



Can the Positive and Negative Syndrome scale (PANSS) differentiate treatment-resistant from non-treatment-resistant schizophrenia? A factor analytic investigation based on data from the Pattern cohort study

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A B S T R A C T

Treatment-Resistant Schizophrenia (TRS) and Non-Treatment-Resistant Schizophrenia (NTRS) may represent different subtypes of schizophrenia. However, few studies have investigated their PANSS symptom dimensions by Exploratory (EFA) or Confirmatory (CFA). Data from the present study are derived from 1429 patients of the Pattern study. TRS was defined by the use of clozapine in the previous year whereas NTRS by the use of non-clozapine antipsychotics ("by proxy"). Factors were chosen based on the Kaiser criterion and considered valid when loadings were greater than or equal to 0.5. The fit to the data was evaluated by CFA in comparison with well-established PANSS models, using fit indexes. The EFA yielded similar five-factor model in both groups: Negative, Positive, Anxiety/Depression, Cognitive and Excited. CFA showed a satisfactory, but not perfect, fit to the data, as compared with the previous PANSS factor analytic models. Despite the limitations regarding the 'by proxy' definition of TRS, the results of the present study show that there are no differences in the factorial structure of PANSS in patients with TRS and NTRS.

1. Introduction

Schizophrenia is a heterogeneous disorder that affects 0.4% (McGrath et al., 2008) of the world population and has a broad range of symptoms. These include positive or psychotic symptoms (delusions, hallucination, bizarre behavior and formal thought disorder) (Tamminga, 2008), negative symptoms (such as affective flattening, alogia and avolition), disorganization of speech and behavior, affective symptoms (depression or mania) and cognitive impairment in various domains. Except for cognition, symptoms of schizophrenia are generally assessed by scales such as the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), or the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

The majority of guidelines and algorithms for the treatment of schizophrenia agree that when patients do not respond to treatment with at least two different types of antipsychotic in monotherapy, with

adequate doses of 4- to 6-week duration, they are considered to have Treatment-Resistant Schizophrenia (TRS) (Elkis, 2007) (Howes et al., 2017). Although the true prevalence of TRS is unknown, it is generally estimated to account for 30–40% of patients with schizophrenia (Elkis and Buckley, 2016).

Clozapine is the gold standard treatment for TRS as compared to first- or second-generation antipsychotics (Siskind et al., 2016), although its use varies considerably worldwide (Bachmann et al., 2017). However, there is no specific treatment, with a solid evidence of efficacy, which proved to be effective in patients with resistance to clozapine (Wagner et al., 2019) except perhaps for electroconvulsive therapy (Wang et al., 2018).

It has been proposed that TRS may represent a distinct category or subtype of schizophrenia (Gillespie et al., 2017) and a recent international consensus guideline has recommended that standardized, validated symptom rating scales such as the BPRS (Overall and

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Goerham, 1962) or the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) should be used in order to adequately measure symptom severity in TRS (Howes et al., 2017).

In fact, the PANSS is considered the worldwide gold standard for the measurement of symptoms of schizophrenia and it is composed of 30 items grouped in three subscales: Positive (P1 to P7), Negative (N1 to N7) and General Psychopathology (G1 to G16) (Kay et al., 1987).

However, factor analyses (FA) of the original 30 item PANSS items cluster in more than the three dimensions as for example, the four-factor model ('Pyramidal') (Kay and Sevy, 1990) but, since the original five-factor model was published (Lindenmayer et al., 1994), various models have been replicated showing that the PANSS has 5 factors domains namely Positive, Negative, Disorganization, Cognitive and Excitement.

Further studies received different denominations, as is the case the "Pentagonal model" (White et al., 1997) and the Marder model (Marder et al., 1997). In terms of validity the National Institute of Mental Health's (NIMH) model, which was obtained by consensus (Wallwork et al., 2012) has shown to have a good fit to the data when compared cross nationally (Stefanovics et al., 2014).

However various PANSS factor analytical models have different number of factors, different numbers of items assigned to each factor and different goodness of fit index to the data (Lindenmayer, 2017), even when obtained from large samples such as the case of the van der Gaag model (VDAAG) (van der Gaag et al., 2006b) which may explained by the heterogeneity of methodological aspects of FA, such sample size, type of rotation employed, as well as ethnic and cultural differences (Stefanovics et al., 2014). The models are displayed in Table 1.

There are two studies which used PANSS FA to identify symptom domains in samples which included patients with TRS, as it is the case of Lindenmayer et al. (Lindenmayer et al., 2004), which investigated 157 TRS patients assigned to clozapine or other antipsychotics and Woodward et al. (Woodward et al., 2013) which compared symptoms of 610 patients with different types of resistant psychosis (schizophrenia, schizoaffective, bipolar and major depression). However, to the best of our knowledge, there are no studies that used FA comparing patients with TRS with patients with NTRS using the PANSS using a large sample of patients.

Therefore it would be of clinical as well as heuristic value to compare two populations of patients with TRS with NTRS in terms of the factorial structure of the PANSS and therefore, aim of the present study is to use Exploratory Factor Analysis (EFA) to investigate whether patients with TRS have a distinct PANSS factor structure when compared with patients with NTRS. For this, we used data from the cross-sectional phase of the Pattern study -an international, multicenter, non-interventional, prospective, cohort study with 1429 subjects (Haro et al., 2015).

The secondary aim of the study is to use Confirmatory Factor Analysis (CFA) to test the fit of the factorial structures found in the present study in comparison with well-established PANSS factor models, namely: "Original" (three- factor) (Kay et al., 1987), "Pyramidal" (four-factor) (Kay and Sevy, 1990), "Pentagonal" (five-factor), the "NIMH" or consensus model (five-factor) (White et al., 1997), VDAAG or van de Gaag's model (five-factor) (van der Gaag et al., 2006b), and a TRS model (Lindenmayer) (Lindenmayer et al., 1994) which has a similar structure to the original five-factor model (Lindenmayer et al., 1994).

2. Material and methods

2.1. Population: the Pattern study

Data from this work were drawn from the Pattern study, an international, multicenter, non-interventional (observational), prospective study sponsored by Roche. It aimed to investigate the impact of persistent symptoms on the course and burden of illness in outpatients with schizophrenia attending psychiatric centers in eight countries. The Pattern study had two phases:

- 1 The cross-sectional phase that constituted a baseline observation for the longitudinal phase;
- 2 The longitudinal phase that consisted of a 24-month follow-up to collect data from all patients who were not in recovery at the baseline assessment.

Patients met the inclusion criteria for the baseline phase if they had a diagnosis of schizophrenia according to the DSMIV TR or ICD 10,

Table 1
Factor structure of PANSS subscales according to different models.

PANSS items	PANSS FACTORIAL MODELS					
	Original PANSS (Kay et al,1987)	Pyramidal (Kay,et al,1990)	Pentagonal (White et al,1997)	VDAAG (van derGaag et al, 2006 b)	NIMH (Wallmayer et al, 2012)	Lindenmayer (Lindenmayer et al,2004)
P1 – Delusion	Positive	Positive	Positive	Positive	Positive	Positive
P2 – Conceptual disorganization				Disorganized	Disorganized	Cognitive
P3 – Hallucinatory behavior		Positive	Positive	Positive	Positive	Positive
P4 – Excitement		Excited	Activation	Excited	Excited	Excited
P5 – Grandiosity		Positive	Positive	Positive	Positive	Positive
P6 – Suspiciousness/Persecution				Positive		Positive
P7 - Hostility		Excited	Activation	Excited	Excited	Excited
N1- Blunted affect	Negative	Negative	Negative	Negative	Negative	Negative
N2- Emotional withdrawal		Negative	Negative	Negative	Negative	Negative
N3- Poor rapport		Negative	Negative	Negative	Negative	Negative
N4- Passive/apathetic		Negative	Negative	Negative	Negative	Negative
N5- Difficulty in abstract things			Autistic Preoccupation	Disorganized	Disorganized	Cognitive
N6- Lack of spontaneity and flow of conversation		Negative	Negative	Negative	Negative	Negative
N7- Stereotyped thinking			Autistic Preoccupation	Disorganized		
G1- Somatic concern	General Psychopathology	Depressive	Dysphoric Mood	Positive		
G2- Anxiety		Depressive	Dysphoric Mood	Emotional distress	Depressed	Depressive
G3- Guilt feelings		Depressive	Dysphoric Mood	Emotional distress	Depressed	Depressive
G4- Tension		Excited	Dysphoric Mood	Emotional distress		Depressive
G5- Mannerism and posturing		Negative	Autistic Preoccupation	Disorganized		
G6- Depression		Depressive	Dysphoric Mood	Emotional distress	Depressed	Depressive
G7- Motor retardation		Negative	Negative	Negative	Negative	
G8- Uncooperativeness		Excited	Activation	Excited	Excited	Excited
G9- Unusual thought content		Positive	Positive	Positive	Positive	Positive
G10- Disorientation				Disorganized		
G11- Poor attention		Negative	Autistic Preoccupation	Disorganized	Disorganized	Cognitive
G12- Lack of judgment and insight		Positive		Disorganized		Cognitive
G13- Disturbance of volition		Negative	Negative	Disorganized		
G14- Poor impulse control		Excited	Activation	Excited	Excited	Excited
G15- Preoccupation		Depressive	Autistic Preoccupation	Disorganized	Positive	Cognitive
G16- Active social avoidance		Negative		Negative	Disorganized	Negative

were aged 18 years or older, were in a stable condition without recent acute relapse (within last three months), and were able to give informed consent and willing to comply with study protocol. The exclusion criteria for the baseline phase were: an acute psychotic exacerbation in the 3 months before the baseline observation, concurrent enrollment in an interventional study at the time of baseline observation, or being unable or unwilling to comply with the study (Haro et al., 2015). In order to maximize the generalizability of the study findings, no entry criteria were applied regardless treatment history, comorbidity or history of substance abuse (Sheehan et al., 1998).

For the longitudinal phase, similar criteria were applied, with the additional exclusion of patients found to be in a clinical recovery: both PANSS positive and negative subscales fewer than 28 points. Data from this phase of the Pattern study have been recently published (Haro et al., 2018) but were not included in the present analysis.

Volunteer patients were recruited from 140 centers across eight countries (Argentina, Brazil, Canada, France, Germany, Italy, Spain and the United Kingdom) and provided informed consent. All local internal review boards approved the Pattern study as well as the present investigation; it was approved by the University of São Paulo General Hospital internal review board (Protocol number 1.788.340). Further details of the Pattern study are available in Haro et al. (Haro et al., 2015).

Clinical assessment and patient-reported outcome (PRO) data were captured using a hand-held electronic tablet. Trained professionals used the device, as well as the patients and their family or informal care takers.

Psychiatrists captured data produced by assessment with clinical rating scales, while patients captured PRO questionnaire data independently at the clinic. The assessment by the participating psychiatrists included socio-demographic and clinical variables using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Clinical Global Impression for Schizophrenia (CGI) (Haro et al., 2003) and Personal and Social Performance Scale (PSP) (Morosini et al., 2000).

A total of 1429 patients were recruited in 8 countries (Argentina $N = 110$, Brazil $N = 100$, Canada $N = 117$, France $N = 237$, Germany $N = 250$, Italy $N = 219$, Spain $N = 207$, and the United Kingdom $N = 139$). Socio-demographic information was similar across countries. Most patients (70.56%) were male, and the mean age was 42.1 years. Fourteen percent of the patients had at least one psychiatric co-morbidity, and 35% had experienced a substance use problem. The mean total PANSS score was 77.98 points.

Regarding medication treatment, 98% of patients were using antipsychotics, and 31% were on combination regimens. Clozapine was the most frequently prescribed antipsychotic (29%) followed by risperidone (22%), olanzapine (16%) and aripiprazole (15%) (Haro et al., 2015).

2.2. Study data

We analyzed data derived exclusively from the cross-sectional phase of the Pattern study. The original protocol of the study defines TRS according to two criteria:

- Definition 1: “patients who have been treated with clozapine at any time over the previous year as indicated by the treating psychiatrist”
- Definition 2: “patients who, in the opinion of the investigator, have been treatment resistant at any time during the previous year according to the standard definition of failing to respond to two or more adequate trials of medication”.

However, this second definition is problematic. A recent authoritative review of response and resistance in schizophrenia established minimum requirements for the definition of TRS that include an adequate assessment of present and past response to treatment using validated instruments, as well as evaluation of factors that may interfere

with response e.g., adherence to treatment (Howes et al., 2017). Since the Pattern study was non-interventional, prospective evaluation of adequate response to treatment or adherence was not possible, thus compromising the definition of TRS exclusively based on clinician judgment of past response to treatment.

Therefore, in the present study, the definition of TRS based on current use of clozapine was adopted. It is well established that this medication is the drug of choice in TRS (Elkis and Buckley, 2016) (Howes et al., 2017). Consequently, those patients taking non-clozapine antipsychotics were defined as NTRS.

2.2.1. Statistical analyses

The analyses included all patients who fulfilled the eligibility criteria for the cross-sectional phase ($N = 1429$). Demographic variables were compared between both groups using *t*-test or chi-squared techniques.

EFA was based on the extraction of a principal component analysis (PCA) using the varimax orthogonal rotation for all PANSS items. We chose the number of factors according to the Kaiser criteria (‘eigenvalue’ equal to or greater than 1). The Kaiser-Meyer-Olkin and Bartlett’s test of sphericity were used to measure the adequacy of the sample. Loadings equal to or greater than 0.5 were used to define factors.

CFA is an appropriate method to confirm the dimensions of latent structures as well as to evaluate the fit to the data. CFA starts from a previous theoretical solution defined by the researchers; it tests whether a hypothetical latent structure is consistent or inconsistent with the empirical data using structural equation models (SEM) (Schumacker and Lomax, 1996).

The fit of data to the models uses robust weighted least squares estimators under the polychoric correlation matrix. The following goodness-of-fit indexes were used: Chi-square, Comparative Fit Index (CFI), Non-Normed Fit Index (TLI/NNFI) and the Root Mean Squared Error of Approximation (RMSEA) (Schreiber et al., 2006).

The following models were tested: the model obtained in the present study using EFA (‘Present model’), the original three dimensional PANSS model (‘Original’) (Kay et al., 1987), the four-factor model (‘Pyramidal’) (Kay and Sevy, 1990), the ‘pentagonal’ five-factor model (‘Pentagonal’) (White et al., 1997), the model obtained by Lindenmayer et al. using TRS patients (‘Lindenmayer’) (Lindenmayer et al., 2004) as well as models obtained by consensus or large samples such as the van der Gaag model (‘VGAAG’) (van der Gaag et al., 2006b) and the National Institute of Mental Health (‘NIMH’) model (Wallwork et al., 2012). These models are described in Table 1.

Statistical analyses were conducted using SPSS 23.0 and the R program version 3.2.2.

3. Results

Table 2 presents the relationship between the two definitions of treatment resistance used in the Pattern study, namely: use of clozapine in the previous year (definition 1), or failure to respond to two antipsychotic treatments during the previous year (definition 2). The agreement was highly significant ($p = 0.0001$) with only 6.4% of patients who fulfilled definition 2 not meeting definition 1. The demographic characteristics of the sample are presented in Table 3.

3.1. Exploratory factor analysis

A principal component analysis (PCA) was performed for the PANSS in TRS and NTRS patients to differentiate subsyndromes. Before performing PCA, the suitability of the data for factor analysis was checked in the TRS and NTRS samples; the Kaiser-Meyer-Olkin values were 0.928 and 0.944 respectively, exceeding the recommended value of 0.6. Bartlett’s test of sphericity, which indicates the correlation among items, was sufficiently large, supporting the factorability of the

Table 2
Association between the two different definitions of treatment resistance used in the Pattern study.

Treatment Resistance according to Definition 2 (failure to respond to two past antipsychotic treatments)	Treatment Resistance according to definition 1 (use of clozapine in the previous year) (present study)			total
	Yes	No	total	
Yes	409 (28.6%)	92 (6.4%)	501 (35%)	
No	0	928 (65%)	928 (65%)	
Total	409 (28.6%)	1020 (71.4%)	1429	
$\chi^2 = 1058$; d.f. = 1; $p = 0.0001$				

correlation matrix (See Supplementary Material).

In patients with TRS, an evaluation of the Scree plot and eigenvalue criteria (exceeding one) indicated five distinct and interpretable factors. After performing varimax rotation, a five-factor model was obtained, accounting for 57.37% of the variance (See Supplementary Material).

In this analysis, the factor with the highest loadings (Factor 1) was the Negative Factor, composed of items N1 + N2 + N3 + N4 + N6 + G7 + G16. It explained 17.74% of the variance. The second factor was the Positive Factor (Factor 2) that explained 11.31% of the variance and was composed the following items: P1 + P3 + P5 + P6 + G9. The third factor was named “Anxiety/Depression” (Factor 3); it was formed of G2 + G3 + G4 + G6 items and explained 10.34% of the variance. The fourth factor, designated “Cognitive” (Factor 4), explained 9.28% of the variance and was composed of the P2 + N5 + N7 + G5 items. Finally, the items P7 + G8 + G14 formed the Excited Factor (Factor 5), that explained 8.70% of the variance. The rotated factor structure is presented in **Table 4**.

In patients with NTRS, an evaluation of the Scree plot and eigenvalue criteria (exceeding one) converged on a five-factor solution. Varimax rotation evidenced the same five factors; these accounted for 60.62% of the variance (See Supplementary Material).

The factor with the highest loadings (Factor 1) was the Negative Factor, formed by the items N1 + N2 + N3 + N4 + N6 + G7 + G16. It explained 17.41% of the variance. The second factor was the Positive Factor (Factor 2), composed of P1 + P3 + P5 + P6 + G9, explaining 12.53% of the variance. The third, Anxiety/Depression Factor (Factor 3), explained 11.77% of the variance and consisted of G1 + G2 + G3 + G4 + G6 items. The fourth, Cognitive Factor (Factor 4), was composed of P2 + N5 + G5 + G11 and explained 10.39% of the variance. Finally, the Excitement Factor (Factor 5) was represented by P7 + G8 + G14 and explained 8.52% of the variance (**Table 4**).

Table 3
Demographics and clinical aspects of the study. Patients are divided according to the Pattern's definition 1 of Treatment Resistance (use of clozapine in the past year).

	Total (N = 1429) N (%)	NTRS (N = 1020) N (%)	TRS (N = 409) N (%)	χ^2 (df)	p-value
Gender: male	973 (70.56%)	697 (68.3%)	312 (76.3%)	8.892 (1)	0.003
Alcohol abuse or Dependence	264 (18.47%)	195 (19.1%)	69 (16.87%)	0.979 (1)	0.322
Drug abuse or Dependence	360 (25.19%)	261 (25.58%)	99 (24.20%)	0.296 (1)	0.586
Tabaco use	939 (65.71%)	682 (66.86%)	257 (62.83%)	2.100 (1)	0.147
	Mean (SD)	Mean (SD)	Mean (SD)	t (df = 1427)	p-value
Age	42.2 (11.50)	42.78 (11.88)	40.13 (10.25)	- 3.952	< 0.001
PANSS negative score	22.42 (7.44)	22.42 (7.46)	22.42 (7.40)	0.008	0.993
PANSS positive score	21.05 (7.87)	20.73 (7.88)	21.85 (7.78)	2.440	0.015
PANSS general score	37.86 (12,094)	37,64 (12,51)	38.41 (10,986)	1084	0.005
PANSS total score	77.98 (22.97)	77.32 (23.84)	78.41 (21.42)	2.930	0.770
Overall PSP score	52.63 (18.71)	52.95 (19.20)	51.85 (17.43)	- 1.006	0.315
Age of onset (years)	26.94 (9.26)	28.17 (9.55)	23.85 (7.69)	- 8.154	< 0.001
Duration of illness (years)	15.08 (10.41)	14.60 (10.91)	16.27 (8.93)	2.758	0.006
Duration of untreated psychosis	0.05 (1.51)	0.04 (1,66)	0.07 (1.03)	0.293	0.770
Duration of Persistent Negative Symptoms	114.65 (104.92)	109.28 (107)	128.37 (98.36)	3.121	0.002
Duration of Persistent Positive Symptoms	105.16 (114.53)	94.85 (113.57)	130.83 (113.02)	5.427	< 0.001
Number of previous hospitalizations	0.18 (0.60)	0.19 (0.628)	0.16 (0.560)	- 0.736	0.462
Number of previous suicide attempts	0.36 (1.13)	0.31 (1.022)	0.46 (1.390)	2.170	0.030

NTRS = non-treatment resistant schizophrenia; TRS = treatment resistant schizophrenia.

The two models (TRS and NTRS) differed in the composition of the Anxiety/Depression and Cognitive factors. In the TRS-model, the Anxiety/Depression Factor did not include the G1 item, and the Cognitive factor included the N7, but not the G11 item.

The following items, in NTRS patients, did not load onto any Factor: P4, N7, G10, G12, G13 and G15. In TRS patients the factors that did not load were P4, G1, G10, G11, G13 and G15.

3.2. Confirmatory factor analysis

The six models exhibited significant results in both samples (TRS and NTRS). Although a good model fit would be indicated by a non-significant χ^2 result, this test is known to be highly sensitive to sample size and variable distribution. For any hypothesis testing, a large sample size increases the probability of better estimates and reduces the probability of small errors; thus, increasing the chances of identifying proposed underlying latent models.

Therefore, we used several additional absolute and incremental indices to evaluate the goodness of fit. Two indexes were used in combination: the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). The CFI should be 0.9 or higher, and the RMSEA should be 0.06 or lower (Bentler and Yuan, 1999) (Marsh et al., 2004). The results of the CFA for the previously published models are presented in **Table 5**.

In comparison with previous models for patients with TRS, the Present model showed a better fit to the data when compared with the Original, Pyramidal and NIMH models, and a worse fit when compared with the Lindenmayer, VDAAG and Pentagonal models. For NTRS patients, the Present model showed the second best fit to data: the VDAAG and Pentagonal models had the same fit and were superior to the Present model.

In the case of TRS patients, the VDAAG model, regarded as the best

Table 4

Factors loadings obtained through exploratory factor analysis of PANSS comparing patients with Treatment-Resistant Schizophrenia (TRS) ($n = 409$) (bolded) with patients Non-Treatment Resistant Schizophrenia (NTRS) ($n = 1020$).

Group	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5	
	NTRS	TRS								
%Variance	17.41	17.74	12.53	11.31	11.77	10.34	10.39	9.28	8.52	8.70
P1. Delusions			0.827	0.837						
P2. Conceptual disorganization							0.650	0.538		
P3. Hallucinatory behavior			0.735	0.728						
P4. Excitement										
P5. Grandiosity			0.584	0.627						
P6. Suspiciousness			0.644	0.586						
P7. Hostility									0.744	0.714
N1. Blunted affect	0.789	0.788								
N2. Emotional withdrawal	0.805	0.850								
N3. Poor rapport	0.749	0.813								
N4. Passive/apathetic social withdrawal	0.737	0.814								
N5. Difficulty in abstract thinking							0.530	0.624		
N6. Lack of spontaneity and flow of conversation	0.740	0.754								
N7. Stereotyped thinking								0.530		
G1. Somatic concern					0.549					
G2. Anxiety					0.755	0.743				
G3. Guilt Feelings					0.673	0.653				
G4. Tension					0.659	0.634				
G5. Mannerisms and posturing							0.664	0.592		
G6. Depression					0.721	0.719				
G7. Motor retardation	0.676	0.651								
G8. Uncooperativeness									0.755	0.705
G9. Unusual thought content			0.743	0.776						
G10. Disorientation										
G11. Poor attention							0.610			
G12. Lack of judgment and insight										
G13. Disturbance of volition										
G14. Poor impulse control									0.643	0.637
G15. Preoccupation										
G16. Active social avoidance	0.637	0.683								

NTRS: Non-Treatment Resistant Schizophrenia; TRS: Treatment Resistant Schizophrenia. Factor loadings smaller than 0.5 were not included.

model, achieved the best fit to the data, whereas the Pentagonal and VDAAG model showed a better fit in NTRS patients. In addition, in the TRS sample, Lindenmayer's model had a good fit when compared with the VDAAG model. All the CFI values reached 0.90 or higher and none of the RSMEA reached 0.06 or lower. Therefore, none of the models achieved a perfect fit.

4. Discussion

To the best of our knowledge, this is the first study to investigate PANSS dimensions comparing TRS and NTRS patients, using both EFA and CFA, in a large population of patients with schizophrenia. The main finding of the present study was that the factorial structure of the PANSS was almost identical in patients with TRS and those with NTRS.

Additional findings were that patients with TRS had a significantly lower mean age of onset, with higher duration of illness, PANSS positive and general scores and duration of persistent negative and positive symptoms. There was no difference in the duration of untreated psychosis. These findings are in accordance with previous studies that have compared TRS with NTRS (Elkis and Buckley, 2016) (Meltzer et al., 1997) (Lançon et al., 2000) (Henna Neto and Elkis, 2007) (Werneck et al., 2011) (Altamura et al., 2007). However, NTRS patients had a significantly higher number of previous suicide attempts, and substance abuse/dependence was more frequent amongst these patients. There was no difference in the number of hospitalizations, contrasting with previous studies from our group (Alves et al., 2005).

The results of the EFA in TRS and NTRS patients replicate earlier factor analytic studies that found a PANSS five-factor structure composed of Negative, Positive, Affective, Cognitive and Excitement dimensions. Additionally, our results replicated other studies that found an important internal consistency of the Negative factor (Lançon et al.,

2000), in both TRS and NTRS patients.

The use of CFA to compare the factorial structure obtained in the present study with other established PANSS models showed that neither TRS nor NTRS groups obtained a very good fit. Some models may be considered to have a better fit; namely, the Pentagonal model for the NTRS, the Lindenmayer model for the TRS group and the VDAAG model for both groups.

These results are similar to findings from Lindenmayer's et al. study (Lindenmayer et al., 2004) who conducted an EFA of PANSS dimensions and found no difference between TRS and NTRS patients.

The superiority of the VDAAG model compared to other models is explained by its larger sample size (5769 subjects), despite this, it could not distinguish TRS from NTRS. It is of note that although the study by Lindenmayer et al. had only 157 subjects, the PANSS factorial model they obtained achieved a very good fit (Stefanovics et al., 2014).

It seems that a perfect fit to the data is rarely achieved either in systematic reviews studies of the PANSS (van der Gaag et al., 2006a) or cross-national studies (Stefanovics et al., 2014). In our case, the imperfect fit may be explained by the clinical heterogeneity of schizophrenia and the variability resulting from the use of different PANSS raters in different centers, with no attempt to evaluate the inter-rater reliability.

4.1. Strengths

It is assumed that TRS makes up at least 30% of the population with schizophrenia (Kane et al., 1988). However, as identified in a recent study, the definition of TRS is very heterogeneous, and its prevalence may be even higher. Indeed, this heterogeneity of definition means the exact prevalence of TRS in patients with schizophrenia is unknown (Howes et al., 2017).

Table 5

Fit to the data of models obtained through exploratory factor analysis with PANSS established factorial models using confirmatory factor analysis. Models with the best fit (which achieved higher values of CFI and lower values of RMSEA) are bolded.

	χ^2	df	CFI	TLI/NNFI	RMSEA	IC90%(RMSEA)	
						Lower	Upper
Total sample							
<i>Original</i>	15,668.32	402	0.917	0.911	0.163	0.160	0.166
<i>Pyramidal</i>	6541.30	246	0.944	0.937	0.134	0.130	0.138
<i>Pentagonal</i>	4592.22	265	0.966	0.961	0.107	0.103	0.111
<i>VDAAG</i>	6650.99	395	0.966	0.963	0.105	0.102	0.108
<i>NIMH</i>	4367.92	179	0.959	0.952	0.128	0.124	0.133
<i>Lindenmayer</i>	4360.26	242	0.968	0.963	0.109	0.105	0.113
<i>Present Model</i>	6576.29	395	0.967	0.963	0.105	0.102	0.108
NTRS sample							
<i>Original</i>	10,923.08	402	0.929	0.923	0.160	0.157	0.164
<i>Pyramidal</i>	4353.94	246	0.954	0.948	0.128	0.124	0.133
<i>Pentagonal</i>	3377.48	265	0.969	0.965	0.107	0.103	0.112
<i>VDAAG</i>	5022.31	395	0.969	0.966	0.107	0.104	0.111
<i>NIMH</i>	3062.22	179	0.964	0.957	0.126	0.120	0.131
<i>Lindenmayer</i>	3214.04	242	0.970	0.966	0.110	0.105	0.115
<i>Present Model</i>	2829.81	219	0.972	0.968	0.108	0.103	0.113
TRS sample							
<i>Original</i>	5417.46	402	0.877	0.867	0.175	0.170	0.180
<i>Pyramidal</i>	2518.14	246	0.912	0.901	0.150	0.144	0.157
<i>Pentagonal</i>	1608.88	265	0.954	0.948	0.111	0.105	0.118
<i>VDAAG</i>	2207.19	395	0.955	0.951	0.106	0.100	0.112
<i>NIMH</i>	1504.41	179	0.945	0.935	0.135	0.126	0.143
<i>Lindenmayer</i>	1470.86	242	0.958	0.952	0.112	0.104	0.119
<i>Present Model</i>	1953.33	246	0.946	0.940	0.130	0.123	0.138

Original: Original 3 factor PANSS model (positive, negative, general psychopathology); *VDAAG*: van der Gaag's Model; *NIMH*: NIMH model; *Pyramidal*: Pyramidal model (four-factor model); *Lindenmayer*: Lindenmayer's model; *Pentagonal*: Pentagonal model; *Present Model*: Obtained in the present study. CFI = comparative fit index; TLI/NNFI = non-normed fit index; RMSEA: root mean squared error of approximation.

The validity of defining TRS 'by proxy', based on the use of clozapine in the previous year, is supported by the fact that patients labeled as TRS (or NTRS) in this study showed demographic and clinical features consistent with previous descriptions of these syndromes. In the present study, patients with TRS showed an earlier age of onset, a longer duration of illness and a male predominance (Table 3). These characteristics have been observed in previous studies that adequately distinguished patients with TRS from those with NTRS (Meltzer et al., 1997) (Henna Neto and Elkis, 2007) (Werneck et al., 2011).

Another strength the present study is that the sample size surpassed the number needed for a satisfactory EFA. That is, by general consensus, at least 20 times as many subjects as variables. In this case, using the PANSS, roughly 600 subjects would be required; the present study had a sample consisting of 1429 patients – significantly more than twenty subjects per each item of the scale, as generally recommended (Johnson and Wichern, 2007) (Hair et al., 1988).

There is some degree of subjectivity involved in the interpretation of all factor analytical processes, especially in EFA (e.g., type of analysis, rotation method and factor loading cut-off). Despite these potential limitations, this is the first study to use CFA to evaluate comparatively the six-main factor analytical models of PANSS symptoms in TRS patients.

4.2. Limitations

One limitation of this study is that patients were classified as having TRS based only on clozapine usage. Since clozapine has other indications such as tardive dyskinesia, aggressive behavior or reduction of suicide risk (Meltzer et al., 2003), some patients may have been incorrectly classified as having TRS.

Conversely, it is possible that patients not receiving clozapine, and

therefore defined as NTRS, could be classified as having TRS based on the other criteria, for example, failure to respond to two or more trials with non-clozapine antipsychotics, as defined in various guidelines and algorithms (Elkis and Buckley, 2016). It is noteworthy that 26% of patients in the Pattern study were receiving clozapine. This is roughly as expected given the estimated prevalence of TRS in patients with schizophrenia (Elkis, 2007) (Elkis and Buckley, 2016).

The Pattern study was non-interventional and aimed to evaluate the impact of symptoms on patient function. Thus, the use of standardized rating scales for treatment response and resistance, as currently proposed (Howes et al., 2017), was not the focus of the study. As such, we chose a "proxy" definition of TRS based on the prescription of clozapine, an approach used in previous studies (Lally et al., 2016) that has been shown to have good specificity (Ajnakina et al., 2018).

Additionally, although the ideal number of subjects for a PANSS EFA would be 600 or more (30 variables x 20), our sample of 409 subjects with TRS is satisfactory given it has been proposed that a lower limit of 10 subjects per variable (i.e., 300 patients) is sufficient to perform an adequate FA (Hair et al., 1988).

The Pattern study itself has some limitations. Firstly, it was conducted with clinically stable patients with chronic schizophrenia attending outpatient clinics. Patients with different degrees of severity such as those living in institutions or with minimal symptoms were not included, as they do not attend outpatient clinics. Secondly, patients who fulfilled recovery criteria were also not included in the study. Thirdly, since the inclusion criteria in the Pattern study required informed consent, only adherent patients were selected. Finally, inter-rater reliability was not evaluated.

In the Pattern study, as in all cross-sectional studies, the findings represent stable traits. This feature presents a limitation, as it is known that symptom clusters detectable at one time may change during the illness (Haro et al., 2015). Additionally, in our sample the frequency of NTRS was four times greater than the frequency of TRS. This difference may interfere in the comparison of CFA models.

It is important to recognize that about 30% of patients with TRS may be partial responders to clozapine (i.e., approximately 10% of the total sample) (Elkis and Buckley, 2016). These patients are characterized by a predominance of positive symptoms (Henna Neto and Elkis, 2007) with a distinct clinical profile when compared to TRS patients, thus contributing to the heterogeneity of the TRS sample.

Finally, it can be argued that the failure to separate patients with TRS from patients with NTRS using PANSS factor analysis is due to treatment resistance not representing distinct subtypes of schizophrenia, but rather a continuum of illness severity, as proposed by Brenner and Merlo (Brenner and Merlo, 1995).

There are strong arguments favoring the view that response to treatment represents a new paradigm for subtyping schizophrenia (Lee et al., 2015). Recent genetic studies, as well as functional and structural neuroimaging research, has found that patients with TRS can be distinguished from those who respond to treatment (NTRS) based on a series of parameters. These include increased glutamatergic activity in the anterior cingulate, a normal dopaminergic activity in the striatum, and significant decrease in grey matter as well as a higher familial genetic loading (Gillespie et al., 2017) (Demjaha et al., 2017) (Mouchlianitis et al., 2016) (Jauhar et al., 2017).

The absence of evidence is not evidence of absence. It is conceivable that since clozapine is highly effective for the treatment of most psychopathological dimensions of schizophrenia (Elkis and Buckley, 2016) (Siskind et al., 2016), TRS patients in the present cross-sectional study, who have been treated with clozapine for many years, may exhibit a degree of symptom severity similar to those classified as NTRS. Furthermore, the PANSS data were collected at different centers across different countries resulting in methodological bias due to multiple interviewers and clinical heterogeneity. These factors could contribute to the poor model fit and the lack of difference between TRS and NTRS groups.

Therefore, an ideal study to identify clear differences in the factor structure of the PANSS would be a prospective trial based on well-established algorithms for the treatment of schizophrenia, such as the International Psychopharmacological Treatment Project (IPAP) (www.ipap.org), with an adequate evaluation of treatment response and resistance by a valid instrument such as the PANSS, according to the guidelines proposed by the TRRIP (Howes et al., 2017).

The analysis of factor structure at each time point of such a study would be clinically relevant for the identification of underlying psychopathological factors, which may represent important predictors of treatment response and resistance. However, Lindenmayer has critically reviewed this aspect, arguing that the failure to replicate a common factorial structure of the PANSS lead to development of shorter versions of the scale (Lindenmayer, 2017).

In fact, there were many attempts to reduce the PANSS in order to obtain clusters of items which could represent valid and reliable factors to better measure severity of illness (Ortiz et al., 2014) or predict treatment response, (Ortiz et al., 2014). Of note is the fact that the Item Response Theory, and not FA, has been proposed as the method of choice for such endeavor (Levine et al., 2011) as is case of the PANSS-6 (Ostergaard et al., 2018), composed by delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/ apathetic social withdrawal and lack of spontaneity. This reduced scale proved to be a valid and sensitive instrument for the evaluation of severity, remission and efficacy in patients with TRS of phase 2E of the CATIE study (McEvoy et al., 2006).

5. Conclusions

The present study, using the large sample of patients with schizophrenia from the Pattern study, conducted in 8 countries, showed a very similar factorial structure of the PANSS, when patients with TRS were compared with those with NTRS, in terms of exploratory factor analysis. Both analyses yielded a five-factor structure whose symptom dimensions could be generally named negative, positive, anxiety-depression, cognitive and excited. Confirmatory factor analyses showed that, when compared with well-established PANSS factor models, both factorial structures showed a satisfactory, although not perfect, fit to the data.

The identification of a specific group of symptoms differentiating TRS from NTRS would be not only of heuristic but also of clinical importance. An analysis of longitudinal data from the Pattern study (Haro et al., 2018), and other sources, may shed light to this important question.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2019.05.002](https://doi.org/10.1016/j.psychres.2019.05.002).

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