Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms

Ying Li [a,b,c], Wen-xiu Li [c], Ying-min Zou [a,b], Zhuo-ya Yang [a,b], Dong-jie Xie [a,b], Yin Yang [a], Simon S.Y. Lui [a,d], Gregory P. Strauss [e], Eric F.C. Cheung [d], Raymond C.K. Chan [a,b,*]

[a] Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China
[b] Department of Psychology, University of Chinese Academy of Sciences, Beijing, China
[c] Haidian District Mental Health Prevent-Treatment Hospital, Beijing, China
[d] Castle Peak Hospital, Hong Kong Special Administrative Region, China
[e] Department of Psychology, University of Georgia, United States of America

ARTICLE INFO

Article history:
Received 24 February 2018
Received in revised form 18 June 2018
Accepted 1 July 2018
Available online xxxx

Keywords:
CAINS
Persistent negative symptoms
Schizophrenia
ROC curve

ABSTRACT

Objective: The present study aimed to validate a severity cut-off of negative symptoms for persistent negative symptoms (PNS) identification using the Clinical Assessment Interview for Negative Symptoms (CAINS).
Method: A total of 206 patients with schizophrenia were recruited and divided into the PNS group ($n = 57$) and the Non-PNS group ($n = 149$) using PNS criteria based on the SANS and the SAPS. To determine the appropriate cut-offs on the CAINS in identifying PNS, Receiver Operating Characteristic (ROC) curve analysis was conducted in the PNS and Non-PNS groups.
Results: Our results showed that the cutoffs for identifying PNS on the CAINS total score, the Motivation and Pleasure (MAP) subscale score and the Expression (EXP) subscale score were 25, 17, and 5 respectively. Area Under the Curve (AUC) analysis indicated excellent discrimination of the PNS group from the Non-PNS group using the cut-off for the CAINS total score. However, discrimination was somewhat better for the MAP subscale score than the EXP subscale score. The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the MAP subscale were 81.54% and 97.16%.
Conclusion: We found that the cut-off scores derived from the CAINS to identify PNS are comparable to existing scales. The CAINS offers an alternative means in identifying PNS patients in clinical trials that overcomes methodological and conceptual limitations of older scales.

1. Introduction

Negative symptoms, a major contributor to poor functional outcomes (Kirkpatrick et al., 2006), are often more persistent than positive symptoms (Kirkpatrick and Fischer, 2006; Tandon et al., 2010). The construct of Persistent Negative Symptoms (PNS) has been put forward to describe negative symptoms that are enduring, trait-like and resistant to currently available treatment (Buchanan, 2007). The PNS classification is based on longitudinal and cross-sectional evaluation of negative symptoms. These symptoms should reach at least a moderate level of severity with low level of positive symptoms, depressive symptoms and extrapyramidal symptoms assessed by a validated rating scale and should persist for at least six months. The PNS concept is designed to be inclusive and easy to identify for research purposes, and it has been recognized by a National Institute of Mental Health consensus statement in 2006 (Kirkpatrick et al., 2006). However, many researchers have used different scales with different criteria to identify PNS which may lead to heterogeneous results (Bottlender et al., 2003; Edwards et al., 1999; Malla et al., 2004).

Studies have identified PNS cut-offs using several existing negative symptom scales. For example, using the Scale for the Assessment of Negative Symptoms (SANS), PNS criteria are met if a global item reaches a score of 3 or more (excluding the attentional impairment domain because this is no longer part of the negative symptom construct) (Malla et al., 2004). Using the Positive and Negative Syndrome Scale (PANSS), a PNS cut-off of 21 has been identified for the negative subscale (Hovington and Lepage, 2012). Other criteria must also be present for a PNS classification to be made on the PANSS or SANS. For example, negative symptoms should demonstrate clinical stability for at least six months, and patients should have low severity of common secondary negative symptoms, including positive, depressive, disorganization and extrapyramidal symptoms (Buchanan, 2007).

However, there are conceptual and methodological limitations with early scales, like the SANS and PANSS (Kirkpatrick et al., 2006). To

* Corresponding author at: Institute of Psychology, Chinese Academy of Sciences, 16 Lincui Road, Beijing 100101, China.
E-mail address: rckchan@psych.ac.cn (R.C.K. Chan).

https://doi.org/10.1016/j.schres.2018.07.005
0920-9964/

address these limitations, the NIMH recommended the development of new negative symptom rating scales. Two next-generation clinical instruments resulted from this recommendation: the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) and the Clinical Assessment Interview for Negative Symptoms (CAINS). These measures were developed based on current conceptualization of negative symptoms (Daniel, 2013), informed by evidence from affective neuroscience (Horan et al., 2011; Knutson and Greer, 2008), and have demonstrated strong psychometric properties. Although they are becoming the gold-standard measures in the field, PNS score cut-offs have yet to be validated for the CAINS or the BNSS. Deriving PNS proxy procedures, similar to what was done for the PANSS and SANS, is of critical importance for clinical trials and the use of these new measures to identify more clinically homogeneous subgroups. The present study aimed to validate a severity cut-off of negative symptoms for PNS identification on the CAINS. ROC curve analysis was used to derive a cutoff score on the CAINS and determine its sensitivity and specificity. Area Under the Curve (AUC) was also calculated to ascertain the accuracy of the CAINS in identifying PNS. We hypothesized that both the subscales of the CAINS and the whole scale would have excellent validity.

2. Methods

2.1. Participants

Participants in the study were patients recruited from the Haidian District Psychiatry Hospital and several Community Health Service Centres in the Haidian District. Diagnoses were made by experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID-IV). The study protocol was approved by the Ethics Committee of the Haidian District Psychiatry Hospital Authority. All participants provided written informed consent before the study. Exclusion criteria included: 1) a history of head injury and neurological disorder; 2) comorbid substance dependence or abuse; 3) any serious medical condition; and 4) having fewer than nine years of education. A total of 220 patients with schizophrenia were recruited in this study. Six patients were excluded according to the exclusion criteria and finally 214 patients with 110 males and 104 females were included in present study. The mean age was 44.72 years (standard deviation = 8.69), the mean length of education was 11.89 years (standard deviation = 2.79), the mean age of onset was 24.67 years (standard deviation = 7.97), the mean duration of illness was 20.89 years (standard deviation = 9.92), and the mean antipsychotic dose was 361.23 mg (standard deviation = 197.32).

2.2. Instruments

2.2.1. CAINS

The CAINS (Kring et al., 2013) includes 13 items, each of which is scored on a five-point scale from 0 (corresponding to no impairment) to 4 (corresponding to severe deficit). The CAINS has a two-factor structure, namely “Motivation and Pleasure” and “Expression”, corresponding to the Motivation And Pleasure (MAP) subscale and the Expression (EXP) subscale. The MAP subscale includes ratings on motivation and pleasure for relevant social, vocational and recreational activities, while the EXP subscale assesses emotion expression including vocal prosody, gestures, facial expressions and speech. Items 1 to 9 correspond to the MAP subscale, while items 10 to 13 correspond to the EXP subscale. This two-factor structure has been shown to be stable in the Spanish, German and Chinese versions (Chan et al., 2015; Engel et al., 2014; Valiente-Gomez et al., 2015).

The CAINS is a semi-structured interview requiring at least 30 min to complete. Probes and descriptive anchor points are provided throughout the interview. In this study, we used the Chinese version of the CAINS, which has been translated and shown to possess good reliability (Cronbach's alpha for the MAP, EXP and the whole scale were 0.85, 0.90, and 0.91 respectively) and divergent and convergent validity in the Chinese context (Chan et al., 2015; Kring et al., 2013). Two clinical raters with master degree and one experienced psychiatrist were trained in conducting the CAINS, with good inter-rater reliability (Intraclass Correlation Coefficient ≥ 0.85).

2.2.2. Other instruments

The SANS (Andreasen, 1989) was used to identify PNS based on an established method. The PANSS (Kay et al., 1987) was used to assess positive, negative and general psychopathology symptoms of schizophrenia. The negative subscale of the PANSS was also used for PNS identification. The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) was used to assess positive symptoms. The Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) was used to measure extrapyramidal side effects. Functioning was assessed using the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976). The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993), a semi-structured interview with nine items, was used to assess depressive symptoms.

Inter-rater reliability between all raters in this study was established for all the aforementioned instruments. A total of three raters attended training in conducting all the aforementioned instruments by watching five interview videos. Inter-rater reliability was calculated after watching and assessing the five interview videos. The Inter-rater reliability of all instruments was ≥0.85: CAINS (0.86), PANSS (0.91), SANS (0.85), SAS (0.87), SAPS (0.88), CDSS (0.85) and GAF (0.89). In the baseline assessment and follow-up assessment, the three raters were blind to each other and conducted the assessment independently. Patients were assigned to each rater randomly at each assessment.

The type and dosage of antipsychotic medications taken were recorded and converted into chlorpromazine equivalence.

2.3. Identification of the PNS and the non-PNS group

To identify PNS, the following inclusion criteria were formulated. Inclusion criteria of the PNS group were (Buchanan, 2007; Mucci et al., 2017): 1) a score of ≥3 in at least one global Item of the SANS (excluding the global item of attentional impairment), except if the global rating on “affective flattening” or “alogia” was based entirely on the score of the items “inappropriate affect” or “poverty of content of speech”; 2) a score of <3 on the global items of the SAPS and a total SAPS score of <10 (low level of positive symptoms) (Andreasen et al., 1995); 3) a total SAS score of <3 (low level of extrapyramidal symptoms) (Blanchet and Rompre, 2014); and 4) a total CDSS score of <4 (low level of depressive symptoms) (Xiao et al., 2009). For the Non-PNS group, no global item on the SANS was ≥3.

A total of 214 patients with schizophrenia were recruited in the present study (Fig. 1). They underwent baseline assessment using the instruments listed above. According to inclusion criteria 1, we divided the whole group into the PNS group and the Non-PNS group based on scores on the global items of the SANS. A total of 149 patients were classified into the Non-PNS group. The PNS group then underwent follow-up assessment after three and six months. Participants whose follow up assessment results met criteria 1 to 4 on both occasions were identified as patients with PNS. At the end of six months, 57 patients were included in the PNS group according to the above method (Table 1).

2.4. Data analysis

Data were analyzed with SPSS 19.0 and MedCalc 17.6. First, we conducted independent *t*-tests or chi-square test to compare the demographic and clinical characteristics of the PNS group ($N = 57$) and the Non-PNS group ($N = 149$). We then performed ROC curve analysis to calculate the applicable cutoff score of the PANSS negative symptoms subscale (PANSS-N), the CAINS and its subscales and the corresponding sensitivity and specificity. Ninety-five percent confidence intervals (CI)

Please cite this article as: Li, Y., et al., Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.07.005

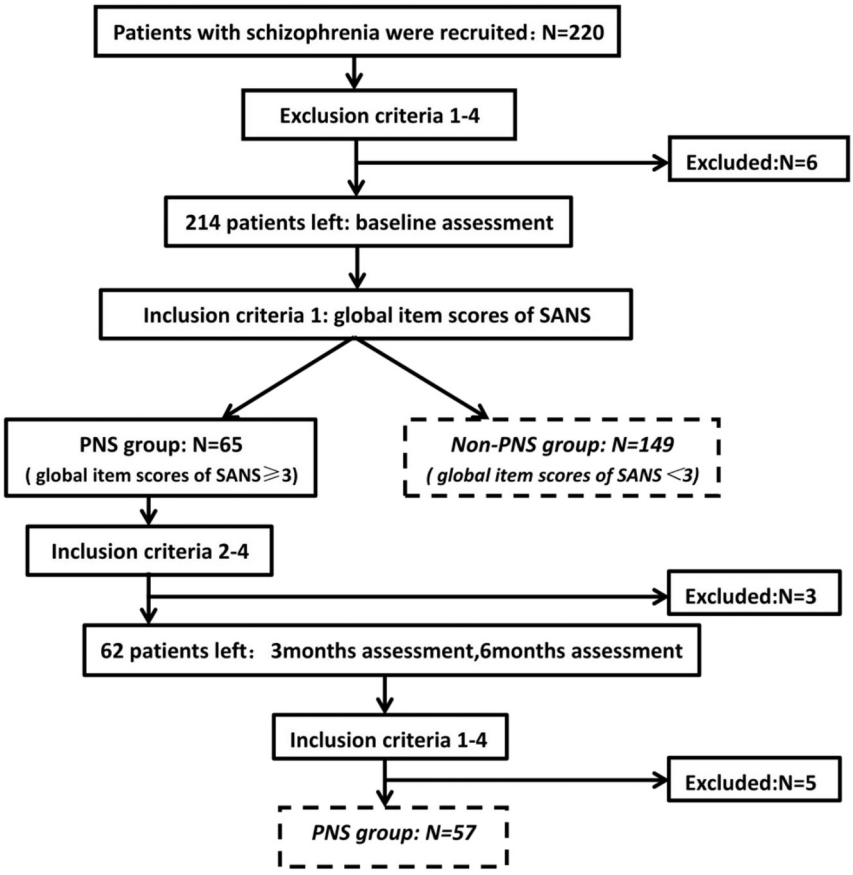

Fig. 1. Flow chart for the recruitment of participants (including PNS group and Non-PNS group).

were reported where relevant. Then, Area Under the Curve (AUC) was calculated to assess the discriminatory property of the CAINS (Linden, 2006). We defined an AUC of 0.7–0.79 as indicating acceptable level of discrimination, an AUC of 0.8–0.89 as indicating excellent discriminatory property, and an AUC of 0.9–1.0 as indicating outstanding discriminatory property (Albeck and Borgesen, 1990). Finally, z-test was used to compare the AUC of the PANSS-N, CAINS and its subscales (alpha was set at 0.05). In order to compare the diagnostic performance of the SANS and the CAINS in identifying PNS, the PPV and NPV of the MAP subscale and items 16 and 21 from the SANS (SANS16/SANS21) (mainly assessing anhedonia and amotivation) were also calculated. Chi-square test was used to compare the PPV and NPV of the MAP subscale and SANS16/SANS21 (alpha was set at 0.05).

Table 1
Descriptive and clinical information for patients with PNS and Non-PNS

	PNS (N = 57)	Non-PNS (N = 149)	Statistics (t/χ^2)	P
Sex (male/female)	34/23	76/73	1.237	0.266
Age (years)	45.70 (7.94)	44.38 (9.57)	0.925	0.356
Education (years)	11.00 (3.24)	12.12 (2.58)	−2.839	0.005
Onset age (years)	26.07 (8.17)	23.85 (7.91)	1.789	0.075
Duration Of illness (years)	19.91 (9.87)	21.42 (10.00)	−0.973	0.332
Antipsychotic dose (mg)	348.18 (153.64)	368.18 (208.18)	−0.660	0.510
GAF	65.23 (6.33)	69.01 (6.98)	−3.569	<0.001
PANSS-N	18.88 (4.54)	13.02 (3.29)	10.237	0.000
PANSS-P	9.46 (3.48)	10.42 (3.64)	−1.725	0.086
PANSS-G	25.30 (4.93)	23.93 (5.01)	1.766	0.079
SAPS	8.32 (9.21)	8.53 (9.5)	−1.620	0.107
SANS	32.68 (10.50)	17.91 (8.66)	10.317	0.000
SAS	0.77 (1.70)	0.85 (1.90)	−0.280	0.780
CDSS	1.51 (1.92)	1.7 (1.87)	1.389	0.166
CAINS Total	29.05 (4.99)	18.89 (5.43)	12.292	<0.001
CAINS-MAP	21.54 (3.85)	13.85 (4.10)	12.244	<0.001
CAINS-EXP	7.51 (1.74)	5.03 (1.70)	9.274	<0.001

GAF: the Global Assessment of Functioning Scale; PANSS: the Positive and Negative Syndrome Scale (PANSS); PANSS-N: the negative symptoms subscale of PANSS; PANSS-P: the Positive symptoms subscale of PANSS; PANSS-G: the general pathology scale of PANSS: SAPS: the Scale for the Assessment of Positive Symptoms; SANS: the Scale for the Assessment of Negative Symptoms (SANS); SAS: the Simpson-Angus Scale; CDSS: the Calgary Depression Scale for Schizophrenia; CAINS: the Clinical Assessment Interview for Negative Symptoms; CAINS-MAP: the Motivation And Pleasure (MAP) subscale of CAINS; CAINS-EXP: the expression subscale of CAINS. (Non-PNS data from initial assessment and PNS data from the last assessment.)

3. Results

3.1. Demographic and clinical characteristics of participants

The prevalence of PNS was 27.67% based on the SANS. Table 2 shows the clinical data of the 207 schizophrenia patients who were classified into the PNS ($n = 57$) and the Non-PNS ($n = 149$) group. Independent sample *t*-tests revealed that patients in the PNS group had a significantly shorter length of education compared with the Non-PNS group ($P < 0.05$). The PNS group had more severe negative symptoms assessed by the SANS, the PANSS-N and the CAINS compared with the Non-PNS group ($P < 0.05$). The PNS group also had poorer global function measured by the GAF ($P < 0.05$). The two groups did not differ in other clinical parameters such as duration of illness, depressive symptoms, positive symptoms and extrapyramidal symptoms.

Table 2 shows clinical data of the PNS group on follow-up assessment. Skewness and Kurtosis were also calculated to describe the shape of the probability distribution. Furthermore, we used the baseline assessment and the three-month assessment to calculate the test-retest reliability of the CAINS total and subscale scores, which were 0.92 (total), 0.89 (MAP) and 0.87 (EXP).

Please cite this article as: Li, Y., et al., Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.07.005

Table 2
Clinical data of PNS group in follow-up assessment

	Baseline				3-month follow-up				6 months			
	Mean	SD	Skewness	Kurtosis	Mean	SD	Skewness	Kurtosis	Mean	SD	Skewness	Kurtosis
SANS	32.37	9.69	0.81	1.45	32.02	9.17	0.723	1.23	32.12	9.13	0.983	0.284
CAINS	29.02	4.97	1.65	3.81	28.21	4.85	1.43	2.66	28.58	5.05	1.76	4.00
PANSS-N	18.88	4.54	0.75	0.61	19.12	4.13	0.59	−0.27	18.82	4.19	0.88	1.24

PANSS-N: the negative symptoms subscale of PANSS; SANS: the Scale for the Assessment of Negative Symptoms; CAINS: the Clinical Assessment Interview for Negative Symptoms.

3.2. Cutoff score, sensitivity and specificity of the CAINS and the PANSS-N

Table 3 shows the cutoff scores for the PANSS-N subscale, the CAINS total and the MAP and EXP subscales of the CAINS with the corresponding sensitivity and specificity values. The cutoff scores for the CAINS total (ranged from 21 to 26) showed high sensitivity (98.25–71.93) and specificity (63.76–91.95). The cutoff scores for the PANSS-N subscale (ranged from 13 to 16) also showed high sensitivity (89.47–70.18) and specificity (61.07–83.89). The maximum Youden's index was used as a criterion for selecting the optimum cutoff point when a diagnostic test gives a numeric rather than a dichotomous result. According to the ROC curve analysis, the cutoff score with the maximum Youden's index was 25 when the CAINS total score was used to identify PNS. The suggested cutoff score for the PANSS-N subscale was 16. The cutoff score of the MAP subscale ranged from 15 to 19 and showed high sensitivity (100–71.93) and specificity (66.77–89.93). The cutoff score of the EXP subscale ranged from 5 to 6 with high sensitivity (91.23–71.93) and specificity (61.07–79.87). According to the ROC curve analysis, 17 on the MAP subscale and 5 on the EXP subscale were the best cutoffs of the two subscales.

Table 3
The cutoff points and corresponding sensitivity and specificity of PANSS-N, total and subscale scores of CAINS

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
CAINS						
≥6	100.00	93.7–100.0	0.00	0.0–2.4	1.00	–
>20	100.00	93.7–100.0	58.39	50.0–66.4	2.40	0.00
>21	98.25	90.6–100.0	63.76	55.5–71.5	2.71	0.028
>22	96.49	87.9–99.6	69.13	61.0–76.4	3.13	0.051
>23	91.23	80.7–97.1	81.21	74.0–87.1	4.85	0.11
>24	87.72	76.3–94.9	87.25	80.8–92.1	6.88	0.14
>25	***85.96***	***74.2–93.7***	***89.93***	***83.9–94.3***	***8.54***	***0.16***
>26	71.93	58.5–83.0	91.95	86.4–95.8	8.93	0.31
>27	49.12	35.6–62.7	95.97	91.4–98.5	12.20	0.53
>28	43.86	30.7–57.6	97.99	94.2–99.6	21.78	0.57
>29	35.09	22.9–48.9	100.00	97.6–100.0	–	0.65
>46	0.00	0.0–6.3	100.00	97.6–100.0	–	1.00
MAP						
≥4	100.00	93.7–100.0	0.00	0.0–2.4	1.00	–
>15	100.00	93.7–100.0	65.77	57.6–73.3	2.92	0.00
>16	91.23	80.7–97.1	73.83	66.0–80.7	3.49	0.12
>17	***89.47***	***78.5–96.0***	***79.87***	***72.5–86.0***	***4.44***	***0.13***
>18	78.95	66.1–88.6	88.59	82.4–93.2	6.92	0.24
>19	71.93	58.5–83.0	89.93	83.9–94.3	7.15	0.31
>20	56.14	42.4–69.3	94.63	89.7–97.7	10.46	0.46
>21	45.61	32.4–59.3	97.99	94.2–99.6	22.65	0.56
>22	36.84	24.4–50.7	99.33	96.3–100.0	54.89	0.64
>23	22.81	12.7–35.8	100.00	97.6–100.0	–	0.77
>34	0.00	0.0–6.3	100.00	97.6–100.0	–	1.00
EXP						
≥1	100.00	93.7–100.0	0.00	0.0–2.4	1.00	–
>3	100.00	93.7–100.0	13.42	8.4–20.0	1.16	0.00
>4	94.74	85.4–98.9	41.61	33.6–50.0	1.62	0.13
>5	***91.23***	***80.7–97.1***	***61.07***	***52.8–68.9***	***2.34***	***0.14***
>6	71.93	58.5–83.0	79.87	72.5–86.0	3.57	0.35
>7	54.39	40.7–67.6	89.93	83.9–94.3	5.40	0.51
>8	15.79	7.5–27.9	100.00	97.6–100.0	–	0.84
>12	0.00	0.0–6.3	100.00	97.6–100.0	–	1.00
PNASS-N						
≥7	100.00	93.7–100.0	0.00	0.0–2.4	1.00	
>11	100.00	93.7–100.0	34.90	27.3–43.1	1.54	0.00
>12	94.74	85.4–98.9	46.31	38.1–54.7	1.76	0.11
>13	89.47	78.5–96.0	61.07	52.8–68.9	2.30	0.17
>14	80.70	68.1–90.0	71.14	63.2–78.3	2.80	0.27
>15	73.68	60.3–84.5	77.85	70.3–84.2	3.33	0.34
>16*	***70.18***	***56.6–81.6***	***83.89***	***77.0–89.4***	***4.36***	***0.36***
>17	59.65	45.8–72.4	90.60	84.7–94.8	6.35	0.45
>18	49.12	35.6–62.7	94.63	89.7–97.7	9.15	0.54
>19	42.11	29.1–55.9	95.97	91.4–98.5	10.46	0.60
>20	29.82	18.4–43.4	97.32	93.3–99.3	11.11	0.72
>21	22.81	12.7–35.8	98.66	95.2–99.8	16.99	0.78
>22	17.54	8.7–29.9	100.00	97.6–100.0	–	0.82
>33	0.00	0.0–6.3	100.00	97.6–100.0	–	1.00

CAINS: the Clinical Assessment Interview for Negative Symptoms; MAP: the Motivation and Pleasure subscale of CAINS; EXP: the expression subscale of CAINS; PANSS-N: the negative symptoms subscale of PANSS; CI: confidence interval; +LR: Positive Likelihood Ratio; -LR: Negative Likelihood Ratio. The bold and italic items were the suggested cutoff scores.

3.3. Diagnostic accuracy comparison between the CAINS and the PANSS-N

Fig. 2 illustrate the diagnostic accuracy of the PANSS-N subscale, and the CAINS and its subscales. The AUC was 0.938 (CI = 0.896 to 0.967) for the CAINS total and 0.928 (CI = 0.883 to 0.959) for the MAP subscale, indicating outstanding discriminatory property. The AUC was 0.842 (CI = 0.785 to 0.889) for the EXP subscale and the AUC of the PANSS-N subscale was 0.860 (CI = 0.805 to 0.904), indicating excellent discriminatory property.

Pairwise comparison analysis of ROC curves between the CAINS and its subscales revealed no significant difference between the AUC of the CAINS and the MAP subscale (z = 1.284, $P = 0.199$), but both of their AUCs were larger than that of the EXP subscale (EXP to CAINS: z =

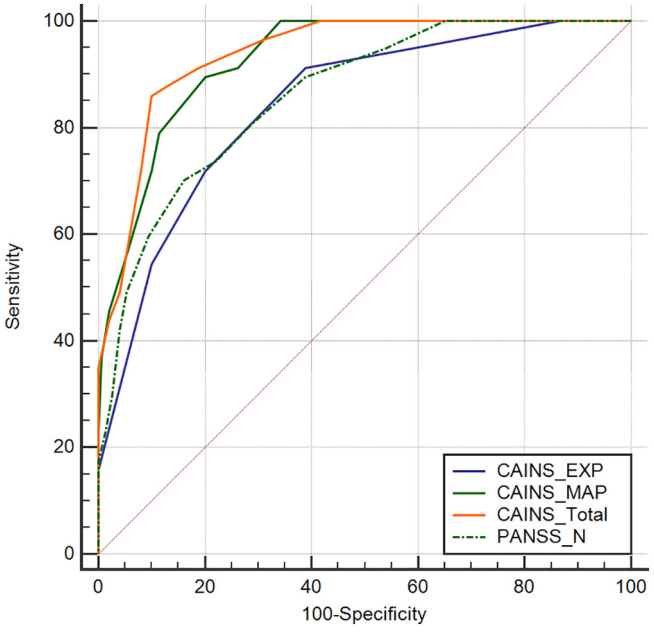

Fig. 2. ROC curves of PANSS-N, CAINS and its subscales. The yellow one was CAINS, blue one was EXP, green one was MAP, and the green dotted one was PANSS-N. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Please cite this article as: Li, Y., et al., Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.07.005

3.720, $P = 0.002$; EXP to MAP: z = 2.737, $P = 0.006$). However, pairwise comparison between the CAINS and the PANSS-N subscale showed that the AUC of the CAINS were larger than that of the PANSS-N subscale (z = 2.662, $P = 0.0078$).

3.4. Diagnostic accuracy comparison between the CAINS and the SANS

We also conduct additional analysis in the supplementary materials. We used the PANSS to classify the PNS and the Non-PNS groups. The criterion for identifying PNS was a score of ≥21 on the PANSS-N subscale (Hovington et al., 2012; Hovington and Lepage, 2012). Based on this criterion, 36 patients were classified into the PNS group and 170 into the Non-PNS group. ROC analysis was conducted to calculate the cutoff score and compare the AUCs of the CAINS and SANS. According to the ROC curve analysis, the cutoff score with the maximum Youden's index was 24 (Youden's index = 0.5103) when the CAINS total score was used to identify PNS, while the cutoff score of SANS was 28 (Youden's index = 0.5735). Moreover, through pairwise comparison of the AUCs between the CAINS and the SANS, we found that there was no significant difference between them (z = 0.188, $P = 0.8507$).

Furthermore, we compared the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of the CAINS and the SANS. The PPV and the NPV of the CAINS were 85.62% and 96.31%, while those for the SANS were 75.43% and 92.28%. Both the PPV and the NPV of the CAINS were significantly larger than that of the SANS ($\chi^2 = 5.456$, $P = 0.021$; $\chi^2 = 4.535$, $P = 0.034$).

4. Discussion

This present study developed and validated a proxy procedure for classifying PNS using the CAINS in relation to established PNS proxy procedures validated on other scales. We found that the applicable proxy score for identifying PNS was 25 using the CAINS, while it was 16 using the PANSS-N subscale. The proxy score was 17 for the MAP subscale and 5 for the EXP subscale. The CAINS and the MAP subscale showed outstanding discriminatory properties, while the EXP subscale and the PANSS-N subscale showed excellent discriminatory property. The AUCs of both the CAINS total and the MAP subscale was significantly larger than that of the EXP subscale. Moreover, the AUC of PANSS-N subscale was significantly smaller than that of the CAINS. Our results provide a solid foundation from which to explore the CAINS as a more robust means of identifying PNS patients.

We found that the prevalence of PNS identified by the SANS was 27.67%, which is close to the estimates reported in recent studies (Galderisi et al., 2013; Ucok and Ergul, 2014). In addition, only eight of the 65 participants exhibiting moderate severity on at least one SANS item no longer exhibited significant negative symptoms on follow-up assessments, suggesting the temporal stability of primary negative symptoms. However, due to the small number of patients whose negative symptoms did not persist, we were unable to calculate the discriminant validity of the proxies for PNS. Further studies should recruit more patients with moderate level of negative symptoms and compare the discriminant validity of the SANS and the CAINS.

Our results suggest that the CAINS appears to be a suitable and robust means for the identification of PNS in schizophrenia patients, which could facilitate future research. We recommend using the proxy score of >25 on the CAINS total or the proxy score of >17 on the MAP subscale to identify PNS in future studies. In the past, researchers have predominantly used first-generation negative symptoms scales such as the SANS and the PANSS to identify patients with PNS in previous studies on negative symptoms (Buchanan, 2007; Malla et al., 2004). The lack of a "gold standard" for identifying PNS has been an important issue in research on negative symptoms (Buchanan, 2007; Kirkpatrick et al., 2006). For example, most studies used a score of 3 or above on at least one global item of the SANS as a cutoff (Buchanan et al., 2012; Chang et al., 2011), while some studies regarded a score of 2 or above on a global item of the SANS as the criterion of PNS and several studies defined PNS as a score of 3 or above on at least two global items on the SANS (Hovington et al., 2012; Malla et al., 2004).

Secondly, according to the previous criteria of PNS, PNS can be identified with one global item of the SANS reaching moderate level, which may only reflect one facet of negative symptoms. Using a suitable cutoff score on the CAINS may be a more comprehensive alternative in defining PNS. In the present study, we found a cutoff score of 25 on the CAINS and a cutoff of 16 on the PANSS-N. Given the significant difference between the AUC of the PANSS-N and the CAINS, the CAINS appears to be a more suitable tool to identify PNS. Moreover, the comparable AUCs of the CAINS and the SANS suggests that the CAINS is as good as the SANS in identifying PNS.

Negative symptoms include a cluster of symptoms such as alogia, blunted affect, asociality, anhedonia and avolition (Kane, 2013). First-generation tools have been found to be insufficient in capturing all dimensions of negative symptoms (Lincoln et al., 2017). The inclusion of multiple aspects of the temporal dynamics of pleasure in the CAINS may enhance its sensitivity for capturing individual differences in symptom severity and changes in different stages of schizophrenia (Barch, 2013). In this study, by comparing the PPV and NPV between the MAP subscale and SANS16/SANS21, we found that the MAP subscale, which includes the anticipatory and consummatory aspects of anhedonia, was superior in identifying PNS than the SANS.

In this study, we also found that the MAP subscale possessed greater discriminatory power than the EXP subscale. The two-factor model of negative symptoms includes the anhedonia/amotivation dimension corresponding to the MAP subscale and expression deficits corresponding to the EXP subscale (Barch, 2013; Kring et al., 2013). However, anhedonia and amotivation have been regarded as the core features of negative symptoms associated with poor functional outcome in schizophrenia (Kring and Barch, 2014). Motivational/hedonic deficits in schizophrenia have also been associated with various cognitive deficits including executive function and working memory deficits, while expression deficits may only affect verbal fluency (Faerden et al., 2009; Konstantakopoulos et al., 2011; Roth et al., 2004). Our findings suggest that deficits in hedonic capacity and motivation may be more closely associated with PNS.

In this study, the CAINS was shown to possess outstanding discriminatory properties in identifying PNS. It is known that sensitivity and specificity may vary and sensitivity is inversely related to specificity (Cook, 2008; Hoo et al., 2017; Yang and Carlin, 2000). The cutoff scores for the CAINS total which ranged from 21 to 26 showed good to very good sensitivity and specificity. However, using only sensitivity and specificity as measures to determine the accuracy of the CAINS is problematic since these measures depend on a threshold for positivity which is often chosen arbitrarily. As a result, 25 on the CAINS total with the highest Youden's index was chosen as the appropriate cutoff scores for identifying PNS.

This study has two main limitations. First, we recruited patients with chronic schizophrenia with moderate level of negative symptoms. The results may therefore not be generalizable to schizophrenia patients in other stages of illness. Secondly, we did not assess the Non-PNS group longitudinally. Future study should examine the fluctuation of negative symptoms of the Non-PNS groups.

In conclusion, we found that the CAINS is a valid and robust tool in identifying PNS in patients with schizophrenia. Its psychometric properties in identifying PNS in patients with schizophrenia are comparable to the SANS and superior than the PANSS-N. The appropriate cutoff scores for identifying PNS based on the CAINS were also determined. Validation of a novel tool like the CAINS, which captures important aspects of pleasure experience, could facilitate future research in negative symptoms.

Conflicts of interest

The authors declared no biomedical financial interests or potential conflicts of interest.

Please cite this article as: Li, Y., et al., Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.07.005

Contributors

Ying Li designed the study, collected and analyzed the data, and wrote up the first draft of the manuscript. Ying-ming Zou, Zhuo-ya Yang, Dong-jie Xie, Yin Ying, collected the data, did the literature search and helped wrote up the first draft of the manuscript. Wen-xiu Li, Simon Lui, Gregory Strauss, and Eric Cheung gave critical comments for the different versions of the manuscript. Raymond Chan conceptualized the study, interpreted the findings and commented different versions of the manuscript critically. All authors read and approved the final version of the manuscript.

Role of funding source

The funding agents had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the manuscript; and in the decision to submit the paper for publication.

Acknowledgements

This study was supported by the National Science Fund China (81571317), National Key Research and Development Programme (2016YFC0906402), the Beijing Municipal Science and Technology Commission Grant (Z161100000216138), and the Beijing Training Project for the Leading Talents in Science and Technology (Z151100000315020).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.07.005.

References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. Br. J. Psychiatry Supplement(22), 39–44.
Albeck, M.J., Borgesen, S.E., 1990. ROC-curve analysis. A statistical method for the evaluation of diagnostic tests. Ugeskr. Laeger 152 (23), 1650–1653.
Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SAPS) Modern Problems of Pharmacopsychiatry. University of Iowa, Iowa City,US.
Andreasen, N.C., 1989. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br. J. Psychiatry Supplement(7), 49–58.
Andreasen, N.C., Arndt, S., Miller, D., Flaum, M., Nopoulos, P., 1995. Correlational studies of the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms: an overview and update. Psychopathology 28 (1), 7–17.
Barch, D.M., 2013. The CAINS: theoretical and practical advances in the assessment of negative symptoms in schizophrenia. Am. J. Psychiatry 170 (2), 133–135.
Blanchet, P.J., Rompre, P.H., 2014. Clinimetric evaluation of the Simpson-Angus Scale in older adults with schizophrenia. J. Clin. Psychopharmacol. 34 (1), 36–39.
Bottlender, R., Sato, T., Jager, M., Kunze, I., Groll, C., Borski, I., Moller, H.J., 2003. Does considering duration of negative symptoms increase their specificity for schizophrenia? Schizophr. Res. 60 (2–3), 321–322.
Buchanan, R.W., 2007. Persistent negative symptoms in schizophrenia: an overview. Schizophr. Bull. 33 (4), 1013–1022.
Buchanan, R.W., Panagides, J., Zhao, J., Phiri, P., den Hollander, W., Ha, X., Kouassi, A., Alphs, L., Schooler, N., Szegedi, A., Cazorla, P., 2012. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. J. Clin. Psychopharmacol. 32 (1), 36–45.
Chan, R.C., Shi, C., Lui, S.S., Ho, K.K., Hung, K.S., Lam, J.W., Wang, Y., Cheung, E.F., Yu, X., 2015. Validation of the Chinese version of the Clinical Assessment Interview for Negative Symptoms (CAINS): a preliminary report. Front. Psychol. 6, 7.
Chang, W.C., Hui, C.L., Tang, J.Y., Wong, G.H., Lam, M.M., Chan, S.K., Chen, E.Y., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr. Res. 133 (1–3), 22–28.
Cook, N.R., 2008. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin. Chem. 54 (1), 17–23.
Daniel, D.G., 2013. Issues in selection of instruments to measure negative symptoms. Schizophr. Res. 150 (2–3), 343–345.
Edwards, J., McGorry, P.D., Waddell, F.M., Harrigan, S.M., 1999. Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. Schizophr. Res. 40 (2), 147–158.
Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33 (6), 766–771.
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 (1–2), 659–663.
Faerden, A., Friis, S., Agartz, I., Barrett, E.A., Nesvag, R., Finset, A., Melle, I., 2009. Apathy and functioning in first-episode psychosis. Psychiatr. Serv. 60 (11), 1495–1503.
Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Fleischhacker, W.W., Kahn, R.S., Eufest Study, G., 2013. Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. Eur. Neuropsychopharmacol. 23 (3), 196–204.
Hoo, Z.H., Candlish, J., Teare, D., 2017. What is an ROC curve? Emerg. Med. J. 34 (6), 357–359.
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 (2–3), 140–145.
Hovington, C.L., Lepage, M., 2012. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. Expert. Rev. Neurother. 12 (1), 53–69.
Hovington, C.L., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2012. Identifying persistent negative symptoms in first episode psychosis. BMC Psychiatry 12, 224.
Kane, J.M., 2013. Tools to assess negative symptoms in schizophrenia. J. Clin. Psychiatry 74 (6), e12.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Kirkpatrick, B., Fischer, B., 2006. Subdomains within the negative symptoms of schizophrenia: commentary. Schizophr. Bull. 32 (2), 246–249.
Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32 (2), 214–219.
Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. Schizophr. Bull. 37 (2), 300–305.
Knutson, B., Greer, S.M., 2008. Anticipatory affect: neural correlates and consequences for choice. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 363 (1511), 3771–3786.
Konstantakopoulos, G., Ploumpidis, D., Oulis, P., Patrikelis, P., Soumani, A., Papadimitriou, G.N., Politis, A.M., 2011. Apathy, cognitive deficits and functional impairment in schizophrenia. Schizophr. Res. 133 (1–3), 193–198.
Kring, A.M., Barch, D.M., 2014. The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. Eur. Neuropsychopharmacol. 24 (5), 725–736.
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 (2), 165–172.
Lincoln, T.M., Dollfus, S., Lyne, J., 2017. Current developments and challenges in the assessment of negative symptoms. Schizophr. Res. 186, 8–18.
Linden, A., 2006. Measuring diagnostic and predictive accuracy in disease management: an introduction to receiver operating characteristic (ROC) analysis. J. Eval. Clin. Pract. 12 (2), 132–139.
Malla, A.K., Norman, R.M., Takhar, J., Manchanda, R., Townsend, L., Scholten, D., Haricharan, R., 2004. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J. Nerv. Ment. Dis. 192 (7), 455–463.
Mucci, A., Merlotti, E., Ucok, A., Aleman, A., Galderisi, S., 2017. Primary and persistent negative symptoms: concepts, assessments and neurobiological bases. Schizophr. Res. 186, 19–28.
Roth, R.M., Flashman, L.A., Saykin, A.J., McAllister, T.W., Vidaver, R., 2004. Apathy in schizophrenia: reduced frontal lobe volume and neuropsychological deficits. Am. J. Psychiatry 161 (1), 157–159.
Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand. Suppl. 212, 11–19.
Tandon, R., Nasrallah, H.A., Keshavan, M.S., 2010. Schizophrenia, "just the facts" 5. Treatment and prevention. Past, present, and future. Schizophr. Res. 122 (1–3), 1–23.
Ucok, A., Ergul, C., 2014. Persistent negative symptoms after first episode schizophrenia: a 2-year follow-up study. Schizophr. Res. 158 (1–3), 241–246.
Valiente-Gomez, A., Mezquida, G., Romaguera, A., Vilardebo, I., Andres, H., Granados, B., Larrubia, J., Pomarol-Clotet, E., McKenna, P.J., Sarro, S., Bernardo, M., 2015. Validation of the Spanish version of the Clinical Assessment for Negative Symptoms (CAINS). Schizophr. Res. 166 (1–3), 104–109.
Xiao, W., Liu, H., Zhang, H., Liu, Q., Fu, P., Chen, J., Wang, X., Wang, G., Li, L., Shu, L., 2009. Reliability and validity of the Chinese version of the Calgary Depression Scale for Schizophrenia. Aust. N. Z. J. Psychiatry 43 (6), 548–553.
Yang, H., Carlin, D., 2000. ROC surface: a generalization of ROC curve analysis. J. Biopharm. Stat. 10 (2), 183–196.

Please cite this article as: Li, Y., et al., Revisiting the persistent negative symptoms proxy score using the Clinical Assessment Interview for Negative Symptoms, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.07.005