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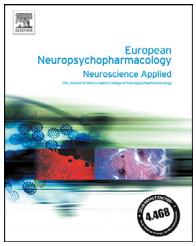

Clinical utility of the Negative Symptom Assessment-16 in individuals with schizophrenia

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Abstract
This study examined the clinical utility of the Negative Symptom Assessment-16 (NSA-16) in schizophrenia. 274 individuals with schizophrenia were assessed on the NSA-16, Positive and Negative Syndrome Scale (PANSS), Clinical Assessment for Negative Symptoms (CAINS), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale (SOFAS) and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS). Factor analyses were conducted and Cronbach's alpha was computed. Correlations were assessed using Spearman's correlation coefficient. The 5-factor model of the NSA-16 did not give good fit statistics from our sample. Exploratory factor analysis on a randomly selected split-half of the sample followed by confirmatory factor analysis on the remaining sample supported a 4-factor structure with 12 items. The factors were: Restricted speech, Poor quality of speech, Affective blunting and Amotivation. The NSA-16 with the 12 items was termed as the NSA-12. The NSA-12 showed good internal reliability. The NSA-12 total score and global negative symptom rating had strong correlations with CAINS total and PANSS negative factor scores, suggesting good convergent validity. Weak correlations of the NSA-12 total score and global negative symptom rating with PANSS positive, CDSS and SAS scores suggested good divergent validity. The NSA-12 total score and global negative symptom rating were strongly and inversely associated with SOFAS and positively associated with NSA-12 global level of functioning. In conclusion, the NSA-12 is useful to evaluate negative symptoms in clinical and research settings in individuals with

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schizophrenia. Our study results also support a 4-factor structure of the NSA-12 in outpatients with schizophrenia.

1. Introduction

Management of negative symptoms remains a challenge to clinicians despite efforts to investigate various treatment strategies for them, including various pharmacological and non-pharmacological interventions (Moller and Czobor, 2015; Remington et al., 2016). Clinical trials exploring treatment options for negative symptoms require suitable rating scales that can comprehensively measure negative symptoms across its various domains.

The Negative Symptom Assessment-16 (NSA-16) was developed to assess the presence, severity and range of negative symptoms in schizophrenia (Alphs et al., 1989; Axelrod et al., 1993). A principal components analysis of initial work with the NSA-16 suggested a 5-factor structure when used to assess negative symptoms in hospitalised individuals with schizophrenia with a broad array of negative symptoms of varying severity. The 5 factors identified were communication (items 1–4), emotion/affect (item 5-7), social involvement (items 8-10), motivation (items 11-14) and retardation (items 15 and 16) (Axelrod et al., 1993). Popp et al. (2012) used confirmatory factor analyses and suggested a 3-factor structure of the NSA-16, by combining the communication and social factors into the first factor (items 1–4, 9, 10), emotion/affect and retardation into the second factor (items 5–7, 15, 16), and motivation being the third factor (items 8, 11–14).

The NSA-16 has good convergent and divergent validity and is able to predict disease severity and impairment in individuals with schizophrenia (Cazorla et al., 2008). It has been reported to have good interrater reliability across different cultures (Daniel et al., 2011a) and requires only brief training to use it (Axelrod and Alphs, 1993). Moreover, it is sensitive to change in negative symptoms over time (Eckert et al., 1996). Notably, the NSA-16 is the only instrument to have a single item measuring the global or overall severity of negative symptoms. This allows for the comparison of component elements of the negative symptom construct included in the NSA-16 against a global clinical understanding of the construct. In a survey of 39 clinical trials raters, NSA-16 was rated to be the most effective rating scale to measure negative symptoms and with maximum clarity of anchors, when compared to the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1982; Daniel et al., 2011b).

Although the NSA-16 is easy to use and sensitive to the multidimensional structure of negative symptoms in schizophrenia, few studies have explored its clinical utility in different patient settings and cultures. This study aimed to examine the clinical utility of the NSA-16 in individuals with schizophrenia. We assessed the psychometric properties of the NSA-16 when used to assess negative symptoms in outpatients with schizophrenia. The association between negative symptoms assessed by the validated model of the NSA-16 and functioning was also explored.

2. Experimental procedures

2.1. Setting and study participants

Participants for this study were recruited from the outpatient clinics at the Institute of Mental Health (IMH), Singapore. Participants were either referred by their healthcare professionals when they came for their regular clinic visits, or were identified through databases of previous research studies. The latter had previously consented to being re-contacted for future research studies. These potential participants were contacted in person or by phone by study team members, and invited to take part in the study. Those who agreed to participation in the study were then screened for eligibility.

Inclusion criteria were: (i) a diagnosis of schizophrenia, (ii) ages 21–65 and (iii) able to speak English. Exclusion criteria for the study were (i) a current alcohol or substance use disorder, (ii) mental retardation, or (iii) a history of head injury or neurological disorder. Diagnosis of schizophrenia was confirmed using the Structured clinical Interview for DSM-IV (SCID I) (First et al., 2002). Recruitment period for the study was from August 2014 to December 2017, and a total of 277 participants were recruited. Three participants withdrew from the study, and were not assessed on the NSA-16, leaving a total study sample of 274.

Ethics approval was provided by the National Healthcare Group's Domain Specific Review Board at Singapore. Written informed consent was obtained from all the participants prior to study assessments.

2.2. Study assessments

The NSA-16 has 16 items rated on a 7-point Likert scale, with anchor points ranging from the symptoms being absent (1) to severe (6) or not ratable (9), and two global scores rating the global severity of negative symptoms and global level of functioning. The NSA-16 global negative symptoms rating scores range from 1 (no impairment) to 7 (extremely severe negative symptoms). The NSA-16 global level of functioning is also rated from 1 (no impairment in functioning) to 7 (extremely severe impairment in functioning). Information for rating was obtained through a semi-structured interview, and the time frame used for rating was last one week.

The PANSS (Kay et al., 1987) was used to assess the severity of schizophrenia psychopathology. It consists of 30 items: 7 positive, 7 negative, and 16 general psychopathology items. Each item is rated on a 7-point Likert scale, from 1 (absent) to 7 (severe). PANSS factor scores were computed based on a 5-factor structure validated in our local population with schizophrenia; the factors were: positive, negative, excitement, depression and cognitive (Jiang et al., 2013). Using the PANSS, negative symptoms have been reported to have 2 subdomains: diminished emotional expression (DEE) consisting of items N1, N3, N6, G7 and G13 and social amotivation (SA) consisting of items N2, N4 and G16 of the PANSS (Lim et al., 2016). The DEE and SA factor scores were also computed. The PANSS negative, DEE and SA factor scores were used to assess the convergent validity of

the NSA-16, whereas the PANSS positive scores were used to assess the divergent validity of the NSA-16.

Severity of negative symptoms was also assessed on the Clinical Assessment for Negative Symptoms (CAINS) (Forbes et al., 2010; Horan et al., 2011). It has 13 items, and each item is rated on a 5-point scale, from absent (0) to severe (4). The CAINS was found to have 4 factors when validated in our local schizophrenia population: motivation-pleasure (MAP) social, MAP work, MAP recreation and expression (EXP) (Rekhi et al., 2019). The MAP factors measure motivation and pleasure related to social, occupational, and recreational activities. The EXP factor comprises of items to assess facial expression, expressive gestures, vocal expression and quantity of speech. The CAINS was used to assess convergent validity of the NSA-16.

Depressive symptoms were assessed on the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). It has 9 items rated from 0 to 3. Extrapyramidal side effects of antipsychotics were measured on the Simpson-Angus Extrapyramidal Side Effects Scale (SAS), which has 10 items rated from 0 to 4 (Simpson and Angus, 1970). The total scores on these measures were computed. The Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess functioning in the last week, ranging from excellent (100) to grossly impaired (0) (Goldman et al., 1992).

One research clinician, one master level research psychologist and one bachelor level research psychologist were raters for the study. Each rater had at least 2 years' experience in administering rating scales on individuals with schizophrenia. Further training was provided to rate on the NSA-16 and other rating scales. Intra-class correlation coefficients above 0.80 were obtained among the raters for ratings on the NSA-16, CAINS and PANSS. Regular supervision was provided by a research clinician, and bi-monthly case discussions were conducted to maintain the agreement in rating.

2.3. Statistical analyses

Descriptive statistics were used for socio-demographic data and to calculate means of scores on the rating scales. A confirmatory factor analysis (CFA) was done to assess if the 5-factor structure originally reported for the NSA-16 could fit our data by evaluation of goodness of fit indices like Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI). The fit indices on the CFA were not acceptable; therefore, the sample was randomly split into two datasets of approximately equal size. Exploratory factor analysis (EFA) using oblique rotation was conducted on the first split-half sample ($n = 133$). The number of factors was determined by the goodness of fit indices. Only items with loading >0.32 were included in a factor, and items with cross-loading were excluded (Tabachnick and Fidell, 2001). A CFA was conducted on the remaining sample ($n = 141$) to confirm which EFA model had the best fit. Factor scores were evaluated using summation method. Cronbach's alpha coefficient (Cronbach, 1951) was calculated to assess internal consistency of the validated model of the NSA-16 and its factors. Spearman's correlation coefficient was used to assess correlations. Factor analyses were conducted using M-plus version 7.4, all other statistical analyses were performed using IBM SPSS Statistics 23.

3. Results

3.1. Socio-demographic and clinical characteristics of the study sample

The socio-demographic and clinical characteristics of the study participants are shown in Table 1. The sample consisted of almost equal number of males ($n = 152$, 55.5%) and females ($n = 122$, 44.5%). Most of the participants were of Chinese ethnicity ($n = 231$, 84.3%) and living with their families (which included parents, spouse/partner, siblings and/or other relatives) ($n = 215$, 78.5%). Almost half of the study participants were employed ($n = 126$, 46.0%). The mean PANSS positive, negative, DEE and SA factor scores were 8.31 (SD = 4.35), 11.28 (SD = 4.05), 11.01 (SD = 4.05) and 6.64 (SD = 2.27), respectively. A mean SOFAS score of 55.57 (SD = 11.20) suggested moderate difficulty in social, occupational or school functioning.

Table 1 Socio-demographic and clinical characteristics of the study participants.

Socio-demographic characteristics		
	N	*%*
Gender		
Male	152	55.5
Female	122	44.5
Ethnicity		
Chinese	231	84.3
Indians	20	7.3
Malay	22	8.0
Others	1	0.4
Marital status		
Married	35	12.8
Unmarried/separated/divorced/widowed	239	87.2
Living arrangement		
With family	215	78.5
Not with family	59	21.5
Highest education level		
Secondary school & below	101	36.9
Higher than Secondary school	173	63.1
Employment status		
Employed	126	46.0
Unemployed	148	54.0
	Mean	*S.D.*
Age (years)	40.42	10.17
Clinical characteristics	*Mean*	*S.D.*
Duration of psychosis (years)	17.31	9.64
NSA-16 total score	44.17	10.38
Communication	8.39	3.27
Affect	9.85	2.81
Social	9.64	2.99
Motivation	12.37	3.36
Retardation	3.92	1.86
PANSS total score	58.11	12.88
CAINS total score	16.66	7.85
Social	4.76	3.39
Work	3.81	2.56
Recreation	3.37	2.45
Expression	4.72	3.74
CDSS total score	2.84	3.18
SAS total score	1.96	2.71
SOFAS	55.57	11.20

NSA, Negative symptom assessment; PANSS, Positive and Negative Syndrome Scale; CAINS, Clinical Assessment for Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; SAS, Simpson-Angus Extrapyramidal Side Effects Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

Table 2 Descriptive statistics of the NSA-16 items.

	Minimum	Maximum	Mean	S.D.	Skewness	Kurtosis
1. Prolonged time to respond	1	6	1.68	1.195	1.932	3.083
2. Restricted speech quantity	1	6	2.92	1.637	0.139	-1.38
3. Impoverished speech content	1	5	2.19	1.137	0.383	-1.128
4. Inarticulate speech	1	5	1.59	1.027	1.652	1.691
5. Emotion: Reduced range	1	6	3.49	1.232	-0.620	-0.336
6. Affect: Reduced modulation of intensity	1	6	2.93	1.377	0.125	-0.933
7. Affect: Reduced display on demand	1	6	3.43	1.28	0.01	-0.46
8. Reduced social drive	1	6	3.73	1.316	-0.602	-0.747
9. Poor rapport with interviewer	1	6	2.01	1.145	0.886	-0.052
10. Interest in Emotional and Physical Intimacy	1	6	3.89	1.75	-0.118	-1.341
11. Poor grooming and hygiene	1	5	1.74	1.027	1.448	1.696
12. Reduced sense of purpose	1	6	3.52	1.394	-0.255	-0.668
13. Reduced interests	1	5	3.34	1.173	-0.42	-0.553
14. Reduced daily activity	1	6	3.77	1.2	-0.63	-0.492
15. Reduced expressive gestures	1	6	2.53	1.488	0.421	-1.129
16. Slowed movements	1	4	1.4	0.745	1.772	2.111
Global Negative Symptoms Rating	1	6	3.81	1.04	-.309	-.448
Global Level of Functioning	1	6	3.95	1.08	-.362	-.411

NSA, Negative symptom assessment.

Table 3 Factor analyses results of the NSA-16.

	EFA fit stats ($n = 133$)			*CFA fit stats* ($n = 141$)		
	RMSEA (90% CI)	CFI	TLI	RMSEA (90% CI)	CFI	TLI
2-factor model	0.070 (0.050-0.090)	0.935	0.912	0.137 (0.111-0.163)	0.934	0.912
3-factor model	0.034 (0.000-0.062)	0.987	0.979	0.084 (0.057-0.110)	0.971	0.961
4-factor model	0.022 (0.000-0.058)	0.995	0.991	0.064 (0.034 -0.090)	0.981	0.973
5-factor model	Model not feasible as one of the factors had only 1 item NA					

NSA, Negative symptom assessment.

3.2. Descriptive statistics of NSA-16 items

Table 2 shows the range of negative symptoms endorsed by the study participants on the NSA-16. The maximum rating was 6 for all items, except for items 3 (Impoverished speech content), 4 (Inarticulate speech), 11 (Poor grooming and hygiene), 13 (Reduced interests) and 16 (slowed movements). Skewness and kurtosis of the items ranged from −0.63 to 1.932 and −1.38 to 3.083, respectively.

3.3. Construct validity of the NSA-16 (the NSA-12)

The 5-factor model of the NSA-16 (Axelrod et al., 1993) did not give good fit statistics: RMSEA = 0.084, CFI =0.922 and TLI = 0.900 (Hooper et al., 2008). The EFA of the NSA-16 items using first split-half of the dataset suggested solutions with 2–4 factors. EFA fit stats were acceptable for 2-factor solution but good for 3-factor and 4-factor solutions. CFA on the remaining sample yielded poor fit stats for the 2-factor and 3-factor models but good fit stats for the 4-factor model (Table 3). Therefore, the 4-factor model was chosen to be the final model for our sample. The factor loadings of the NSA-16 items from EFA are shown in supplementary table 1. Item 5 (Emotion: Reduced range), 7 (Affect: Reduced display on demand), 10 (Interest in Emotional and Physical Intimacy) and 11 (Poor grooming and hygiene) had loadings <0.32 when EFA was done, and were therefore, not included in any of the 4 factors. The NSA-16 with the 12 items derived from factor analyses was termed as the "NSA-12".

Table 4 shows the factor loadings of the NSA-12 items from CFA. The factors were: factor 1 (Restricted speech), factor 2 (Poor quality of speech), factor 3 (Affective blunting) and factor 4 (Amotivation). The correlations between factors were weak ($r = 0.280$ to 0.316, $p < 0.05$). The poor quality of speech and affective blunting factors were not found to be significantly correlated. All factors were significantly correlated to the NSA-12 global negative symptoms rating ($r_s = 0.458$, 0.378, 0.550, 0.820, respectively; all $p < 0.001$).

The NSA-12 total score was 31.61 (SD = 8.50). Correlation between the NSA-12 total score and the NSA-12 global negative symptoms rating was strong and statistically significant ($r_s = 0.804$, $p < 0.01$).

3.4. Internal consistency reliability of the NSA-12

Cronbach's alpha for the NSA-12 was 0.805. Cronbach's alpha for factors 1, 2, 3 and 4 were 0.799, 0.499, 0.690 and 0.735 respectively.

Table 4 Factor loadings of the NSA-12 items from Confirmatory factor analysis.

Items from NSA-16	Factor 1: Restricted speech	Factor 2: Poor Quality of Speech	Factor 3: Affective blunting	Factor 4: Amotivation
1. Prolonged time to respond			0.559	
2. Restricted speech quantity	0.964			
3. Impoverished speech content		0.941		
4. Inarticulate speech		0.536		
6. Affect: Reduced modulation of intensity			0.960	
8. Reduced social drive				0.681
9. Poor rapport with interviewer	0.891			
12. Reduced sense of purpose				0.754
13. Reduced interests				0.534
14. Reduced daily activity				0.631
15. Reduced expressive gestures			0.827	
16. Slowed movements			0.451	

NSA, Negative symptom assessment

Table 5 Convergent and Divergent validity of the NSA-12.

	NSA-16 total	Factor 1: Restricted speech	Factor 2: Poor Quality of Speech	Factor 3: Affective blunting	Factor 4: Amotivation
	r_s	r_s	r_s	r_s	r_s
CAINS					
MAP Social	.449**	.273**	.260**	.208*	.506**
MAP Work	.439**	.175*	.234**	.196*	.594**
MAP Recreation	.328**	.132*	.148*	.119*	.451**
Expression	.782**	.680**	.230**	.900**	.352**
Total	.802**	.520**	.335**	.609**	.714**
PANSS negative factor	.825**	.861**	.361**	.571**	.582**
PANSS DEE factor	.851**	.852**	.376**	.772**	.456**
PANSS SA factor	.606**	.427**	.323**	.319**	.648**
PANSS positive factor	.192*	.066	.200**	.142*	.186*
CDSS total	-.007	-.139*	-.001	.035	.069
SAS total	.346**	.223**	.178*	.366**	.198*

NSA, Negative symptom assessment; r_s, Spearman's rho; CAINS, Clinical Assessment for Negative Symptoms; MAP, Motivation and Pleasure; PANSS, Positive and Negative Syndrome Scale; DEE, Diminished Emotional Expression; SA, Social Amotivation; CDSS, Calgary Depression Scale for Schizophrenia; SAS, Simpson-Angus EPS Scale.
**$p < 0.001$.
*$p < 0.05$.

3.5. Convergent and divergent validity of the NSA-12

Strong correlations were found between NSA-12 total and CAINS total and PANSS negative factor scores. Similarly, the NSA-12 global negative symptoms rating was strongly correlated with the CAINS total (r_s= 0.759, $p < 0.001$) and the PANSS negative factor scores ($r_s = 0.631$, $p < 0.001$). On the other hand, NSA-12 total score and its factor scores had weak correlations with the PANSS positive factor, CDSS total score and SAS total scores. Similarly, the NSA-12 global negative symptoms rating was weakly correlated with the PANSS positive ($r_s = 0.222$, $p < 0.001$), CDSS ($r_s = 0.127$, $p < 0.001$) and SAS scores ($r_s = 0.292$, $p < 0.001$) (Table 5).

The restricted speech factor was most strongly correlated with CAINS EXP and PANSS DEE factor, but weakly correlated with the three CAINS MAP factors. The poor quality of speech factor had weak to very weak correlations with all of the CAINS factors and with the PANSS negative, SA and DEE factors. The affective blunting factor was strongly correlated with CAINS EXP and PANSS DEE, and weakly correlated with the three CAINS MAP factors and the PANSS SA factor. The amotivation factor was most strongly correlated with the PANSS SA factor and weakly correlated with the CAINS EXP factor. Correlations among NSA-12factor scores and CDSS and SAS scores were either very weak or statistically insignificant. These results further support the construct validity of the NSA-12.

3.6. Association of the NSA-12 scores with functioning

The NSA-12 total score was strongly and inversely correlated with the SOFAS ($r_s = -0.644$, $p < 0.001$) and strongly and positively correlated to the NSA-12 global level of functioning ($r_s = 0.693$, $p < 0.001$). The NSA-12 global negative symptom rating was also strongly and inversely correlated

with the SOFAS ($r_s = -0.783$, $p < 0.001$) and strongly and positively correlated to the NSA-12 global level of functioning ($r_s = 0.874$, $p < 0.001$). The amotivation factor was strongly and inversely associated with SOFAS ($r_s = -0.755$, $p < 0.001$), whereas the restricted speech, poor quality of speech and affective blunting factors were weakly and inversely correlated with the SOFAS ($r_s = -0.313$, -0.350, -0.328, respectively; all $p < 0.001$). The four NSA-12 factors were also significantly correlated with the NSA-12 global level of functioning ($r_s = 0.355$, 0.357, 0.425 and 0.770, respectively; all $p < 0.001$)."

4. Discussion

This study sought to examine the clinical utility of the NSA-16 in individuals with schizophrenia. The NSA-16 with the 12 items derived from factor analyses in our study was termed as the "NSA-12". The results of this study suggest that the NSA-12 has good psychometric properties and is useful for clinicians to assess negative symptoms in individuals with schizophrenia in the local Singapore population. The NSA-12 items loaded on the following 4 factors: restricted speech, poor quality of speech, affective blunting and amotivation. This structure is different from the original 5-factor structure of the NSA-16 reported by Axelrod et al. (1993) and the 3-factor structure suggested by Popp et al. (2012). This could be due to two reasons. Cultural differences might affect symptoms of schizophrenia. Socio-cultural factors influence appraisal of emotional situations, expression of emotions as well as rating of intensity of emotional expressions (Lim, 2016; Matsumoto and Ekman, 1989; Mesquita and Walker, 2003). Therefore, it is possible that the NSA-16 structure validated in western populations does not fit our Asian population sample. Our study sample might differ from the two reference studies in other ways. Our study population only included outpatients with mild-moderate severity of illness, based on the mean total PANSS score of 58.11 (SD = 12.88) in our sample (Leucht et al., 2005), whereas the reference studies also included more severely ill subjects.

The restricted speech factor consists of items measuring restricted speech quantity and poor rapport. Since poor rapport is often associated with the participant's sharing less information with the interviewer, restricted speech is one of the factors considered when rating rapport, irrespective of the rating scale used. Similarly, a participant who talks less is likely experienced as less engaged with the interviewer, leading to higher ratings when measuring rapport. This may explain why these two items loaded together on a single factor.

The poor quality of speech factor consists of NSA-12 impoverished speech content and inarticulate speech items. Interestingly, these 2 items separated from the restricted speech item of the NSA-12. This may be due to differences in the neurobiological and neurocognitive mechanisms underlying the deficits assessed by these items (Allen et al., 1993; Silverstein et al., 1991). The NSA-12 impoverished speech content item is conceptually similar to the SANS item "poverty of content of speech" item. Similar to the restricted speech quantity item of the NSA-12, in some SANS factor analytic studies, the SANS poverty of speech item was reported to load on different factors than the poverty of content of speech item factors (the inattention-alogia and the disorganization factors) (Buchanan and Carpenter, 1994; Kirkpatrick et al., 2006; Marder and Galderisi, 2017). The inarticulate speech item seems to be more closely related to motor impairments in speech. Another reason could be the challenges in rating these items accurately. Accurate rating on these items can only be done if an adequate amount of speech is produced. Ideally, this amount would be standardized, however, variations in speech quantity are a manifestation of the disease, preventing such standardization, leading to difficulty in accurately rating these items (Sayers et al., 1996).

Items measuring prolonged time to respond, reduced modulation of intensity, reduced expressive gestures and slowed movements loaded onto the affective blunting factor. This factor is similar to the emotion and retardation factor of the NSA-16 identified by Popp et al. (2012). Expressive gestures are a part of the affective blunting/diminished expression domain of negative symptoms (Ahmed et al., 2018; Garcia-Portilla et al., 2015; Keefe et al., 1992; Kring et al., 2013), although in the original work with the NSA-16, this symptom loaded on a motor retardation factor. Prolonged time to respond and slowed and reduced movements (motor retardation) are components of psychomotor slowing in schizophrenia (Morrens et al., 2007). In the 2 and 3 factor models of negative symptoms, psychomotor slowing and affective blunting loaded onto a single factor (Keefe et al., 1992; Liddle, 1987). Moreover, both affective blunting and motor retardation may be caused by intake of neuroleptics, also leading them to load together.

Reduced social drive, reduced sense of purpose, reduced interests and reduced daily activity loaded on the amotivation factor. In the original NSA-16 model, reduced social drive was part of a separate social factor. However, reduced social drive may also be considered as social amotivation and etiologically related to the reward system dysfunction, similar to drivers of symptoms of avolition (Liemburg et al., 2013; Messinger et al., 2011; Najas-Garcia et al., 2018). Additionally, all the items in this factor are rated based on reports from the participant. This may be another reason why they cohere into a single factor. This factor is similar to the NSA-16 motivation factor suggested by Popp et al. (2012), SANS social amotivation factor suggested by Sayers et al. (1996) and a social dysfunction factor suggested by Keefe et al. (1992).

Items measuring reduced range of emotion, reduced affective display on demand, interest in Emotional and Physical Intimacy and poor grooming and hygiene were not included in the final NSA-12 model. Cultural differences might affect expression and recognition of emotions, as well as disclosure of information related to interest in emotional and physical intimacy (Mesquita and Walker, 2003; Nakanishi, 1986; Tang et al., 2013; Tsai et al., 2007). The western culture is more individualist and individuals are encouraged to express their emotions, feelings and interests. In contrast, eastern culture is collectivist and promotes suppression of individual feelings, desires and interests (Tsai et al., 2007). This could have led to the difference in the rating and behaviour of item measuring range of emotion in an Asian sample when compared to data from Western countries. It was also suggested that individuals

from different cultures might judge display of emotions differently; they might rate emotional intensity differently when judging the same emotional expresser (Huang et al., 2001; Zhu et al., 2013). Both these reasons could have led to the difference in behaviour of item measuring affective display on demand in our sample. When compared to Americans, East-Asians were reported to be less comfortable in disclosing intimate information to others, especially to strangers (Nakanishi, 1986; Tang et al., 2013). This might have affected the range of ratings on the NSA-16 item on interest in emotional and physical intimacy. Lastly, most of our participants ($n = 215$, 78.5%) reported living with their families. It is possible that family members would help or support individuals with schizophrenia in personal grooming and maintaining hygiene. These reasons could explain why item measuring poor grooming and hygiene behaved differently in our sample.

Our study results suggest good internal consistency for the NSA-12. Cronbach alpha coefficients for all NSA-12 factors were adequate, except for factor 2. Cronbach alpha coefficient exceeding 0.7 is preferable, an alpha of at least 0.6 is reported to be adequate (Aron and Aron, 1994), while an alpha of 0.5 has been mentioned as acceptable for rating scales with few items in some previous studies (Dall'Oglio et al., 2010; Ryff and Keyes, 1995), as it is affected by the number of items in a scale (Streiner, 2003). The low alpha for factor 2 could be due to the small number of items in this factor.

The results also suggest good convergent validity of the NSA-12 with its factors. The NSA-12 total and NSA-12 global negative symptom rating were strongly correlated with CAINS total and PANSS negative factor scores. All the NSA-12 factors, except poor quality of speech were at least moderately correlated with CAINS and PANSS negative scores. Strong correlations of the restricted speech factor with CAINS EXP and PANSS DEE factors and weak correlations with CAINS MAP factors suggest that these are related to a broader expression domain within the negative symptom construct. Similarly, the affective blunting factor was strongly correlated with the CAINS EXP and PANSS DEE, and weakly correlated with all the CAINS MAP factors and PANSS SA factor. This supports its validity as an expression factor within the negative symptom construct. The amotivation factor was strongly correlated with PANSS SA and moderately correlated with the three CAINS MAP factors, suggesting that it belongs to an amotivation or avolition domain of negative symptoms. The poor quality of speech factor was weakly correlated with all CAINS and PANSS negative symptom factors. The CAINS and PANSS negative symptom factors do not have items measuring impoverished or inarticulate speech. This could be the reason for weak correlations between this factor and CAINS and PANSS factors. Further, weak correlations of NSA-12 total, NSA-12 global negative symptom rating, and NSA-12 factor scores with the PANSS positive, CDSS and SAS scores suggested good divergent validity of the NSA-12.

Negative symptoms measured by the NSA-12 correlated strongly and inversely with functioning. Several studies have reported an association between severity of negative symptoms and impairments in functioning in schizophrenia (Hunter and Barry, 2012; Milev et al., 2005; Rabinowitz et al., 2012). The amotivation factor was found to be most strongly associated with functioning in our study. This is consistent with previous research that among the negative symptom domains, amotivation is the major contributor to the association between negative symptoms and functioning (Engel et al., 2014; Foussias and Remington, 2010; Sayers et al., 1996).

Our study has some limitations. All our study subjects were outpatients with mild to moderate symptom severity; therefore, these results may not be generalizable to patients with more severe psychopathology. Test-retest reliability of the NSA-12 could not be assessed since the study was cross-sectional. Moreover, all the rating scales for each participant were administered by a single rater, which could lead to higher correlations between the scores on the scales assessing negative symptoms.

In conclusion, the NSA-12 demonstrates good psychometric properties when used to evaluate negative symptoms in individuals with schizophrenia. Our study results also support a 4-factor structure of the NSA-12 in outpatients with mild to moderate symptoms of schizophrenia. Further research is needed to evaluate the utility of the NSA-12 and the NSA-16 in different patient settings.

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Conflict of interest

Dr. Larry Alphs is the original author of the NSA-16. He has stock in Newron Pharmaceuticals, LLC and is employed by them. He has stock in Johnson & Johnson. All other authors declare that they have no conflicts of interest in relation to the subject of this study.

CRediT authorship contribution statement

Gurpreet Rekhi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft, Writing - review & editing. **Larry Alphs:** Methodology, Writing - review & editing. **Mei San Ang:** Data curation, Investigation, Methodology, Writing - review & editing. **Jimmy Lee:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing - review & editing.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.009.

References

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophr. Res. 3, 247–251.

Ahmed, A.O., Kirkpatrick, B., Galderisi, S., Mucci, A., Rossi, A., Bertolino, A., Rocca, P., Maj, M., Kaiser, S., Bischof, M., Hartmann-Riemer, M.N., Kirschner, M., Schneider, K., Garcia-Portilla, M.P., Mane, A., Bernardo, M., Fernandez-Egea, E., Jiefeng, C., Jing, Y., Shuping, T., Gold, J.M., Allen, D.N., Strauss, G.P., 2018. Cross-cultural validation of the 5-factor structure of negative symptoms in schizophrenia. Schizophr. Bull.

Allen, H.A., Liddle, P.F., Frith, C.D., 1993. Negative features, retrieval processes and verbal fluency in schizophrenia. Br. J. Psychiatry 163, 769–775.

Alphs, L.D., Summerfelt, A., Lann, H., Muller, R.J., 1989. The negative symptom assessment: a new instrument to assess negative symptoms of schizophrenia. Psychopharmacol. Bull. 25, 159–163.

Andreasen, N.C., 1982. Negative symptoms in schizophrenia. Definition and reliability. Arch. Gen. Psychiatry 39, 784–788.

Aron, A., Aron, E., 1994. Statistics for Psychology. Prentice Hall, Upper Saddle River, NJ.

Axelrod, B.N., Alphs, L.D., 1993. Training novice raters on the Negative Symptom Assessment Scale. Schizophr. Res. 9, 25–28.

Axelrod, B.N., Goldman, R.S., Alphs, L.D., 1993. Validation of the 16-item negative symptom assessment. J. Psychiatr. Res. 27, 253–258.

Buchanan, R.W., Carpenter, W.T., 1994. Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. J. Ner. Ment. Dis. 182, 193–204.

Cazorla, P., Alphs, L., Hill, C., Stewart, M., Wilson, J., Morlock, R., 2008. Psychometric evaluation of the Negative Symptom Assessment (NSA-16) scale in schizophrenic patients with predominant negative symptoms. Schizophr. Res. 98, 3–199.

Cronbach, L.J., 1951. Coefficient alpha and the internal structure of tests. Psychometrika 16, 297–334.

Dall'Oglio, A.M., Rossiello, B., Coletti, M.F., Caselli, M.C., Ravà, L., di Ciommo, V., Orzalesi, M., Giannantoni, P., Pasqualetti, P., 2010. Developmental evaluation at age 4: validity of an Italian parental questionnaire. J. Paediatr. Child Health 46, 419–426.

Daniel, D.G., Alphs, L., Cazorla, P., Bartko, J.J., Panagides, J., 2011a. Training for assessment of negative symptoms of schizophrenia across languages and cultures: comparison of the NSA-16 with the PANSS Negative Subscale and Negative Symptom factor. Clin. Schizophr. Relat. Psychoses 5, 87–94.

Daniel, D.G., Velligan, D.I., Greco, N.I.V., Bartko, J.J., 2011b. Comparing measures of negative symptoms of schizophrenia in clinical trials: the investigators' view. Poster presented at the 7th Annual International Society for Clinical Trials Methodology (ISCTM) Scientific Meeting Washington, DC on February 21–23.

Eckert, S.L., Diamond, P.M., Miller, A.L., Velligan, D.I., Funderburg, L.G., True, J.E., 1996. A comparison of instrument sensitivity to negative symptom change. Psychiatry Res. 63, 67–75.

Engel, M., Fritzsche, A., Lincoln, T.M., 2014. Validation of the German version of the Clinical Assessment Interview for Negative Symptoms (CAINS). Psychiatry Res. 220, 659–663.

First, M.B., Spitzer, Robert L, Miriam, Gibbon, Williams, Janet B.W, 2002. Structured Clinical Interview for DSM-!V-TR Axis I Disorders, Research Version, Patient Edition Biometric Research, New York State Psychiatric Institute, New York (SCID-I/P).

Forbes, C., Blanchard, J.J., Bennett, M., Horan, W.P., Kring, A., Gur, R., 2010. Initial development and preliminary validation of a new negative symptom measure: the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr. Res. 124, 36–42.

Foussias, G., Remington, G., 2010. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr. Bull. 36, 359–369.

Garcia-Portilla, M.P., Garcia-Alvarez, L., Mane, A., Garcia-Rizo, C., Sugranyes, G., Berge, D., Bernardo, M., Fernandez-Egea, E., Bobes, J., 2015. The negative syndrome of schizophrenia: three -underlying components are better than two. Schizophr. Res. 166, 115–118.

Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising axis V for DSM-IV: a review of measures of social functioning. Am. J. Psychiatry 149, 1148–1156.

Hooper, D., Coughlan, J., Mullen, M.R., 2008. Structural equation modelling: guidelines for determining model fit. by Daire Hooper, Joseph Coughlan et al.. Electron. J. Bus. Res. Methods 6, 53–60.

Horan, W.P., Kring, A.M., Gur, R.E., Reise, S.P., Blanchard, J.J., 2011. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr. Res. 132, 140–145.

Huang, Y., Tang, S., Helmeste, D., Shioiri, T., Someya, T., 2001. Differential judgement of static facial expressions of emotions in three cultures. Psychiatry Clin. Neurosci. 55, 479–483.

Hunter, R., Barry, S., 2012. Negative symptoms and psychosocial functioning in schizophrenia: neglected but important targets for treatment. Euro. Psychiatry 27, 432–436.

Jiang, J., Sim, K., Lee, J., 2013. Validated five-factor model of positive and negative syndrome scale for schizophrenia in Chinese population. Schizophr. Res. 143, 38–43.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keefe, R.S., Harvey, P.D., Lenzenweger, M.F., Davidson, M., Apter, S.H., Schmeidler, J., Mohs, R.C., Davis, K.L., 1992. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia: negative symptoms. Psychiatry Res. 44, 153–165.

Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32, 214–219.

Kring, A.M., Gur, R.E., Blanchard, J.J., Horan, W.P., Reise, S.P., 2013. The clinical assessment interview for negative symptoms (CAINS): final development and validation. Am. J. Psychiatry 170, 165–172.

Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? Schizophr. Res. 79, 231–238.

Liddle, P.F., 1987. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br. J. Psychiatry 151, 145–151.

Liemburg, E., Castelein, S., Stewart, R., van der Gaag, M., Aleman, A., Knegtering, H., 2013. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. J. Psychiatr. Res. 47, 718–725.

Lim, J., Lee, S.A., Lam, M., Rapisarda, A., Kraus, M., Keefe, R.S., Lee, J., 2016. The relationship between negative symptom subdomains and cognition. Psychol. Med. 46, 2169–2177.

Lim, N., 2016. Cultural differences in emotion: differences in emotional arousal level between the East and the West. Integr. Med. Res. 5, 105–109.

Marder, S.R., Galderisi, S., 2017. The current conceptualization of negative symptoms in schizophrenia. World Psychiatry 16, 14–24.

Matsumoto, D., Ekman, P., 1989. American-Japanese cultural differences in intensity ratings of facial expressions of emotion. Motiv. Emot. 13, 143–157.
Mesquita, B., Walker, R., 2003. Cultural differences in emotions: a context for interpreting emotional experiences. Behav. Res. Ther. 41, 777–793.
Messinger, J.W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A.D., Malaspina, D., 2011. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clin. Psychol. Rev. 31, 161–168.
Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. 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 162, 495–506.
Moller, H.J., Czobor, P., 2015. Pharmacological treatment of negative symptoms in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 265, 567–578.
Morrens, M., Hulstijn, W., Sabbe, B., 2007. Psychomotor slowing in schizophrenia. Schizophr. Bull. 33, 1038–1053.
Najas-Garcia, A., Carmona, V.R., Gomez-Benito, J., 2018. Trends in the study of motivation in schizophrenia: a bibliometric analysis of six decades of research (1956–2017). Front. Psychol. 9, 63.
Nakanishi, M., 1986. Perceptions of self-disclosure in initial interaction a Japanese sample. Hum. Commun. Res. 13, 167–190.
Popp, D., Williams, J.B.W., Cohen, E.A., Detke, M.J., 2012. Poster #176 NSA-16 revisited: identifying latent factors of negative symptoms in schizophrenia. Schizophr. Res. 136, S344.
Rabinowitz, J., Levine, S.Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C.G., Kapur, S., 2012. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. Schizophr. Res. 137, 147–150.
Rekhi, G., Ang, M.S., Yuen, K.Y.C., Ng, W.Y., Lee, J., 2019. Assessing negative symptoms in schizophrenia: validity of the clinical assessment interview for negative symptoms in Singapore. Schizophr. Res 206, 177–182.
Remington, G., Foussias, G., Fervaha, G., Agid, O., Takeuchi, H., Lee, J., Hahn, M., 2016. Treating negative symptoms in schizophrenia: an Update. Curr. Treat. Options Psychiatry 3, 133–150.
Ryff, C.D., Keyes, C.L., 1995. The structure of psychological well-being revisited. J. Pers. Soc. Psychol. 69, 719–727.
Sayers, S.L., Curran, P.J., Mueser, K.T., 1996. Factor structure and construct validity of the Scale for the Assessment of Negative Symptoms. Psychol. Assess. 8, 269–280.
Silverstein, M.L., Marengo, J.T., Fogg, L., 1991. Two types of thought disorder and lateralized neuropsychological dysfunction. Schizophr. Bull. 17, 679–687.
Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 212, 11–19.
Streiner, D.L., 2003. Starting at the beginning: an introduction to coefficient alpha and internal consistency. J. Pers. Assess. 80, 99–103.
Tabachnick, B.G., Fidell, L.S., 2001. Using Multivariate Statistics. Allyn and Bacon.
Tang, N., Bensman, L., Hatfield, E., 2013. Culture and sexual self-disclosure in intimate relationships. Interpersona 7, 227–245.
Tsai, J.L., Miao, F.F., Seppala, E., Fung, H.H., Yeung, D.Y., 2007. Influence and adjustment goals: sources of cultural differences in ideal affect. J. Pers. Soc. Psychol. 92, 1102–1117.
Zhu, Z., Ho, S.M.Y., Bonanno, G.A., 2013. Cultural similarities and differences in the perception of emotional valence and intensity: a comparison of Americans and Hong Kong Chinese. Am. J. Psychol. 126, 261–273.