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# 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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## 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 best treatment option for TRS 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 high level of evidence, 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 Gorham, 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 it 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 ('Pyramidical') (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. These models received different names across studies as is the case of

Further studies which received different denominations, as is the case the "Pentagonal model" (White et al., 1997) and the Marder model (Marder et al., 1997). Wallwork et al, using the vote counting method. 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.**

However, to the best of our knowledge, there are no studies that used FA comparing patients with TRS with patients with NTRS. Two FA studies included patients with TRS, as it is the case of Lindenmayer's et al (Lindenmayer et al., 2004), which investigated the symptom profile of 157 TRS patients assigned to clozapine or other antipsychotics, and the Woodward's et al (Woodward et al., 2013), which compared patients with TRS with other types of diagnosis. Both studies found no substantial difference from models yielded as compared with the original PANSS five- factor model (Lindenmayer et al., 1994).

Thus, we think 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), "Pyramidical " ( four-factor)(Kay and Sevy, 1990), "Pentagonal" ( five- factor), the "NIMH" or consensus model ( five-factor) (White et al., 1997), VGAAG 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 DSM IV TR or ICD 10, 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 1,429 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 analysis

The analyses included all patients who fulfilled the eligibility criteria for the cross-sectional phase (*N*=1,429). 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 ('Pyramidical') (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 ('VDGAAG') (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.

## 2) 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 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 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)**.

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 $\chi 2$ 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, Pyramidical 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 VDGAAG model, regarded as the best 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 VDGAAG 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 greater mean age of onset, duration of illness, PANSS positive score 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 VDGAAG model for both groups.

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

The superiority of the VDGAAG 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 the case of the present study it may be explained by the clinical heterogeneity of schizophrenia as well as methodological bias introduced by having multiple interviewers from various centers in different countries, with no evaluation of PANSS inter-rater reliability among them.

### 4.2) 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).

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.

### 4.3) 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, interrater 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 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, 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 could represent important predictors of treatment response and resistance. However, Lindenmayer have 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 Item Response Theory , and not FA, has been proposed as the method of choice for such endeavor {Levine, 2011 #454 and a recent study based on this method which used the PANSS-6 (Ostergaard et al., 2018) (composed by delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/ apathetic social withdrawal and lack of spontaneity) proved to be a valid and sensible 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, which used data of a large sample of patients with schizophrenia of the Pattern study, which was 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 which could differentiate TRS from NTRS would be not only of heuristic but also of clinical importance. Thus, a new analysis of the longitudinal data of the Pattern study, which was recently published (Haro et al., 2018), based on exploratory and confirmatory models, or by new methods such item response theory, may shed light to this important question.

## References

Ajnakina, O., Horsdal, H.T., Lally, J., MacCabe, J.H., Murray, R.M., Gasse, C., Wimberley, T., 2018. Validation of an algorithm-based definition of treatment resistance in patients with schizophrenia. Schizophr Res. 197:294-297.

Altamura, A.C., Bobo, W.V., Meltzer, H.Y., 2007. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. Int Clin Psychopharmacol 22 (5), 249-267.

Alves, T.M., Pereira, J.C., Elkis, H., 2005. The psychopathological factors of refractory schizophrenia. Rev Bras Psiquiatr 27 (2), 108-112.

Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fusté, A., Furu, K., Garuolienė, K., Hoffmann, F., Hollingworth, S., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., López, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Piovani, D., Reutfors, J., Saastamoinen, L.K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Siskind, D., Skurtveit, S., Verdoux, H., Wang, L.J., Zara Yahni, C., Zoëga, H., Taylor, D., 2017. International trends in clozapine use: a study in 17 countries. Acta Psychiatr Scand 136 (1), 37-51.

Bentler, P.M., Yuan, K.H., 1999. Structural Equation Modeling with Small Samples: Test Statistics. Multivariate Behav Res 34 (2), 181-197.

Brenner, H., Merlo, M., 1995. Definition of therapy-resistant schizophrenia and its assessment. Eur Psychiatry 10 Suppl 1, 11s-17s.

Demjaha, A., 2017. On the brink of precision medicine for psychosis: Treating the patient, not the disease: A commentary on: Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment by Krivoy et al. 2017. Schizophr Res.193:487-488.

Elkis, H., 2007. Treatment-resistant schizophrenia. Psychiatr Clin North Am 30 (3), 511-533.

Elkis, H., Buckley, P.F., 2016. Treatment-Resistant Schizophrenia. Psychiatr Clin North Am 39 (2), 239-265.

Gillespie, A.L., Samanaite, R., Mill, J., Egerton, A., MacCabe, J.H., 2017. Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? a systematic review. BMC Psychiatry 17 (1), 12.

Hair, J., Anderson, R., Tatham, R., Black, W., 1988. Multivariate Data Analysis. Prentice Hall, New Jersey.

Haro, J.M., Altamura, C., Corral, R., Elkis, H., Evans, J., Krebs, M.O., Zink, M., Malla, A., Mendez, J.I., Bernasconi, C., Lalonde, J., Nordstroem, A.L., 2018. Understanding the course of

persistent symptoms in schizophrenia: Longitudinal findings from the pattern study. Psychiatry Res 267, 56-62.

Haro, J.M., Altamura, C., Corral, R., Elkis, H., Evans, J., Malla, A., Krebs, M.O., Zink, M., Bernasconi, C., Lalonde, J., Nordstroem, A.L., 2015. Understanding the impact of persistent symptoms in schizophrenia: Cross-sectional findings from the Pattern study. Schizophr Res 169 (1-3), 234-240.

Haro, J.M., Kamath, S.A., Ochoa, S., Novick, D., Rele, K., Fargas, A., Rodríguez, M.J., Rele, R., Orta, J., Kharbeng, A., Araya, S., Gervin, M., Alonso, J., Mavreas, V., Lavrentzou, E., Liontos, N., Gregor, K., Jones, P.B., Group, S.S., 2003. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl(416), 16-23.

Henna Neto, J., Elkis, H., 2007. Clinical aspects of super-refractory schizophrenia: a 6-month cohort observational study. Rev Bras Psiquiatr 29 (3), 228-232.

Howes, O.D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N.J., Birnbaum, M.L., Bloomfield, M.A., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., Castle, D.J., Citrome, L., Daskalakis, Z.J., Davidson, M., Drake, R.J., Dursun, S., Ebdrup, B.H., Elkis, H., Falkai, P., Fleischacker, W.W., Gadelha, A., Gaughran, F., Glenthøj, B.Y., Graff-Guerrero, A., Hallak, J.E., Honer, W.G., Kennedy, J., Kinon, B.J., Lawrie, S.M., Lee, J., Leweke, F.M., MacCabe, J.H., McNabb, C.B., Meltzer, H., Möller, H.J., Nakajima, S., Pantelis, C., Reis Marques, T., Remington, G., Rossell, S.L., Russell, B.R., Siu, C.O., Suzuki, T., Sommer, I.E., Taylor, D., Thomas, N., Üçok, A., Umbricht, D., Walters, J.T., Kane, J., Correll, C.U., 2017. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry 174 (3), 216-229.

Jauhar, S., Veronese, M., Rogdaki, M., Bloomfield, M., Natesan, S., Turkheimer, F., Kapur, S., Howes, O.D., 2017. Regulation of dopaminergic function: an [(18)F]-DOPA PET apomorphine challenge study in humans. Transl Psychiatry 7 (2), e1027.

Johnson, R., Wichern, D., 2007. Applied Multivariate Statistical Analysis, 6th ed.

Kane, J.M., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine in treatment-resistant schizophrenics. Psychopharmacol Bull 24 (1), 62-67.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13 (2), 261-276.

Kay, S.R., Sevy, S., 1990. Pyramidical model of schizophrenia. Schizophr Bull 16 (3), 537-545.

Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., Mondelli, V., Reis Marques, T., Pariante, C., Dazzan, P., Shergil, S.S., Howes, O.D., David, A.S., MacCabe, J.H., Gaughran, F., Murray, R.M., 2016. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol Med 46 (15), 3231-3240.

Lançon, C., Auquier, P., Nayt, G., Reine, G., 2000. Stability of the five-factor structure of the Positive and Negative Syndrome Scale (PANSS). Schizophr Res 42 (3), 231-239.

Lee, J., Takeuchi, H., Fervaha, G., Sin, G.L., Foussias, G., Agid, O., Farooq, S., Remington, G., 2015. Subtyping Schizophrenia by Treatment Response: Antipsychotic Development and the Central Role of Positive Symptoms. Can J Psychiatry 60 (11), 515-522.

Lindenmayer, J.P., 2017. Are Shorter Versions of the Positive and Negative Syndrome Scale (PANSS) Doable? A Critical Review. Innov Clin Neurosci 14 (11-12), 73-76.

Lindenmayer, J.P., Bernstein-Hyman, R., Grochowski, S., 1994. A new five factor model of schizophrenia. Psychiatr Q 65 (4), 299-322.

Lindenmayer, J.P., Czobor, P., Volavka, J., Lieberman, J.A., Citrome, L., Sheitman, B., McEvoy, J.P., Cooper, T.B., Chakos, M., 2004. Effects of atypical antipsychotics on the syndromal profile in treatment-resistant schizophrenia. J Clin Psychiatry 65 (4), 551-556.

Marder, S.R., Davis, J.M., Chouinard, G., 1997. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 58 (12), 538-546.

Marsh, H.W., Wen, Z., Hau, K.T., 2004. Structural equation models of latent interactions: evaluation of alternative estimation strategies and indicator construction. Psychol Methods 9 (3), 275-300.

McEvoy, J.P., Lieberman, J.A., Stroup, T.S., Davis, S.M., Meltzer, H.Y., Rosenheck, R.A., Swartz, M.S., Perkins, D.O., Keefe, R.S., Davis, C.E., Severe, J., Hsiao, J.K., 2006. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 163 (4), 600-610.

McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30, 67-76.

Meltzer, H.Y., Alphs, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., Krishnan, R., Lindenmayer, J.P., Potkin, S., Group, I.S.P.T.S., 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 60 (1), 82-91.

Meltzer, H.Y., Rabinowitz, J., Lee, M.A., Cola, P.A., Ranjan, R., Findling, R.L., Thompson, P.A., 1997. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. Am J Psychiatry 154 (4), 475-482.

Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand 101 (4), 323-329.

Mouchlianitis, E., McCutcheon, R., Howes, O.D., 2016. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. Lancet Psychiatry 3 (5), 451-463.

Ortiz, B.B., Gadelha, A., Higuchi, C.H., Pitta, J.C., Kagan, S., Vong, M.R., Noto, C., Hallak, J.E., Bressan, R.A., 2014. What are the PANSS items most related with global improvements in patients with schizophrenia? Toward a reduced version of the PANSS. Schizophr Res 158 (1-3), 277-278.

Ostergaard, S., Foldager, L., Mors, O., Bech, P., CU, C., 2018. The validity and sensitivity of PANSS-6 in treatment-resistant schizophrenia. Acta Psychiatrica Scandinavica 138, 420-431.

Overall, J., Gorham, D., 1962. The Brief Psychiatric Rating Scale. 10, 799-812.

Schreiber, J.B., Nora, A., Stage, F.K., Barlow, E.A., King, J., 2006. Reporting Structural Equation Modeling and Confirmatory Factor Analysis Results: A Review. The Journal of Educational Research, 323-337.

Schumacker, R., Lomax, R., 1996. A begginer's guide to structural equation modelling. Lawrence Erlbaum, New Jersey.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20, 22-33; 34-57.

Siskind, D., McCartney, L., Goldschlager, R., Kisely, S., 2016. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 209 (5), 385-392.

Stefanovics, E.A., Elkis, H., Zhening, L., Zhang, X.Y., Rosenheck, R.A., 2014. A cross-national factor analytic comparison of three models of PANSS symptoms in schizophrenia. Psychiatry Res 219 (2), 283-289.

Tamminga, C.A., 2008. Domains of dysfunction in schizophrenia: implications for diagnosis. World Psychiatry 7 (1), 34-35.

van der Gaag, M., Cuijpers, A., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., van Meijel, B., van Harten, P.N., Valmaggia, L., de Hert, M., Wiersma, D., 2006a. The five-factor model of the Positive and Negative Syndrome Scale I: confirmatory factor analysis fails to confirm 25 published five-factor solutions. Schizophr Res 85 (1-3), 273-279.

van der Gaag, M., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., van Meijel, B., van Harten, P.N., Valmaggia, L., de Hert, M., Cuijpers, A., Wiersma, D., 2006b. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr Res 85 (1-3), 280-287.

Wagner, E., Lohrs, L., Siskind, D., Honer, W.G., Falkai, P., Hasan, A., 2019. Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance. J Psychopharmacol 33 (4), 423-435.

Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res 137 (1-3), 246-250.

Wang, G., Zheng, W., Li, X.B., Wang, S.B., Cai, D.B., Yang, X.H., Ungvari, G.S., Xiang, Y.T., Correll, C.U., 2018. ECT augmentation of clozapine for clozapine-resistant schizophrenia: A meta-analysis of randomized controlled trials. J Psychiatr Res 105, 23-32.

Werneck, A.P., Hallak, J.C., Nakano, E., Elkis, H., 2011. Time to rehospitalization in patients with schizophrenia discharged on first generation antipsychotics, non-clozapine second generation antipsychotics, or clozapine. Psychiatry Res 188 (3), 315-319.

White, L., Harvey, P.D., Opler, L., Lindenmayer, J.P., 1997. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology 30 (5), 263-274.

Woodward, T.S., Jung, K., Smith, G.N., Hwang, H., Barr, A.M., Procyshyn, R.M., Flynn, S.W., van der Gaag, M., Honer, W.G., 2013. Symptom changes in five dimensions of the Positive and Negative Syndrome Scale in refractory psychosis. Eur Arch Psychiatry Clin Neurosci 264 (8), 673-682.