness duration, provide more precise evidence on the relationship between negative symptoms and cognition. Since these measures are still extensively utilized, we recommend adopting more rigorous approaches to avoid misleading results.

1. Introduction

"My experience is what I agree to attend to. Only those items which I notice shape my mind." – William James

During the last decade, there has been increasing interest in negative symptoms (NS) of schizophrenia together with a re-evaluation of the scales measuring them. Novel instruments have been developed although they have yet to be generally adopted, whilst studies based on traditional scales appear to be to some extent unreliable.

The characteristics of the Positive and Negative Syndrome Scale (PANSS) [1] and the Scale for the Assessment of Negative Symptoms (SANS) [2] have been a matter of discussion over the last 20 years. For example, further PANSS-subscales including four, five, or six factors have been proposed with several studies underlining that five-factor models show an adequate reliability when tested in different subgroups of individuals with schizophrenia, confirming the suitability of this approach [3,4]. On the other hand, cross-sectional studies of the SANS identify three, four and five different symptom factors; and longitudinal research has replicated three factors [5]. In particular, the NS subscale within the traditional PANSS consists of seven items tapping blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity, and stereotyped thinking. And the original SANS consists of 19 items representing five domains: affective flattering, alogia, avolition-apathy, anhedonia-asociality, and attention.

A number of studies have adapted these scales to provide the two dimensions of NS, Diminished Expression and Amotivation/Avolition. For the PANSS, Liemburg et al. [6] studied the two-factor structure for NS in early psychosis participants. These factors were named "core NS", related to the expressive deficits, and "social emotive withdrawal", described as social amotivation. Similarly,

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Fervaha et al. [7] extended these findings to patients with chronic schizophrenia, calling the two factors "diminished expression" and "amotivation"; and comparable two-factor results were recently published by Lim and colleagues [8]. For the SANS, similar factor models accounting for diminished expression and anhedonia-asociality have emerged. For example Sayers et al. [9] confirmed a general three factor approach for the SANS including "diminished expression", "inattention-alogia" and "social amotivation", while Kelley et al. studied primary and secondary negative symptoms of schizophrenia employing the two factor approach of "affective flattening" and "diminished amotivation" [10].

Factor analysis studies have indicated that cognitive items in the PANSS and SANS do not cohere well with the other NS ratings [11], and cognitive deficit appears to be conceptually distinct from NS [e.g. [12]. Possible confounding instances include items of "difficulty of abstract thinking" and "stereotyped thinking" in the PANSS, and the "attention" subscale in the SANS (See Blanchard and Cohen for a review [13]). As an illustration, Bell et al. [14] demonstrated that performance on neuropsychological tests was associated with the cognitive component of the PANSS ("abstract thinking" and "stereotyped thinking") but not with other NS items within the PANSS. For the SANS, Vadhan et al. [15] found a correlation between the "attention" subscale and neuropsychological tasks which discriminated "attention" from the other SANS subscales. Similarly, Liemburg et al. [6] and Lim et al. [8] reported an association between the "diminished expression" PANSS factor and cognition.

Both cognitive impairment and NS are formally considered as core features of schizophrenia contributing to poor functional and community outcomes (e.g. [16,17]). The present study was motivated by the ongoing utilization of traditional approaches to the PANSS and the SANS albeit the limitations stated above. Our aim is to show possible misleading associations between negative symptoms and cognition when using the original PANSS and SANS factors, and to offer alternatives to overcome them while still utilizing the PANSS and the SANS.

Specifically, our aim is to illustrate how the traditional PANSS and SANS may perform differently on the associations between NS and cognition depending on the factor approaches utilized. Findings from a previous study by our group suggested that NS could hamper the expression of cognition on behavioural tasks and functional outcomes [18]. These findings were of interest since common theoretical backgrounds generally assume that cognition would have an effect on NS (e.g., [19]) but not vice versa.

Finally, illness duration will be taken into account as a confounder variable since the study included chronic and institutionalized participants and this might perform a detrimental effect on both cognition and NS. Our hypothesis is that longer illness duration may have an impact on the association between NS and cognitive performance, particularly in hospitalized participants. A decline in cognition has been also reported after ten years of illness duration [20] and in geriatric patients with schizophrenia [21]. Likewise, chronicity and hypostimulating environments can cause secondary negative symptoms such as decreased spontaneity, reduced curiosity, reduced drive to interact and blunted affect [22,23].

2. Method

2.1. Participants

Two samples of participants with schizophrenia were retrospectively studied. Both groups belonged to the same mental health services from Barcelona metropolitan area and were recruited in independent investigations. *Group 1* involved outpatients recruited with the purpose of studying the efficacy of Cognitive Remediation group treatment [24]. *Group 2* included inpatients recruited to study cognitive impairment in schizophrenia [25]. Both studies were approved by the Parc Sanitari Sant Joan de Déu Ethics Committee.

Group 1- Sixty-two participants with a diagnosis of schizophrenia or schizoaffective disorder following DSM-IV criteria were recruited from Parc Sanitari Sant Joan de Déu community services [26]. To verify the stability of the diagnosis we checked the medical histories to corroborate that the required DSM-IV criteria were appropriately described. Two cases were unconfirmed and the Structured Clinical Interview for DSM-IV (SCID; [27]) was utilized to verify their diagnoses. The participants included were between 18 and 65 years of age, with disease duration of over two years. Patients were excluded if they were suffering acute illness exacerbation that required hospitalization, had intellectual disability or neurological disorder, had switched antipsychotic drugs the month before the assessment, and/or had a diagnosis of alcohol or drug dependence within 6 months prior to inclusion. Initially, 70 participants referred by their community teams or rehabilitation services were assessed for eligibility. Of these, two were excluded for not meeting inclusion criteria (change of diagnosis to bipolar disorder and presence of learning disability), four refused consent, and two were not interested.

Group 2 – Fifty-five participants with schizophrenia were recruited from Parc Sanitari Sant Joan de Déu inpatient services. The diagnosis was made by consensus on the basis of DSM-IV criteria by two experienced psychiatrists who used patient histories and chart reviews. Inclusion criteria were age between 18 and 65, fluency in Spanish, and the capacity to provide informed consent. Exclusion criteria were current or recent alcohol or drug abuse (DSM-IV criteria), organic mental disease, intellectual disability, history of brain injury, dementia, and current severe physical disease. Participants were hospitalized and had been receiving stabilized doses of antipsychotic medication over two weeks at the time of testing. Clinical records were reviewed thoroughly by the psychiatrist recruiting the participants (J Cuevas-Esteban) and only those inpatients meeting all inclusion criteria were asked to participate. The rates of consent were about 75% of those eligible to take part.

For both groups the antipsychotic medication included first-generation antipsychotics (clotiapine, fluphenazine, haloperidol, levomepromazine, zuclopenthixol) as well as second-generation (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone). Predominantly within *Group 2*, participants were taking a combination of two or more antipsychotic drugs and/or were administered benzodiazepines (clonazepam, diazepam, flunitrazepam, lorazepam, lormetazepam) and/or antidepressant (duloxetine, fluoxetine, paroxetine, trazodone) medication.

2.2. Measures

Group 1- The cognitive assessment included the following domains: *Executive Function* using the Behavioural Assessment of the Dysexecutive Syndrome (BADS) [28], which consists of six tests involving cognitive flexibility, inhibition of impulsive responses, planning and organization, working memory, and time-estimation capacity. Attention, processing speed, and cognitive flexibility were measured with The Trail Making Test forms A and B (TMT A; TMT B) [29]. Verbal memory, both immediate and delayed, was assessed with the Logical Memory I and II subscales respectively, from the Wechsler Memory Scale (WMS-III) [30].

Negative symptoms were measured with the Spanish validation of the PANSS [31]. The negative PANSS factors employed in this study were the original 3-factor approach by Kay et al. [1] including 7 items: blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, lack of spontaneity, difficulty

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in abstract thinking, and stereotyped thinking. Also used was the consensual 5-factor approach by Wallwork et al. [3] including 6 items: blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, lack of spontaneity, and motor retardation.

Group 2- Cognition was evaluated through several tasks: Cognitive speed was measured using the WAIS-III [32] Digit Symbol Substitution Test (DSST). The time required to read the whole list of the colour reading part of the Stroop test [33] was recorded to evaluate motor speed. Verbal recall (frequent and rare words) was assessed with 2 lists of words consisting of 16 high-frequency words and 16 low-frequency words [34]. Working memory was measured through the WAIS-III Letter-number span using the total number of correct trials.

Negative symptoms were assessed by means of the Spanish version of the SANS [35] following the traditional evaluation of 5 domains: affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention.

2.3. Statistical analysis

Linear regression models were computed to explore the effect of NS on the cognitive variables targeted. The dependent variables were the BADS, TMT A, TMT B, and the WMS-III subscales for *Group 1*. In contrast, the Digit Symbol Substitution Test, Stroop Test, memory of high-frequency and low-frequency words, and Letter-number span were the dependent variables for *Group 2*. Independent variables were NS measured with the PANSS and the SANS, respectively.

In a first step we computed the regression model with each NS scale for every cognitive outcome without modifications. For *Group 1* this was done using both the PANSS (K) negative by Kay et al. and the PANSS (W) negative by Wallwork et al. For *Group 2* we used the traditional SANS. Next, if the association between NS and cognitive outcomes resulted in $p < 0.1$ in the regression model, the negative factor was computed again without including the cognitive items ("abstract thinking" in the PANSS and "attention" in the SANS) to test them as separate predictors. Therefore, PANSS6 corresponded to the PANSS (K) negative excluding the item of "abstract thinking", and SANS4 was used to refer the SANS without the "attention" subscale. No modifications were applied to the PANSS (W) negative since this factor already excludes the items of "abstract thinking" and "stereotyped thinking". Finally, if the association between NS and the cognitive outcome was still significant, illness duration was controlled in the model. The statistical analysis was conducted using SPSS 17.0 [36].

3. Results

Descriptive characteristics for each group are shown in Table 1.

Group 1- Regression models using the PANSS negative factors by Kay et al. [1] and Wallwork et al. [3] are shown in Table 2.

Results were different depending on the factor approach utilized for the PANSS. Following the original 3-factor model, Executive function and Visual and motor speed appeared to be predicted by NS, also showing a tendency towards association with delayed Logical memory ($p = 0.08$). When the item "abstract thinking" was accounted for separately in the model, the predictive value of negative symptoms over cognitive outcomes lost its significance. The case of the *BADS* was a clear illustration: the standardized regression coefficient (B) for the predictive value of the PANSS negative was initially −0.31, but when controlling for "abstract thinking", the value was considerably reduced (B = −0.07) whilst the B coefficient for "abstract thinking" was −0.41.

Table 1
Descriptive characteristics by group.

Group 1 N = 62	Mean (SD) (min.-max.)	Group 2 N = 55	Mean (SD) (min.-max.)
Sex Man: N (%)	 42 (65.6%)	Sex Man: N (%)	 36 (63.2%)
Age (years)	39.9 (7.7) (20–56)	Age (years)	46.6 (10.6) (21–65)
Education: N (%) Uncompleted primary Completed primary High school completed	 12 (19.4%) 39 (62.9%) 11 (17.7%)	Education: N (%) Uncompleted primary Completed primary High school completed	 22 (40%) 21 (38.2%) 12 (21.8%)
Executive Function (BADS)	85.9 (18.6) (41–119)	Cognitive processing (DSST)	28.6 (14.5) (3–63)
Visual and motor processing speed (TMT A seconds)	65.4 (43.3) (27–303)	Motor processing-seconds (Stroop color)	61.7 (22.7) (37–135)
Processing speed and flexibility (TMT B seconds)	135 (79.3) (47–420)	Verbal recall frequent words	2 (1.8) (0–6)
Immediate verbal memory (Logical memory I)	24.9 (11.1) (4–51)	Verbal recall rare words	1.8 (1.6) (0–7)
Delayed verbal memory (Logical memory II)	13.7 (8.8) (3–41)	Working memory (Letter-number spam)	5.7 (2.7) (2–13)
Illness duration (years)	17.5 (8.8) (3–41)	Illness duration (years)	23.4 (8.9) (9–46)
PANSS Negative Kay et al. [1]	18.7 (4.7) (10–31)	Negative Symptoms SANS	26.5 (13.9) (0–54)
PANSS Negative Wallwork et al. [3]	15.8 (4.3) (7–27)		

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Table 2
Regression models with the PANSS Negative (Group 1).

	PANSS (K) NEGATIVE (Kay et al.)				PANSS (W) NEGATIVE (Wallwork et al.)			
	Variables	B* (95% CI)	t-value	p-value	Variables	B* (95% CI)	t-value	p-value
Executive function	PANSS (K) negative	-0.31	-2.53	**0.01**	PANSS (W) negative	-0.17	-1.35	0.18
BADS	**PANSS NEG6**	-0.07	-0.54	0.60				
	Abstract thinking	-0.41	-3.27	**0.002**				
Visual and motor speed	PANSS (K) negative	0.3	2.47	**0.02**	PANSS (W) negative	0.22	1.74	0.08
TMTA	**PANSS NEG6**	0.07	0.59	0.56	PANSS (W) negative	0.17	1.33	0.2
	Abstract thinking	0.39	3.06	**0.003**	Illness duration	0.19	1.5	0.14
Processing speed & flexibility	PANSS (K) negative	0.18	1.39	0.17	PANSS (W) negative	0.12	0.92	0.36
TMTB								
Immediate verbal memory	PANSS (K) negative	-0.25	-0.19	0.84	PANSS (W) negative	0.11	0.88	0.38
Logical Memory I								
Delayed verbal memory	PANSS (K) negative	-0.22	-1.7	0.08	PANSS (W) negative	-0.08	-0.60	0.55
Logical Memory II	**PANSS NEG6**	0.08	0.66	0.51				
	Abstract thinking	-0.51	-4.1	<**0.0001**				

B* = Standardized regression coefficient (95% confidence interval)**;** PANSS NEG6: blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, lack of spontaneity and stereotyped thinking.

In contrast, the negative factor by Wallwork et al. did not show any significant association with the cognitive outcomes assessed.

Group 2- Results from linear regression using the SANS are shown in Table 3. The regression model applied without controlling for covariables showed that levels of negative symptoms predicted the cognitive outcomes studied, with the exception of Verbal recall of rare words. In the second step, the SANS4 model accounting separately for the "attention" subscale demonstrated a tendency towards significance between Verbal recall of frequent words and "attention" ($p = 0.05$). In a third step, when illness duration was included in the model as a covariable, the association between Verbal recall of frequent words and "attention" proved stronger, but outcomes for Cognitive processing speed, Motor processing speed and Working memory became significantly predicted by illness chronicity. As an example, the SANS4 standardized B coefficient for Working memory was initially −0.31, but when controlling for "attention" and illness duration it became B = −0.05. However, the B coefficient for illness duration was −0.43.

Table 3
Regression models using the SANS (Group 2).

Cognitive Outcomes	Variables	B* (95% CI)	t-value	p-value
Cognitive processing speed	SANS	-0.38	-3.03	**0.004**
	SANS4	-0.37	-2.6	**0.01**
	Attention	-0.02	-0.12	0.90
	SANS4	0.005	0.32	0.97
	Attention	-0.09	-0.75	0.45
	Illness duration	-0.62	-4.81	<**0.0001**
Motor processing speed	SANS	-0.44	-3.6	**0.001**
	SANS4	-0.48	-3.44	**0.001**
	Attention	0.05	0.39	0.7
	SANS4	-0.18	-1.22	0.22
	Attention	-0.008	-0.06	**0.95**
	Illness duration	-0.48	-3.5	**0.001**
Verbal recall frequent words	SANS	-0.42	-3.35	**0.001**
	SANS4	-0.26	-1.91	0.06
	Attention	-0.27	-1.95	**0.05**
	SANS4	-0.1	-0.6	0.55
	Attention	-0.33	-2.4	**0.02**
	Illness duration	-0.27	-1.8	0.07
Verbal recall rare words	SANS	-0.15	-1.1	0.27
Working memory	SANS	-0.39	-3.1	**0.003**
	SANS4	-0.31	-2.16	**0.03**
	Attention	-0.14	-1.01	0.31
	SANS4	-0.05	-0.3	0.76
	Attention	-0.18	-1.34	0.19
	Illness duration	-0.43	-2.95	**0.005**

B* = Standardized regression coefficient (95% confidence interval). SANS4: Affective flattering, alogia, avolition-apathy, anhedonia-asociality.

4. Discussion

Our findings illustrate how traditional factor approaches to NS may actually conflate cognitive processes and negative symptoms (e.g., [11,37]). Additionally, illness duration was demonstrated to predict cognitive performance within the sample of inpatients. According to the present study, the limitations found within the traditional PANSS and SANS can be addressed, so investigations employing these scales are encouraged to adopt more rigorous ways to discriminate NS.

4.1. The PANSS

There is extensive literature covering different factor approaches for the PANSS [1] (see Blanchard and Cohen [13]). Current research has called for a 5-factor solution demonstrating more precise and homogeneous definition of symptom dimensions [4]; the present research shows that the consensual PANSS Negative factor by Wallwork et al. [3] including 6 items (blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, lack of spontaneity, and motor retardation) may be a convenient alternative to the original approach. The factor approach of Marder et al. [38] is among other popular options to fit PANSS data excluding the items of "abstract thinking" and "stereotyped thinking" from the NS domain. In this study, controlling for "abstract thinking" was enough to demonstrate the misleading association between NS and cognition when employing the Kay et al. [1] approach to the PANSS supporting previous findings [39].

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4.2. The SANS

In the case of the SANS this study was carried out involving chronic institutionalized participants. Both the "attention" subscale and illness duration were demonstrated to predict cognitive performance instead of NS. The "attention" subscale was associated with verbal memory; while chronicity predicted deficits in processing speed and working memory ratifying the impact of illness duration on cognition [20,21,40]. There has been ample discussion about the best factor approach fitting the SANS data, with evidence suggesting that the inclusion of "attention" in ratings of NS is somewhat problematic [13]. Research suggests the 3-factor approach (affective-flattering, asociality, and alogia/attentiveness) might be more parsimonious, and it showed better validity [9,5]; but this approach includes items from the "attention" subscale and this may not resolve the link with cognition. We suggest taking the "attention" subscale into account especially when investigations aim to distinguish precisely between cognition and NS.

New measures for the assessment of NS have been developed following the NHIM consensus meeting on NS [41]. These are the Clinical Assessment Interview for Negative Symptoms (CAINS) [42,43] and the Brief Negative Symptom Scale (BNSS) [44,45]. These scales are a stimulating outcome and are promising for the field although they remain to be generally implemented. Nonetheless, recent studies have shown small to moderate associations between the CAINS and cognition, comparable to the associations found when utilizing other negative symptom scales [46]. The BNSS has also pointed to some overlap between diminished expression and cognition [47]. On the whole, it seems necessary to further explore the association and shared pathophysiology between NS and cognition. According to the present results, NS would not have an effect on participants' cognitive performance, but chronicity could have a negative impact on cognition in hospitalized patients. The distinction between NS and cognition has been cause for debate over several years. Some authors have argued that NS may be underpinned by cognitive deficits such as the impaired initiation of novel responses (e.g. [48]) while others have suggested that patients with higher levels of NS have particular impairments in reasoning and executive function (e.g. [49]). However, several studies have failed to establish a relationship between NS and cognition, leading to the conclusion that they represent semi-autonomous disease processes (e.g. [41,50]); and the correlation between cognition and NS may vary as a function of the definition of the NS construct [12]. Therefore, research and clinical communities are still facing the challenging situation of properly recognising and targeting NS. Understanding NS means identifying them among other confounder variables, and being able to measure them in the most precise way. This matter has not been resolved yet, in particular with regard to their association with cognition.

This study has a number of limitations that need to ne noted. First, this is a retrospective analysis with two samples initially recruited for two different purposes. As such, cognitive and clinical measures employed were chosen according to the aims of each particular investigation so the measurement of cognitive variables was not performed with the same scales. In addition, some of the participants from Group 2 were chronic and had had years of institutionalization, which carries confusion with regard to the specific causes of their deficit (e.g., [21,23]). Third, the alternatives suggested to compensate for the cognitive items within the SANS and the PANSS may not to be exhaustive and we have not considered alternative models, for example the PANSS with four and six factors. Finally, some question marks have already arisen concerning the proposed factor approaches (e.g., reporting an association between cognition and NS although convenient modifications were adopted [6,8]), casting some doubt on our findings and supporting the idea that NS and cognitive deficits may overlap and may not be independent to each other.

Despite these limitations, the present study has demonstrated that when relying on old but still widely used measures such as the PANSS and the SANS, it is advisable to avoid items too closely related to cognition. This is especially important in comprehending NS in schizophrenia, and in the development of effective targeted treatment approaches.

Conflicts of interest

None.

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References

[1] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76, doi:http://dx.doi.org/10.1093/schbul/13.2.261.
[2] Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry Suppl 1989;49–58.
[3] Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res 2012;137:246–50, doi:http://dx.doi.org/10.1016/j.schres.2012.01.031.
[4] Nicotra E, Casu G, Piras S, Marchese G. On the use of the Positive and Negative Syndrome Scale in randomized clinical trials. Schizophr Res 2015;165:181–7, doi:http://dx.doi.org/10.1016/j.schres.2015.04.006.
[5] Levine SZ, Leucht S. Psychometric analysis in support of shortening the Scale for the Assessment of Negative Symptoms. Eur Neuropsychopharmacol 2013;23:1051–6, doi:http://dx.doi.org/10.1016/j.euroneuro.2012.11.008.
[6] Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. J Psychiatr Res 2013;47:718–25, doi:http://dx.doi.org/10.1016/j.jpsychires.2013.01.024.
[7] Fervaha G, Foussias G, Agid O, Remington G. Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. Acta Psychiatr Scand 2014;130:290–9, doi:http://dx.doi.org/10.1111/acps.12289.
[8] Lim J, Lee S-A, Lam M, Rapisarda A, Kraus M, Keefe RSE, et al. The relationship between negative symptom subdomains and cognition. Psychol Med 2016;46:2169–77, doi:http://dx.doi.org/10.1017/S0033291716000726.
[9] Sayers S, Curran P, Mueser K. Factor Structure and Construct Validity of the Scale for the Assessment of Negative Symptoms. Psychol Assess 1996;8:269–80, doi:http://dx.doi.org/10.1037//1040-3590.8.3.269.
[10] Kelley ME, van Kammen DP, Allen DN. Empirical validation of primary negative symptoms: independence from effects of medication and psychosis. Am J Psychiatry 1999;156:406–11, doi:http://dx.doi.org/10.1176/ajp.156.3.406.
[11] Blanchard JJ, Kring AM, Horan WP, Gur R. Toward the next generation of negative symptom assessments: the collaboration to advance negative symptom assessment in schizophrenia. Schizophr Bull 2011;37:291–9, doi:http://dx.doi.org/10.1093/schbul/sbq104.
[12] Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr Bull 2006;32:250–8, doi:http://dx.doi.org/10.1093/schbul/sbj011.
[13] Blanchard JJ, Cohen AS. The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. Schizophr Bull 2006;32:238–45, doi:http://dx.doi.org/10.1093/schbul/sbj013.
[14] Bell MD, Mishara AL. Does negative symptom change relate to neurocognitive change in schizophrenia? Implications for targeted treatments. Schizophr Res 2006;81:17–27, doi:http://dx.doi.org/10.1016/j.schres.2005.09.016.
[15] Vadhan NP, Serper MR, Harvey PD, Chou JC, Cancro R. Convergent validity and neuropsychological correlates of the schedule for the assessment of negative symptoms (SANS) attention subscale. J Nerv Ment Dis 2001;189:637–41, doi:http://dx.doi.org/10.1097/00005053-200109000-00011.
[16] Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res 2004;72:41–51, doi:http://dx.doi.org/10.1016/j.schres.2004.09.009.
[17] Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry 2005;162:495–506, doi:http://dx.doi.org/10.1176/appi.ajp.162.3.495.
[18] Farreny A, Aguado J, Ochoa S, Haro JM, Usall J. The role of negative symptoms in the context of cognitive remediation for schizophrenia. Schizophr Res 2013;150:58–63, doi:http://dx.doi.org/10.1016/j.schres.2013.08.008.

[19] Cella M, Stahl D, Morris S, Keefe ERS, Bell MD, Wykes T. Effects of cognitive remediation on negative symptoms dimensions: exploring the role of working memory. Psychol Med 2017;4:1–9, doi:http://dx.doi.org/10.1017/S0033291717000757.
[20] Øie M, Sundet K, Rund BR. Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: evidence from a 13-year follow-up study. Schizophr Bull 2010;36:557–65, doi:http://dx.doi.org/10.1093/schbul/sbn127.
[21] Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, et al. Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. Biol Psychiatry 1999;45:32–40.
[22] Oshima I, Mino Y, Inomata Y. Effects of environmental deprivation on negative symptoms of schizophrenia: A nationwide survey in Japan's psychiatric hospitals. Psychiatry Res 2005;136:163–71, doi:http://dx.doi.org/10.1016/j.psychres.2005.06.001.
[23] Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms — a review of mechanisms, assessment and treatment. Schizophr Res 2017;186:29–38, doi:http://dx.doi.org/10.1016/j.schres.2016.05.003.
[24] Farreny A, Aguado J, Ochoa S, Huerta-Ramos E, Marsà F, López-Carrilero R, et al. REPYFLEC cognitive remediation group training in schizophrenia: looking for an integrative approach. Schizophr Res 2012;142, doi:http://dx.doi.org/10.1016/j.schres.2012.08.035.
[25] Brébion G, Stephan-Otto C, Huerta-Ramos E, Ochoa S, Usall J, Abellán-Vega H, et al. Visual encoding impairment in patients with schizophrenia: contribution of reduced working memory span, decreased processing speed, and affective symptoms. Neuropsychology 2015;29:17–24, doi:http://dx.doi.org/10.1037/neu0000104.
[26] American Psychiatric Association. DSM-IV: Manual diagnóstico y estadístico de los trastornos mentales. Texto revisado. Barcelona: Elsevier Masson; 2002.
[27] First Michael B, Spitzer Robert L, Gibbon Miriam, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen. New York: Biometrics Research; 2002.
[28] Wilson B, Alderman N, Burgess P, Emslie H, Evans J. Behavioural Assessment of the Dysexecutive Syndrome. London: Thames Valley Test Company; 1996.
[29] Reitan R, Wolfson D. Category Test and Trail Making Test as measures of frontal lobe functions. Clin Neuropsychol Neuropsychol 1995;9:50–6.
[30] Wechsler D. WMS-III- Escala de Memoria de Wechsler. Madrid: T.E.A Ediciones. 2004.
[31] Peralta Martín V, Cuesta Zorita MJ. Validation of positive and negative symptom scale (PANSS) in a sample of Spanish schizophrenic patients. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1994;22:171–7.
[32] Wechsler D. WAIS-III: Wechsler Adult Intelligence Scale. Administration and scoring manual. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
[33] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.
[34] Algarabel S, Ruiz JC, Sanmartin J. The University of Valencia's computerized word pool. Behav Res Methods Instrum Comput 1988;20:398–403, doi:http://dx.doi.org/10.3758/BF03202684.
[35] Peralta V, Cuesta MJ. Dimensional structure of psychotic symptoms: an item-level analysis of SAPS and SANS symptoms in psychotic disorders. Schizophr Res 1999;38:13–26.
[36] IBM. IBM SPSS Statistics for Windows. 2013.
[37] Daniel DG. Issues in selection of instruments to measure negative symptoms. Schizophr Res 2013;150:343–5, doi:http://dx.doi.org/10.1016/j.schres.2013.07.005.
[38] Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–46.
[39] Bell MD, Lysaker PH, Milstein RM, Beam-Goulet JL. Concurrent validity of the cognitive component of schizophrenia: relationship of PANSS scores to neuropsychological assessments. Psychiatry Res 1994;54:51–8.
[40] Rajji TK, Mulsant BH. Nature and course of cognitive function in late-life schizophrenia: A systematic review. Schizophr Res 2008;102:122–40, doi:http://dx.doi.org/10.1016/j.schres.2008.03.015.
[41] Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006;32:214–9, doi:http://dx.doi.org/10.1093/schbul/sbj053.
[42] Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res 2011;132:140–5, doi:http://dx.doi.org/10.1016/j.schres.2011.06.030.
[43] Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry 2013;170:165–72, doi:http://dx.doi.org/10.1176/appi.ajp.2012.12010109.
[44] Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull 2011;37:300–5, doi:http://dx.doi.org/10.1093/schbul/sbq059.
[45] Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, et al. Next-generation negative symptom assessment for clinical trials: Validation of the Brief Negative Symptom Scale. Schizophr Res 2012;142:88–92, doi:http://dx.doi.org/10.1016/j.schres.2012.10.012.
[46] Blanchard JJ, Bradshaw KR, Garcia CP, Nasrallah HA, Harvey PD, Casey D, et al. Examining the reliability and validity of the Clinical Assessment Interview for Negative Symptoms within the Management of Schizophrenia in Clinical Practice (MOSAIC) multisite national study. Schizophr Res 2017;185:137–43, doi:http://dx.doi.org/10.1016/j.schres.2017.01.011.
[47] Hartmann-Riemer MN, Hager OM, Kirschner M, Bischof M, Kluge A, Seifritz E, et al. The association of neurocognitive impairment with diminished expression and apathy in schizophrenia. Schizophr Res 2015;169:427–32, doi:http://dx.doi.org/10.1016/j.schres.2015.10.032.
[48] Greenwood KE, Morris R, Sigmundsson T, Landau S, Wykes T. Executive functioning in schizophrenia and the relationship with symptom profile and chronicity. J Int Neuropsychol Soc 2008;14:782–92, doi:http://dx.doi.org/10.1017/S1355617708081198.
[49] Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr Res 2009;113:189–99, doi:http://dx.doi.org/10.1016/j.schres.2009.03.035.
[50] Foussias G, Remington G. Negative symptoms in schizophrenia: Avolition and occam's razor. Schizophr Bull 2010;36:359–69, doi:http://dx.doi.org/10.1093/schbul/sbn094.