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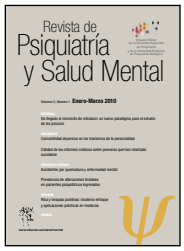

ORIGINAL ARTICLE

Attention Deficits and Response to Drug Therapy in Patients With Treatment-Resistant Schizophrenia: Results Through Confirmatory Factorial Analysis

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KEYWORDS
Treatment-resistant schizophrenia;
Confirmatory factorial analysis;
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Cognitive performance

Abstract
Introduction: There are no experimental data that demonstrate whether patients with neuroleptic-resistant schizophrenia differ or not in their pattern of neuropsychological functioning from patients with adequate drug response.
Method: Fifty-two patients with drug-resistant psychosis (DRS) and 42 patients with schizophrenia not resistant to treatment (NDRS) were recruited following the criteria of Kane et al (1988). A sample of 45 healthy controls matched by age, sex and educational level was also recruited. The clinical evaluations used were the Positive and Negative Symptom (PANSS), functional disability (WHO-DAS) and Clinical Global Impression (CGI) scales.
Results: Through the use of confirmatory factorial analysis, we obtained a latent cognitive structure of six cognitive factors: attention, processing speed, verbal memory, working memory, verbal fluency and executive functions. As expected, the control group performed better than the two patient groups (both DRS and NDRS) in all neuropsychological domains. Additionally, the DRS group scored significantly worse in attention than the NDRS group even though no differences between these two groups were found in age of disease onset, number of hospitalisations or length of hospitalisation. From a clinical point of view, the DRS group showed greater severity of positive symptoms ($P<0.01$) and

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higher global deterioration (P<0.01), which did not translate into greater functional disability.

Conclusions: The results obtained do not allow us to conclude that there is a specific neuropsychological profile in neuroleptic-resistant patients. The only differential parameter was performance in the attention domain. Our findings better fit the hypothesis of a "clinical continuum" and differ from the categoric classification of this mental disorder.

PALABRAS CLAVE
Esquizofrenia resistente a tratamiento;
Análisis factorial confirmatorio;
Psicopatología;
Rendimiento cognitivo

Déficit atencionales y respuesta al tratamiento farmacológico en pacientes con esquizofrenia resistente al tratamiento: resultados mediante análisis factorial confirmatorio

Resumen

Introducción: No hay datos experimentales que confirmen si, en cuanto al patrón de funcionamiento neuropsicológico, los pacientes con esquizofrenia resistente al tratamiento con neurolépticos difieren de los pacientes que muestran una respuesta farmacológica adecuada.

Método: Se reclutó a 52 pacientes con psicosis resistente a tratamiento farmacológico (ERT) y 42 pacientes con esquizofrenia no resistente a tratamiento (ENRT), siguiendo los criterios de Kane et al (1988). Además, se reclutó una muestra de 46 controles sanos (NC) apareados por edad, sexo y nivel educativo. Las medidas clínicas incluidas fueron las escalas PANSS (Escala de Síntomas Positivos y Negativos), de discapacidad funcional (WHO-DAS) y de Impresión Clínica Global (CGI).

Resultados: Mediante el empleo de análisis factorial confirmatorio, obtuvimos una estructura cognitiva latente de seis factores cognitivos: atención, velocidad de procesamiento, memoria verbal, memoria de trabajo, fluidez verbal y funciones ejecutivas. Como era esperable, el grupo control rindió mejor que los dos grupos de pacientes (tanto ERT como ENRT) en todos los dominios neuropsicológicos. Además, el grupo ERT rindió en tareas atencionales significativamente peor que el grupo ENRT, a pesar de que no diferían en edad de inicio de la enfermedad, número de hospitalisaciones y tiempo de hospitalisación. Desde el punto de vista clínico, el grupo ERT presentaba mayor severidad de síntomas positivos (P<0,01) y mayor deterioro general (P<0,01), lo que no se traducía en mayor discapacidad funcional.

Conclusiones: Los resultados obtenidos no permiten concluir la existencia de un perfil neuropsicológico específico en pacientes no respondedores al tratamiento con neurolépticos. El único parámetro diferencial fue el rendimiento en el dominio atencional. Nuestros hallazgos son más coherentes con la hipótesis del "fenómeno clínico continuo" y se distancian de la clasificación categórica de este trastorno mental.

Introduction

Reviewing the scientific literature it can be seen that patients with schizophrenia that improve with antipsychotic treatment and those that continue with severe symptoms in spite of appropriate drug treatment could be two subgroups of patients with a different pathological condition.[1-3] Treatment resistant schizophrenia (TRS) was defined by Kane et al[4] in the Clozapine Registration Trial as the lack of patient response to three different antipsychotic drugs in large doses.

Previous studies that have identified several variables predicting good or bad prognosis in treatment resistant schizophrenia (TRS) concluded that female sex,[5] late age of onset,[6] absence of obstetrics-related complications at birth[7] and reduced presence of minor neurological symptoms[8] are all predictors of good therapeutic response. In contrast, poor premorbid adjustment,[7,9] poor psychosexual adjustment during late adolescence,[10] long non-treated psychosis[11,12] and poor quality of life,[13] are associated with an unfavourable response to antipsychotic treatment. To date, results of studies on other physiological variables have not been conclusive. There is evidence that finding high concentrations of homovalinic acid before treatment could be related to a better response to antipsychotic drugs in schizophrenia patients.[14,15] Furthermore, neuroimaging studies with positron emission (PET) and monophotonic (SPECT) computed tomography have found similar degrees of D2 receptor occupancy in patient with TRS and patients who do respond to typical antipsychotic treatment.[16]

These findings would also explain the lack of improvement in both groups, responders and non-responders, to significant dose increases.[17] All these results support the hypothesis that patients with TRS could have a different schizophrenia fenotype.[1]

The disparity in study results could be due, in part, to the lack of consensus in defining TRS. Originally, the concept of TRS was synonymous of chronic schizophrenia or a history of multiple hospitalisations.[18] The publication of alternative criteria by Kane et al[4] and the Remission in Schizophrenia Working Group[19] let to a better characterisation of the definition of TRS, and in consequence, an increase in experimental research to identify the specific characteristics of this type of shizophrenia.[16,20-22] The Remission in Schizophrenia Working Group based their criteria on the absence or persistence of certain positive or negative symptoms using the PANSS, SANS/SAPS y BPRS scales.

Kane's criteria have shown a series of drawbacks that make this tool difficult to apply in a clinical environment, for the following reasons:

- They are based on the persistence of positive symptoms and ignore the severity of others, such as negative or cognitive symptoms. However, according to subsequent findings,[23] negative symptoms are those responsible to a large extent for the variation in functional disabilities in schizophrenia.
- They establish a rigid classification of patients in responders and non-responders. This does not precisely explain a common fact in clinical practice, which is that the response to treatment is better understood as a continuum rather than a dichotomy. Most patients are included by Barnes et al[17] in the category of "suboptimal responders".

Kane's criteria are too strict for application in clinical practice. However, they are the most reliable criteria for resistance to treatment and those most widely used in research.

Subsequent to the development of this study, the Remission in Schizophrenia Working Group[19] developed a consensus definition of remission, which is applicable to schizophrenia. Remission was defined using an absolute severity threshold for schizophrenia symptoms, rather than a percentage of improvement from baseline. These remission criteria define remission as a low to medium symptom intensity level, in which the limit or slight absence or presence of symptoms does not influence an individual's behaviour. This work group explicitly excluded from their criteria improvements in cognitive symptoms and psychosocial function due to a lack of findings in these areas. Although these criteria precisely define the meaning of remission, they fail when applied to all cases above the symptom severity threshold, therefore, these cannot be considered to be in remission. It is not clear if these cases with no remission should be considered non-responders, refractory cases or patients with TRS.

None of these criteria (Kane and Andreasen) include cognitive or functional factors, in spite of the abundant evidence that supports the relevance of these deficits in schizophrenia, especially in chronic samples. Said literature has confirmed specific and generalised cognitive deterioration in patients with TRS in comparison with patients with non-resistant to treatment schizophrenia (NRTS). Joober et al[24] published the first study specifically based on a subgroup of patients with RTS with the aim of analysing the specific degree of deterioration in seven cognitive domains: attention-vigilance, abstraction-flexibility, spatial organisation, visual motor processing, visual memory, verbal skills and verbal memory. They compared 39 patients with TRS, 36 patients with NTRS and 36 paired controls. Both patients with TRS and those with NTRS had significantly lower scores than the control group in all the assessed domains. However, patients with NTRS had total remission of symptoms, no relapses and had significantly better results than patients with TRS in verbal skills, learning, verbal memory and visual memory. In consequence, Joober et al indicated that a worse response to antipsychotic drugs and cognitive deterioration are the two distinctive characteristics shared by a specific subgroup of patients. Furthermore, the authors concluded that neuropsychological variables could be markers of response to RTS drug treatment. Neuropsychological deficits vary according to the profile and severity of schizophrenia,[25] and said dispersion could hide the characteristics of possible subgroups of the disease.

This interesting finding is opposed to prior hypothesis[1] relating to the difficulty in classifying patients with schizophrenia in subgroups according to their response to drug treatment. Barnes et al[17] pointed out that patients with schizophrenia could be classified in groups: those who have an optimum response to treatment and others that have a less than optimum response, or using a continuous response variable, rather than a categorical one, for groups of responders and non-responders.

As a result, our aim in this study is to analyse the contribution of neuropsychological variables as differential predictors of the response to drug treatment in patients with schizophrenia. We therefore hypothesise that: *a)* patients with TRS and NTRS have significant cognitive deterioration in comparison with the control group; *b)* patients in the TRS group have a greater degree of cognitive deterioration than those in the NTRS group, and *c)* patients in the TRS group have a cognitive profile that relates differentially to clinical and functional results.

Methods

Participants

We recruited 95 patients hospitalised in the Alava Psychiatric Hospital: 76 men and 14 women with 10.17±2.8 years of official education and 18 to 65 years old (mean: 36.09±10.68). The patients were diagnosed with schizophrenia according to DSM-IV criteria,[26] by means of SCID-I semi-structured clinical interviews. Exclusion criteria were: previous history of spinal or cranial trauma with more than 1 hour of loss of consciousness, mental

retardation or a relevant neurological condition (stroke, hypertension of significant sensorial deficit).

The assignation of the groups to TRS or NTRS was done in two steps. First, the patients with a poor response to treatment were identified according to their clinical histories and the psychiatrist's clinical judgement. Second, following the directives of Joober et al,[24] we determined if the patients' complied with the criteria of resistance to antipsychotic treatment or not. We classified 52 patients as TRS and 43 as NTRS, in accordance with the criteria of Kane et al.[4]

Patients with TRS must comply, furthermore, with the following inclusion criteria:

- A history of having had three or more treatment periods during the last 5 years with at least two antipsychotic drugs from different families, with a dose equivalent to 1,000mg/day of chlorpromazine for a period of 6 weeks without significant relief.
- Absence of any period of good functioning during the 5 previous years.
- At the moment of assessment they must have a Brief Psychiatric Rating Scale (BPRS[28]) score >45 and in the CGI scale a score >4.
- A score of 4 (moderate) in at least two of the following BPRS items (conceptual disorganisation, unusual thoughts, hallucinatory and suspicious behaviour).
- Failure to reduce the BPRS in 20%, as also BPRS>35 or a GCI>3 after a treatment trial with haloperidol in doses of 10 to 60mg/day.

To overcome the difficulties of the bioequivalence of the dose of 1,000mg/day of chlorpromazine for new antipsychotic drugs that did not exist at the time the Kane et al criteria published, our team used the solution proposed by Woods.[27]

In the group of patients with NTRS, all the patients that complied with the inclusion criteria but did not comply with criteria for refractoriness were included, that is, who had a clinical history with demonstrable periods of good clinical response to antipsychotic drugs. This was measured by a reduction of BPRS greater than 20% and a total BPRS<35 and CGI<3. A number of TRS cases were selected equal to the size of the non-responder (NTRS) group.

For the control group (CG) 46 healthy control subjects were recruited by means of notices in periodicals or in public institutions. They were selected by age, sex, educational level and socioeconomic characteristics to pair them with the groups of patients. They underwent a clinical interview to rule out current or previous psychiatric disorders, relevant medical conditions affecting the central nervous system or significant sensorial deficits. The groups were similar in age (F=1.09; P=0.34), sex (χ^2=5.93; P=0.06) or years of official education (F=0.77; P=0.47). We excluded 12 CG participants after the initial interview as they did not comply with the inclusion criteria.

All subjects (patients and control group) were volunteers and gave their written consent to participate in the study. The protocol was approved by the hospital ethics committee.

Clinical Evaluation

All the patients were assessed by means of a clinical interview and scored by PANNS,[29] BPRS and CGI. Functional disability was assessed by WHO-DAS.[30] The reliability ratio between examiners for the scales was determined by a kappa=0.8. At the end of the training period, reliability values were between 0.83 and 0.91 for PANSS, BPRS, CGI and WHO-DAS.

Neuropsychological Assessment

Attention

Brief Test of Attention. The BTA[31] consists of two parallel forms that are administered orally. In the N form (numbers), ten lists of letters and numbers that increase progressively in size from 4 to 18 items are read to the patients. The participant's task is to disregard the letters presented and to count how many numbers there were on the list. In the L form (letters) the same list is presented, but in this case the patient has to disregard the numbers and count how many letters there were on the list.

Verbal Memory

The Spanish version of the WAIS-III (WMS-IIII)[32] Memory-III Weschler Scale of logical memory was used. In this test, the examiner reads two stories, stops after each one and requests the participant to write all they remember about the story. After 20min the patient is requested to relate all they remember about the stories. In this way two measurements are taken, immediate memory (IM) and long term memory (LTM).

Executive Functions

Wisconsin Card Sorting Test-CV64.[33] The response cards are numbered from 1 to 64 to ensure standardised application. The participants have to classify the cards according to different criteria which vary during the course of the test.

Work Memory

Direct Digits from the Weschler Adult Intelligence Scale-III (WAIS-III[34]). The number of sequences varies progressively from 2 to 8 digits presented. Once the participant has listened to the list, they have to repeat it in the same order.

Indirect Digits (WAIS-III). The number of sequences varies progressively from 2 to 8 digits presented. Once the participant has listened to the list, they have to repeat it in the reverse order to that of presentation.

Letters and Numbers (WAIS-III). In this test the participant listens to lists of numbers and letters mixed in a random fashion. The order of presentation progressively includes a greater number of items and the patients are requested to repeat the numbers first in ascending order and afterwards the letters in alphabetical order.

Verbal Fluency

Phonological fluency (PF[35]). In this test we request that the patient say the maximum number of words that begin with the letter P in 3 min, with the exception of proper names or the same word with different suffixes.

Semantic Fluency (SF) In this test the patient is requested to name the maximum possible number of animals in 1min.

Processing Speed

Stroop Color[36] colour test. Only the Colour subtest was included. We present the patient with a block of different coloured crosses (red, green and blue), and they have to name the colour of the ink as fast as possible within 45 seconds.

WAIS-III number key. We present the patient with empty squares that have numbers in the upper part. We request the patients to fill in the squares one by one, as fast as possible, with the corresponding symbol, according to the number/symbol code that they must constantly remember.

Trail Making Test-Parte A.[37] The patients are presented with a page with numbers placed randomly from 1 to 25. They are requested to draw a line between the numbers in ascending order as fast as possible.

Data Analysis

Confirmation Factorial Analysis (CFA)

The CFA was used to examine relationships between observed variables and hypothesized underlying constructs. The six-factor model included processing speed (TMT-A, Number keys and Stroop-C), Attention (BTA-L, BTA-N), verbal memory (IM and LTM), Working memory (Direct and inverse digits and letters and numbers) Fluency (PF and SF) and executive functions (WCST, completed categories and persevering errors). This model was compared with a monofactorial model.

The monofactorial model grouped all the tests in a single general cognitive factor similar to factor g.

Analyses were performed using the LISREL 8.8038 maximum probability estimation program. Five statistical measurements of fit were used to assess the fit of the models proposed and data observed.χ^2,χ^2/degrees of freedom (df) (which has the advantage of being less dependent on sample size[39]), Comparative Fit Index (CFI), Root Mean Square Error of approximation (RMSEA) and Non-Normed Fit Index (NNFI).

Values of NNFI and CFI≥0.9[38,42] and values of RMSEA<0.08 reflect a good fit.[40,41] Finally, scores ofχ^2/df<3 are considered adequate.[43]

χ^2 test was used for differences of sex between groups and Student's t test for sociodemographic and clinical characteristics. Multiple analysis of covariance (MANCOVA) was used with group variable as inter-group factor and cognitive factors as group factor. Tuckey's post-hoc test was used for univariable comparisons. Pearson's correlation coefficient was used to determine correlation between variables. All tests were bilateral.

Results

Sociodemographic and Clinical Differences between Groups

Sample sociodemographic and clinical differences are described in Table 1. No differences were found between the 3 groups in age, sex or educational level.

Table 1 Sample Sociodemographic and Clinical Characteristics

	TRS (n=52)	NTRS (n=43)	Controls (n=46)	Differences between groups	*P*
Age (years)	37.28±11.06	35.91±11.2	33.86±11.87	F=1.09	0.34
Sex; n (%)					
Men	39 (75)	40 (93)	35 (76,1)	χ^2=5.93	0.06
Women	13 (25)	3 (7)	11 (23,9)		
Education (years)	9.29±3.31	9.95±3.18	10.48±1.62	F=0.77	0.47
Premorbid fit (vocabulary; WAIS-III)	38.13±12.39	38.44±12.12	48.8±6.89	F=13.65	<0,001
Age of onset (years)	21.35±4.73	22.3±7.06		t=-0.78	0.43
Duration of the disease (years)	15.4±9.73	10.44±9.15		t=5.54	0,01*
Duration of current stay (days)	818.44±1,926.72	485.64±1,186.2		t=0.98	0.34
Number of hospitalisations	10.96±8.73	9.3±6.15		t=1.04	0.3
PANSS-P	27.1±10.49	19.42±9.73		t=3.67	<0,01*
PANSS-N	28.65±9.85	27.12±10.73		t=0.78	0.47
PANSS-G	49.92±15.43	48.16±14.6		t=0.57	0.57
GCI	5.77±0.94	4.3±1.68		t=5.09	<0,01*
WHO-DAS	14.19±3.32	12.88±4.57		t=1.56	0.11

GCI: General clinical impression; WHO-DAS: World Health Organisation Disability Assessment Schedule; NTRS: Non-Treatment Resistant Schizophrenia; TRS: Treatment Resistant Schizophrenia; PANSS-G: General psychopathology subscale of the Positive and Negative Syndrome Scale; PANSS-N: Negative subscale of the Positive and Negative Syndrome Scale; PANSS-P: Positive subscale of the Positive and Negative Syndrome Scale.

Data expressed as n (%) or as mean±standard deviation.

Table 2 Results of the Confirmatory Factorial Analysis for the Six Factor Model for Each Sample with Standardised Factorial Weighing

Factor	Cognitive measurement	All the sample (n=141)	Controls (n=46)	SCHI (n=95)
Speed	TMT-A	−0.76	−0.76	−0.73
	Stroop-C	0.88	0.68	0.76
	Number key	0.92	0.65	0.89
Fluency	Phonological fluency	0.87	0.74	0.81
	Semantic fluency	0.9	0.92	0.81
Verbal memory	Immediate memory	0.96	0.98	0.98
	Long-term memory	0.99	0.99	0.93
Work memory	Direct digits	0.76	0.69	0.81
	Indirect digits	0.73	0.63	0.74
	Letters and numbers	0.9	0.72	0.86
Executive functions	WCST categories	0.95	0.97	0.92
	WCST conceptual answers	0.98	0.91	0.99
	WCST perseverant errors	−0.75	−0.84	−0.67
Attention	BTA-L	0.95	0.75	0.86
	BTA-N	0.83	0.78	0.82

BTA-L: Brief Test of Attention-Letters; BTA-N: Brief Test of Attention-Numbers; SCHI: Schizophrenia; Stroop-C: Colours subtest of Stroop Test; TMT-A: Trail Making Test Part A; WCST: Wisconsin Card Sorting Test-CV64.[33]

As to clinical characteristics, both groups of patients had similar age at onset, duration of current hospitalisation and number of previous hospitalisation (Table 1), although they differed in the duration of the disease from the moment of first diagnosis (P=0.01).

The differences in psychopathology indicated that the patients with TRS had more positive symptoms (in accordance with admission criteria) according to the PANSS scale score (P<0.01). However, no differences were found in negative symptoms or general psychopathology with PANSS. Patients with TRS showed a greater general severity of disease than those in the NTRS group, according to GCI scale (P<0.01). In spite of these results, scores on the WHO-DAS scale indicated that both groups had similar functional disability.

The results obtained with the WIAS-III vocabulary subtest showed significant differences between groups. Tuckey's post-hoc analysis showed that the CG did significantly better than the two groups of patients, whereas there were no significant differences between the two groups of patients. The absence of differences in premorbid functioning between both groups confirms that there were no significant differences in years of formal education received (Table 1).

Confirmatory Factorial Analysis

The goodness-of-fit statistics indicated that the monofactorial model (model g) does not fit the observed data for the complete sample (χ^2/df=6.7; RMSEA=0.2; NNFI=0.81; CFI=0.84). The results were also poor for the schizophrenia group (χ^2/df=5,2; RMSEA=0.21; NNFI=0.63; CFI=0.68) and for the control group (χ^2/df=5.9; RMSEA=0.3; NNFI=0.19; CFI=0.3). As a result, the single factor model is far from being an appropriate latent structure with a good fit for the data obtained.

The results indicate that the hypothesized six factor model has a very good fit for the complete sample (χ^2/df=1.5; RMSEA=0.06; NNFI=0.98; CFI=0.99), as also for the schizophrenia group χ^2/df=1.5; RMSEA=0.07; NNFI=0.95; CFI=0.96) and the control group (χ^2/df=1.3; RMSEA=0.07; NNFI=0.91; CFI=0.9).

Standardised factorial weights are shown in Table 2. All weights were significant, which indicates that the variables were weighted for the factor which they measured. In general, most of the tests showed high factorial weights for their respective factors, from −0.63 to 0.99. The mean factorial weight for the complete sample was 0.87; for the schizophrenia group NC, 0.84 and for the CG, 0.8.

Neuropsychological Differences between the Groups

Table 3 shows cognitive performance and differences between the groups. The Vocabulary Test was used as a co-variable. Tuckey's post-hoc analysis showed that the CG had higher scores than the patients with schizophrenia for all cognitive factors. The main finding was the lack of significant differences between the TRS and NTRS groups in cognitive factors. Only with reference to attention were there significant differences between the 2 subgroups ($p<0.05$), since the NTRS group had a better performance.

The correlation analysis of cognitive factors and clinical variables can be seen in Tables 4 and 5. Correlations for the total sample (Table 4) indicate that cognitive factors are related to negative symptoms, but not with positive or general psychopathology syndromes. Processing speed, fluency and work memory were significantly associated

Table 3 Comparison between Control (CG), Treatment Resistant Schizophrenia (TRS) and Non-Treatment Resistant Schizophrenia (NTRS) Groups in Cognitive Performance after Controlling the Vocabulary Effect

	TRS	NTRS	CG	dof	F	*P*	Effect size (η^2)
PS	−2.49±1.5	−2.16±1.41	0.01±0.89	2,128	28.46	<0.001; NC > TRS/TNRS	0.31
Attn.	−4.58±1.98	−3.57±2	0±0.81	2,128	62.21	<0.001; NC > TNRS > TRS	0.51
VM	−1.6±0.75	−1.44±0.84	0±0.99	2,128	24.79	<0.001; NC > TRS/TNRS	0.28
VF	−1.59±0.82	−1.46±0.86	0±0.91	2,128	27.82	<0.001; NC > TRS/TNRS	0.3
WM	−1.12±0.83	−1.05±1.01	0±0.8	2,128	8.55	<0.001; NC > TRS/TNRS	0.12
EF	−1.71±1.32	−1.43±1.42	0.05±0.91	2,128	13.5	<0.001; NC > TRS/TNRS	0.18

Attn.: Attention; EF: Executive Functions; VF: Verbal Fluency; dof: Degrees of freedom; WM: Work Memory; VM: Verbal Memory; PS: Processing Speed.

Table 4 Correlation between Clinical and Cognitive Variables in the Global Sample

	Attn.	VM	EF	WM	VF	PS
PANSS-P	−0.11	−0.01	0.12	0.03	0.02	0.12
PANSS-N	−0.25[a]	−0.27[b]	−0.32[b]	−0.37[c]	−0.5[c]	−0.42[c]
PANSS-G	−0.16	−0.05	0.03	−0.13	−0.15	0.1
CGI	−0.12	−0.25[a]	−0.09	−0.08	0.1	−0.1
WHO-DAS	−0.18	−0.2	−0.13	−0.24[b]	−0.24[b]	0.34[c]
Duration of disease	−0.15	−0.4[c]	−0.4[c]	−0.25[a]	−0.34[c]	−0.5[c]
Number of hospitalisations	−0.21[a]	−0.15	−0.14	−0.19	−0.24[a]	−0.31[b]

Attn.: Attention; GCI: General Clinical Impression; WHO-DAS: World Health Organisation Disability Assessment Schedule; EF: Executive Functions; VF: Verbal Fluency; WM: Work Memory; VM: Verbal Memory; PANSS-G: General psychopathology subscale of the Positive and Negative Syndrome Scale; PANSS-N: Negative subscale of the Positive and Negative Syndrome Scale; PANSS-P: Positive subscale of the Positive and Negative Syndrome Scale; PS: Processing Speed.
[a] $P<0.05$
[b] $P<0.01$
[c] $P<0.001$

with the functional disability variable, whereas disease duration was related with all factors except attention. The variable number of previous hospitalisations was significantly related to attention, verbal fluency and processing speed performance.

The pattern of correlations for each subgroup of patients can be seen in Table 5. A different pattern of associations was seen for each group. In the NTRS group negative symptoms were related to all cognitive factors except for executive functions and processing speed. In the TRS group, on the contrary, negative symptoms were associated with all factors except attention and verbal memory.

Discussion

Our data has not retorted the previous findings of Joober et al[24] in the characterisation of cognitive profiles in patients with TRS and NTRS, finding a greater deficit in learning and verbal memory in patients with TRS. Therefore, we cannot conclude that there is a differential response to drug treatment with regard to cognitive deficits.

The factor structure of our model is similar to the one proposed by the MATRICS[44] initiative but there are two relevant differences between both proposals. Our group obtained a factor solution in six cognitive domains – attention, processing speed, verbal memory, working memory, fluency and executive functions – whereas the MATRICS proposal also included visual memory. The additional factor in our study is verbal fluency.

In contrast to our results, Joober et al found significant differences between TRS and NTRS patients in relation to neuropsychological functions. There are a series of factors that could explain said discrepancies in the results, for instance, our study has a larger sample. We found no differences in verbal memory or in work memory. These were not assessed in the study performed by Joober et al.

An alternative explanation is related to the evident difference between the groups of patients with TRS in both studies. Joober et al included a sample of patients described as autonomous (capable of functioning independently in society) and with an optimum disease evolution. In spite of the high average time in years of disease evolution in our study (15 years), they included only patients without psychotic relapses during psychiatric treatment. But cases with these times of evolution and therapeutic response are not usual in clinical practice. A more detailed analysis revealed that Joober et al compared two groups with very

Table 5 Correlations between Clinical and Cognitive Variables in TRS and NTRS

	Attn.	VM	EF	WM	VF	PS
ERT						
PANSS-P	0.09	0.05	0.22	0.18	0.16	0.17
PANSS-N	-0.17	-0.26	-0.39[a]	-0.32[b]	-0.52[c]	-0.6[c]
PANSS-G	-0.03	-0.02	0.03	-0.06	-0.13	0.08
CGI	-0.03	-0.37[b]	-0.04	0.04	-0.05	-0.13
WHO-DAS	-0.01	-0.22	-0.09	-0.13	-0.12	-0.35[b]
Duration of the disease	-0.07	-0.5c	-0.33[b]	-0.25	-0.33[b]	-0.41[a]
Number of hospitalisations	-0.22	-0.01	-0.14	-0.24	-0.12	-0.12
ENRT						
PANSS-P	-0.1	0.02	0.13	-0.09	-0.05	0.18
PANSS-N	-0.33[b]	-0.27[b]	-0.24	-0.43[c]	-0.47[c]	-0.23
PANSS-G	-0.26	-0.07	0.04	-0.32[b]	-0.15	0.14
CGI	-0.06	-0.02	-0.07	-0.27	-0.15	0.06
WHO-DAS	-0.32[b]	-0.13	-0.15	-0.39[a]	-0.38[a]	-0.32[b]
Duration of the disease	-0.28	-0.29[b]	-0.47[c]	-0.25	-0.36[a]	-0.59[c]
Number of hospitalisations	-0.19	-0.23	-0.13	0.15	-0.3[b]	-0.46[c]

Attn.: Attention; GCI: General Clinical Impression; WHO-DAS: World Health Organisation Disability Assessment Schedule; NTRS: Non-Treatment Resistant Schizophrenia; TRS: Treatment Resistant Schizophrenia; EF: Executive Functions; VF: Verbal Fluency; WM: Work Memory; VM: Verbal Memory; PANSS-G: General psychopathology subscale of the Positive and Negative Syndrome Scale; PANSS-N: Negative subscale of the Positive and Negative Syndrome Scale; PANSS-P: Positive subscale of the Positive and Negative Syndrome Scale; PS: Processing Speed.

[a] $P<0.01$

[b] $P<0.05$

[c] $P<0.001$

different functional capacities, whereas in our study both groups had very similar functional capacities. If, in spite of this, the neuropsychological differences had remained similar, we could have stated that neuropsychological functions vary during disease according to the response to drug treatment. But the results do not support this conclusion. In accordance with recent data,[45,46] similar deficits in cognitive function are associated with a similar functional result in both groups, with additional evidence of the relationship between cognition and functional autonomy in patients. Both groups showed the same level of deterioration of adaptive capabilities. Considering that the conclusions of Green et al[23] on the relationship between cognitive deterioration and functional results, the absence of differences could be attributable, at least partially, to a similar degree of cognitive deterioration in both groups. Furthermore, the greater presence of productive symptoms in the group of TRS patients did not correlate with an increase in functional deterioration.

In our study the sample of patients with NTRS were patients hospitalised due to a lack of alternatives or the severity of their psychopathology. These patients had worse evolution and functional consequences in spite of responding to treatment. Given the close relationship between cognitive alterations and functional results of schizophrenia,[23,45,46] it is not surprising that better cognitive function is found in a the group with a better functional situation, such as that observed by Joober et al[24] in the group of patients with NTRS.

In summary, we are comparing two different groups of patients with schizophrenia. Whereas Joober et al compared patients with a high degree of psychosocial functioning (patients responding to treatment) with other patients that showed poor psychosocial function, this study compared two groups with poor psychosocial functioning.

Chronic schizophrenia is a concept with fairly determined semantic limits. Although McKenna[47] defined schizophrenia with at least 2 years evolution, sometimes researchers do not want to strictly follow this definition. As a consequence of this lack of precision, the term chronic schizophrenia has been used for both “deficiency states”, “deficit syndrome”, “residual schizophrenia” or “residual schizophrenia”. If we keep strictly to temporal terms, most of our patients that respond to treatment comply with the criteria for chronic schizophrenia.

As has been indicated before, our two samples were homogeneous in age, cognitive deterioration, negative symptoms and functional results. As a result, our study compared patients with TRS and chronic patients with schizophrenia (who were responders to treatment). The results obtained do not allow us to establish different clinical categories according to neuropsychological functioning. However, our study did clearly show some clinical and demographic differences between groups. The group of patients with TRS had more years of disease evolution, a greater proportion of women, greater severity of positive symptoms and greater general severity measured using the GCI. The samples are more homogeneous in

relation to the most relevant aspects of the disease, such as negative symptoms and general PANSS symptoms. Other authors have used alternative explanations for the different profiles found in patients with TRS such as age of onset, number of hospitalisations and differences between hospitalised and non-hospitalised patients,[6,7] but our data overcome some methodological problems seen in previous studies. Furthermore, these results are consistent with the contributions made to this line of research by fields such as neuroimaging.[48] The empirical evidence of these studies does not support the hypothesis of a limited subgroup of patients with TRS. The concept of TRS as a different subgroup of schizophrenia with positive symptoms that do not respond to several antipsychotic treatments would therefore lose all clinical sense. Nonetheless, some authors continue to use the criteria of Kane et al[4] to differentiate not only between patients with refractory and non-refractory schizophrenia, but also to identify groups of patients that are super-refractory to treatment.[13] However, experimental results published by the group do not indicate the existence of a specific profile, but a greater number of positive symptoms in this super-resistant to drugs group.

Since patients' functional capacity can be explained mainly based on negative and cognitive symptoms, therapeutic efforts must be directed to improving these symptoms. In consequence, our group proposes that future definitions of the lack of response to treatment should include these symptoms, as well as positive ones. Therefore, the criteria of Brenner et al[49] have greater clinical value when used to classify patients based on their response to treatment. These seven criteria include an item that assesses cognitive deterioration in multiple areas that interfere with work and social functions. In spite of this attempt, criteria are vaguely formulated and limit quantitative measurement of the severity and functional impact of deterioration. On the other hand, daily clinical reality does not support the categorical distinction between patients that respond to treatment and patients that do not respond. Most patients are in an intermediate situation. We must keep in mind the possibility, still not proven, that each patient's capacity of response to antipsychotic treatment undergoes dynamic evolution. Furthermore, evolution can be modified by natural changes in patients' psychopathology during disease progression. This fact is more noteworthy in patients with more years of disease evolution. Following this line of thinking, Owens et al[50] examined 510 patients hospitalised for more than 1 year (mean: 13 years). Only 30% of this group did not have positive symptoms. The remaining patients (20%) had a maximum level of positive symptoms. Seven percent of the patients in the sample did not have either positive or negative symptoms, although they required longer hospitalisation. In accordance with this data, most patients had a marked functional deficit in spite of the efficacy of treatment, based on classical schizophrenia symptoms.

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Conflict of Interest

The authors affirm that they have no conflict of interest.

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