

The psychopathological factors of refractory schizophrenia

Fatores psicopatológicos da esquizofrenia refratária

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Original version accepted in Portuguese

Abstract

Objectives: The heterogeneity of clinical manifestations in schizophrenia has led to the study of symptom clusters through psychopathological assessment scales. The objective of this study was to elucidate clusters of symptoms in patients with refractory schizophrenia which may also help to assess the patients' therapeutical response. **Methods:** Ninety-six treatment resistant patients were evaluated by the anchored version Brief Psychiatric Rating Scale (BPRS-A) as translated into Portuguese. The inter-rater reliability was 0.80. The 18 items of the BPRS-A were subjected to exploratory factor analysis with Varimax rotation. **Results:** Four factors were obtained: Negative/Disorganization, composed by emotional withdrawal, disorientation, blunted affect, mannerisms/posturing, and conceptual disorganization; Excitement, composed of excitement, hostility, tension, grandiosity, and uncooperativeness, grouped variables that evoke brain excitement or a manic-like syndrome; Positive, composed of unusual thought content, suspiciousness, and hallucinatory behavior; and Depressive, composed of depressive mood, guilt feelings, and motor retardation, clearly related to depressive syndrome. **Conclusions:** The study reproduced the four factors described in the literature, either in refractory or non-refractory patients. The BPRS-A allowed the distinction of psychopathological factors, which are important in the evaluation of treatment response of patients with schizophrenia.

Keywords: Schizophrenia/psychopathology; Brief psychiatric rating scale; Factor analysis, statistical

Resumo

Objetivos: A heterogeneidade das manifestações clínicas na esquizofrenia tem levado ao estudo de agrupamentos sintomatológicos através de escalas de avaliação psicopatológica. O objetivo do presente trabalho foi a elucidação de agrupamentos psicopatológicos em pacientes com esquizofrenia refratária que também podem auxiliar na avaliação da resposta terapêutica dos pacientes. **Métodos:** Noventa e seis pacientes com diagnóstico de esquizofrenia refratária foram avaliados através da Escala Breve de Avaliação Psiquiátrica, versão ancorada e traduzida para o português (BPRS-A). A confiabilidade foi de 0,80. Os 18 sintomas foram submetidos à análise fatorial exploratória com rotação Varimax. **Resultados:** Quatro fatores foram obtidos: Negativo/Desorganização, composto por retraimento afetivo, desorientação, afeto embotado, maneirismo & postura e desorganização conceitual; Excitação, formado por excitação, hostilidade, tensão, idéias de grandeza e falta de cooperação; Positivo, contendo os itens delírio, desconfiança e comportamento alucinatório; e Depressivo, que agrupou humor depressivo, sentimento de culpa e retardo motor. **Conclusões:** O estudo reproduziu os quatro fatores psicopatológicos encontrados na literatura, provenientes de amostras tanto de pacientes com esquizofrenia refratária como não-refratária. A BPRS-A permitiu a distinção de agrupamentos psicopatológicos específicos que têm valor na avaliação da resposta terapêutica destas formas de esquizofrenia.

Descritores: Esquizofrenia/psicopatologia; Escalas de graduação psiquiátrica breve; Análise fatorial

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Introduction

For decades, many efforts have been performed to characterize the clinical symptomatology of schizophrenia. The dichotomy between positive and negative symptoms which was initially proposed for schizophrenia¹ has been modified by studies based on factor analysis,² a statistical method which enable the grouping of symptoms of a scale by means of their correlation. These factors (or psychopathological dimensions) have shown to be associated with certain specific etiological, pathophysiological and therapeutic processes. These analyses have revealed the existence of three,³⁻⁴ four,⁵⁻⁸ five⁹ or more¹⁰⁻¹¹ psychopathological dimensions. However, the results of these studies are limited to the type of assessment instrument employed, to the diagnostic heterogeneity of the diagnosis of schizophrenia, to the disease's different evolution steps and to the patients' medication treatment status.

The Brief Psychiatric Rating Scale (BPRS)¹² is a psychopathological assessment scale composed of 18 items which have been extensively used in the assessment of patients with diagnosis of schizophrenia.¹³ It has also been used in the assessment of the therapeutic response to antipsychotics by Kane et al¹⁴ and in the development of criteria for refractory schizophrenia.

Since the first factor analyses, which were performed by Overall and Klett⁵ or by Guy,⁹ BPRS symptoms have shown to be aggregated into four or five factors (Table 1). However, most of the studies have shown the distribution of symptoms into four factors, namely: "thought disturbance", "withdrawal/motor retardation", "anxiety/depression" and "hostility/suspiciousness" (Table 1).

However, most factor analysis with the BPRS had their respective data derived from patients whose drug treatment status was undefined, without an adequate discrimination between patients who were responsive or refractory to antipsychotic treatment. Only one study¹⁵ used the BPRS to assess a population with refractory schizophrenia and the factor analysis of these patients' data showed that BPRS symptoms aggregated in four factors: "negative symptoms", "reality distortion", "disorganization" and "anxiety/depression" (Table 1).

This study aims to investigate the psychopathological factors in a population of patients with diagnosis of schizophrenia, selected according to a well-defined criterion of refractoriness to antipsychotic treatment.

Methods

This study was approved by the Ethics Committee for Analysis of Research Projects of the Clinical Hospital (Cappesq) of the Medical School of the University of São Paulo (IPq-HC-FMUSP) and was accomplished in the Schizophrenia Outpatient Unit (Projesq). All patients gave their informed consent.

Patients from both genders, above 18 years old, with diagnosis of schizophrenia according to the ICD-10¹⁶ and the DSM - IV¹⁷ were assessed.

Patients were defined as refractory according to modified Kane et al's criteria,¹⁴ namely:

1) Historic criterion: presence of persistent psychotic symptoms in the prior five years, having the patient been submitted to at least three drug treatments with medications from two different biochemical classes, in doses equivalent to chlorpromazine 1,000 mg/day or more for six weeks; and

2) Current psychopathological severity: BPRS-A's total score equal to or higher than 27 points, with score of three (moderate) or more in the items "conceptual disorganization", "suspiciousness", "hallucinations" and "delusion".

The anchored version BPRS-A (18 items), translated into Portuguese,¹⁸ based on Woerner's¹⁹ version, was used as the instrument for psychopathological assessment. It was filled out by choosing one to seven ordinal descriptions of symptoms intensity (anchors), which were: *not present, very mild, mild, moderate, moderately severe, severe, and very severe*, with numeric correspondence from 0 to 6, respectively.²⁰ Semi-structured interviews which lasted for twenty to thirty minutes were performed and their general structure agreed with the standardization by Overall and Gorham,¹² and Rhoades and Overall.²¹ Besides this structure, raters were allowed to introduce their own skills to obtain findings which suffice to assess the severity of symptoms. For the sake of reliability, the

Table 1 – Main factor analysis studies of symptoms of schizophrenia using the Brief Psychiatric Rating Scale (BPRS)

Factor Analysis				
Factors and their components	Authors	Sample (n)	Population	Instrument
4 factors: Thought Disturbance (conceptual disorganization, hallucinatory behavior and uncommon content of thought); Withdrawal/Psychomotor Retardation (affective withdrawal, motor retardation and blunted affect); Anxiety/Depression (anxiety, guilt feelings and depressed mood); Hostility/Suspiciousness (hostility, suspiciousness and uncooperativeness)	Overall e Klett, 1972 ⁴	3.000	Include schizophreniform and affective psychoses	16-item not anchored BPRS, with punctuation from 1 to 7
5 factors: Thought Disturbance (conceptual disorganization, grandiosity, hallucinatory behavior and uncommon content of thought); Lack of energy (emotional withdrawal, motor retardation, blunted affect and disorientation); Anxiety/Depression (somatic concern, anxiety, guilt feelings and depressed mood); Activation (tension, mannerism, posturing and excitement); Hostility/ Suspiciousness (hostility, suspiciousness and uncooperativeness)	ECDEU Assessment Manual for Psychopharmacology Guy, ⁹ 1976	3.596	Patients with diagnosis of schizophrenia	18-item not anchored BPRS, with punctuation from 1 to 7
4 factors: Negative symptoms (emotional withdrawal, motor retardation and blunted affect); Reality distortion (grandiosity, motor retardation, suspiciousness, hallucinatory behavior and delusion); Disorganization (conceptual disorganization, mannerism, posturing and disorientation); Anxiety/Depressive (anxiety, guilt feelings and depressed mood)	McMahon et al, ¹⁵ 2002	1.074	Patients with diagnosis of schizophrenia mostly refractory to antipsychotic treatment	18-item BPRS, with not-informed punctuation

same patient was simultaneously assessed by two raters; the author, a psychiatrist, and one psychologist, both of them with clinical experience. The interview was conducted by the psychiatrist and at the end both filled out independently their scores. Raters were trained by tape-recorded interviews and with real patients before reaching a reliability on the scale's overall mean equal to 0.80, as calculated by the intra-class correlation coefficient (ICC).

One hundred and twenty patients using conventional antipsychotics and who met the historic criterion described above were entered in the study. The application of the BPRS-A, using a cut-off point with the values defined by the current psychopathological severity criterion, has differentiated two groups of patients: ninety-six of them were classified as refractory, with high levels of psychopathological severity, and twenty-four were classified as non-refractory (or responsive), without the same severity level of refractory patients. Refractory patients were treated with clozapine, whereas non-refractory ones received conventional or second-generation antipsychotics. Patients were assessed at six-week intervals and the study lasted for 36 weeks. Data used in factor analysis were those obtained at baseline, i.e., at the first assessment of the study.

Exploratory factor analysis: it was based on the analysis method of extraction of principal components amounts to a varimax rotation, using Kaiser's criterion to determine the number of factors.²² **Model adjustment:** the following measures were considered to accept the factor analysis: Kaiser-Meyer-Olkin measure,²³ Bartlett's test of sphericity;²³ Variance Explained Ratio; Kaiser's Criterion²² ("eigenvalue" or self-value higher than 1).

Factors whose relationship had psychopathological coherence were chosen. Factor loading considered for the interpretation of each of the factors was that equal to or higher than 0.50.

Results

Ninety-six patients were assessed, with mean age of 33.62 years (range from 19 to 75 years and standard deviation of 8.96), schooling of 9.36 years (range from 2 to 17 years and

standard deviation of 3.48), mainly masculine (71.9%), single (93.8%) and Caucasian (85.4%). Most of them were not working (91.7%), part of the sample had worked before the disease onset (40.6%) and was living with (83.3%) and being financially supported by their parents (64.6%). In average, they became ill at 19.29 years of age (range from 5 to 38 years and standard deviation of 4.90), had been admitted 3.76 times (range from 0 to 20 times and standard deviation of 4.17), aged 17.53 years (range between 14 and 37 years and standard deviation of 9.90) at the first admission and had been ill for 13.98 years (range from 5 to 38 years and standard deviation of 7.32).

Five factors were found, being the fifth represented by the symptoms "somatic concern", and "anxiety", with self-value (*eigenvalue*) of 1.6 and contributed with 9% (little loading) for model adjustment. This factor was excluded for not corresponding to the interpretability of the criterion, i.e., not having psychopathological coherence. Therefore, the model obtained with four factors showed good final data adjustment, namely: Kaiser-Meyer-Olkin measure = 0.70, Bartlett's test of sphericity = 772.97, with significance = 0.0001 and Variance Explained Ratio by the model of 63.542; that is, the model represents 63% of the data, and the individual contributions of each factor for the final model are: factor 1 with 18.7%, factor 2 with 17.9%, factor 3 with 14.1% and factor 4 with 12.6%. Each factor was named according to the known psychopathological domains. Factor 1, or Negative/Disorganization, is composed by emotional withdrawal, disorientation, blunted affect, mannerism/posturing and conceptual disorganization; factor 2, or Excitement, formed by excitement, hostility, tension, grandiosity and uncooperativeness, groups variables which resemble symptoms of cerebral excitability or mania-like syndrome; factor 3, or Positive, groups delusion, suspiciousness and hallucinatory behavior; and factor 4, or Depressive, which groups depressed mood, guilt feelings and motor retardation, which are clearly symptoms of the depressive syndrome (Table 2).

Table 2 – Factors after Varimax rotation

Denomination of factors	Components	Factor				Degree of Commonality
		1	2	3	4	
Negative/ Disorganization	Affective withdrawal	0.83				0.719
	Disorientation	0.73				0.582
	Blunted affect	0.72				0.661
	Mannerism/posturing	0.63				0.504
	Conceptual disorganization	0.63				0.575
Excitement	Excitement		0.86			0.761
	Hostility		0.77			0.680
	Tension		0.73			0.680
	Grandiosity		0.69			0.554
	Uncooperativeness		0.65			0.592
Positive	Delusion			0.83		0.775
	Suspiciousness			0.82		0.713
	Hallucinatory behavior			0.75		0.641
Depressive	Depressive mood				0.87	0.815
	Guilt feelings				0.84	0.749
	Motor retardation				0.56	0.623
Self-values (eigenvalues)		3.381	3.223	2.547	2.285	
Variance explained (%)		18.786	17.908	14.151	12.697	63.542

Kaiser-Meyer-Olkin = 0.70

Bartlett's Test of Sphericity: Chi-square = 772.97 df = 153 p = 0.0001

Discussion

The results of this study replicate the factors "positive" and "negative" and evidence that they are found in all studies of factor analysis among schizophrenic patients who are responsive and not-responsive to typical neuroleptics using the BPRS or other instrument for psychopathological measure. The factor "excitement" is similar to the factor "activation" found by Guy⁹ and composed by tension, mannerism/posturing and excitement in one study with 3596 schizophrenic subjects. The components of the factor "depression" are similar to the findings of other studies such as those by Overall and Klett,⁵ Guy,⁹ Acorn,²⁴ Zuardi et al²⁵ and McMahon et al.¹⁵ Of note, the factors 1 and 4 are so clearly distinct, corroborating to the findings by Addington²⁶ and with the idea that depressive and negative symptoms are not part of the same biological substract.

The fifth factor was represented by the symptoms "somatic concern" and "anxiety". This group does not correspond to any known psychopathological syndrome. In the factor model, the aggregation of the symptoms "somatic concern" to the factor "positive" and "anxiety" to the factor "negative/disorganization" was easily accepted, as they show psychopathological coherence. The concern with body alterations, in the majority of delusional cases, could be more coherently integrated to the factor "positive", what did not happen. Besides, patients with somatic delusional ideas were not anxious.

Factor analysis studies using the BPRS as their instrument and in a population with not-specified refractoriness, the symptom "disorganization of thought" has been grouped to the factor "positive symptoms", as shown in Overall and Klett,⁵ Guy⁹ and Zuardi et al²⁵ or grouped to the factor "negative", as seen in Acorn.²⁴ In the studies by Bilder et al³ and Liddle,⁴ an independent factor arises, composed by the symptoms positive formal thought disorder, bizarre behavior, alogia, attentional impairment and inappropriate affect. These, in turn has the limitation of having small samples and to have used different psychopathological assessment instruments. As previously mentioned, this study and McMahon et al's¹⁵ were the only to assess a homogeneous population of refractory patients. McMahon et al found that the symptom conceptual disorganization was aggregated to the symptoms mannerism/posturing and disorientation, conforming the factor called "disorganization". However, in the mentioned study, the symptoms tension, hostility, uncooperativeness and excitement were not grouped into only one factor, differently from what occurred in our sample. Summing up, the isolation of the factor "disorganization" was not constantly found in most of the studies of factor analysis with the BPRS-A.

The debate whether the symptom "disorganization" pertains to the psychotic dimension (factor "positive") or is an independent dimension is important as the concept of treatment resistance has been associated with that of persistence of positive symptoms since nearly one decade.¹⁴ Recently, however, the factor high levels of "disorganization" has been associated with patients resistant to antipsychotics, even when compared to those who are partially or totally responsive to conventional antipsychotics.²⁷

We consider that one of the most important aspects of this study is to have selected one population of patients with refractory schizophrenia based on well-defined criteria. On the other hand, its main limitation lies on the sample size. In this sense, according to Hair et al,²⁸ in a factor analysis, the adequate ratio between the number of observations (patients) and variables is 20:1 (in the case to 18 item of the BPRS-A, patients), but the same author highlights that the ratio of 5:1 (nearly 90 patients,

for the BPRS-A) makes the analysis feasible, i.e., such as that performed in this study.

Conclusion

The factor analysis of this study has found factors which reflect known psychopathological syndromes and replicated findings of factors originated from samples with refractory and not-refractory schizophrenia.

The BPRS-A has shown to be useful in the definition of the psychopathological factors of refractory schizophrenia which may be helpful in the therapeutic follow-up of patients with this type of schizophrenia.

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