Neurocognitive Subtypes of Schizophrenia

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Objective. To empirically identify schizophrenia neurocognitive subtypes and establish their association with clinical characteristics.

Methods. Sustained attention, executive function, facial emotion recognition, verbal learning, and working memory tests were applied to 253 subjects with schizophrenia. We identified neurocognitive subtypes by a latent class analysis of the tests results. After, we made a search for the association of these subtypes with clinic characteristics.

Results. We identified four neurocognitive subtypes: 1) "Global cognitive deficit", 2) "Memory and executive function deficit", 3) "Memory and facial emotion recognition deficit," and 4) "Without cognitive deficit." In comparison with the subtype "without cognitive deficit," we found that the "memory and executive function deficit subtype" and the "global cognitive deficit subtype" had a higher frequency of male, unemployed, severe impairment, and adherence to treatment participants. However, in the "global cognitive deficit subtype" the differences were higher and there was also a lower frequency of past major depressive episodes (OR 0.39; 95%CI: 0.16 to 0.97). The "memory and facial recognition deficit subtype" had a higher probability of severe impairment (OR 5.52; 95%CI: 1.89 to 16.14) and unemployed (OR 2.43; 95%CI: 1.06 to 5.55) participants, but also a lower probability of past depressive episodes (OR 0.21; 95%CI: 0.07 to 0.66).

Conclusion. Our results suggest the existence of four neurocognitive subtypes in schizophrenia with a spectrum of dysfunction and severity. We found higher dysfunction in those with worse cognitive dysfunction, and higher affective psychopathology and less treatment adherence in those with less cognitive dysfunction.

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Subtipos neurocognitivos de esquizofrenia

Objetivo. Identificar empíricamente subtipos neurocognitivos de esquizofrenia y establecer la asociación de estos con características clínicas.

Métodos. Se aplicaron pruebas de atención sostenida, función ejecutiva, reconocimiento facial de emociones, memoria verbal y de trabajo a 253 sujetos con esquizofrenia. A partir de los resultados de estas pruebas se identificaron los subtipos mediante análisis de clases latentes. Posteriormente, se evaluó la asociación de cada subtipo con características clínicas.

Resultados. Se identificaron cuatro subtipos: 1) déficit cognitivo global, 2) déficit de memoria y función ejecutiva, 3) déficit de memoria y reconocimiento de emociones y 4) sin déficit cognitivo. Al comparar con el subtipo sin déficit cognitivo, se observó que tanto el de déficit de memoria y función ejecutiva como el de déficit cognitivo global tenían mayor frecuencia individuos de sexo masculino, desempleados, con deterioro grave y adherentes al tratamiento. Sin embargo, en el subtipo con déficit cognitivo global la diferencia fue más alta y presentaron una frecuencia más baja de antecedentes de episodios depresivos (OR 0,39; IC95%: 0,16 a 0,97). El subtipo de déficit de memoria y reconocimiento emocional tenía más sujetos con deterioro grave (OR 5,52; IC95%: 1,89 a 16,14) y desempleo (OR 2,43; IC95%: 1,06 a 5,55), pero menos con antecedentes de episodios depresivos (OR 0,21; IC95%: 0,07 a 0,66).

Conclusión. Los resultados muestran cuatro subtipos neurocognitivos de esquizofrenia con un posible espectro de severidad, asociándose en un extremo con mayor disfunción, y en el otro con mayor psicopatología afectiva y menor adherencia al tratamiento.

Palabras claves: Esquizofrenia, Subtipos, Neurocognitivo, Neuropsicología, Espectro

INTRODUCTION

The neurocognitive alterations have been known since their conceptualization by Kraepelin and Bleuler as primary characteristics of schizophrenia.[1,2] However, they are not a fundamental criterion in the contemporary diagnostic manuals.[3,4] Given that the cognitive alterations are present during the entire course of the disorder and there is variation in the neurocognitive performance among the patients, it has been proposed to develop subtypes based on neuropsychological variables in order to improve the treatment approach and prediction of the prognosis.[5,6] The subtypes are groups of individuals defined based on certain characteristics, which in this case, would be neuropsychological ones. Such groups would be more homogeneous internally than all the population with the disorder. Consequently, these subtypes could have greater diagnostic validity than those based on clinical manifestations, this having been criticized due to the variation of the symptoms over time and their low middle to long-term predictive capacity.[7,8]

Proposals of subtypes based on neurocognitive disorders have already been made. Some begin with the *a priori* hypothesis and others with empirical approaches using statistics, as the cluster and latent class analyses.[9-12] However, the results vary depending on the neuropsychological tests and functions included. Thus, the way the variables which the subtyping will be made is fundamental.[13] As it is already known that schizophrenia has a genetic component, it is possible that it may be appropriate to make neurocognitive subtypes from candidates to endophenotypes, which are characteristics present in the persons with genetic variants of risk that could be measurable before the clinical manifestations of the disorder appear.[14] The endophenotypes would theoretically be closer to the genetic variants of susceptibility of schizophrenia than the clinical phenotypes and their use could improve the predictive power of the groups that arise and provide greater understanding of the etiopathogenic or physiopathological processes involved.[15] Among the cognitive functions that have been shown to comply with the criteria for being endophenotypes of schizophrenia are verbal working memory, semantic memory, executive function, sustained attention and recognition of emotions.[16,17] Therefore, the purpose of this study is to identify neurocognitive subtypes based on neuropsychological candidates to endophenotypes and to determine the association of these with demographic and clinical characteristics in subjects with schizophrenia.

For the identifications of the subtypes, analysis of latent classes was used on the contrary to previous studies that have mostly used cluster analysis[9,11] because this analysis has the following advantages: it makes the classification based on probabilities; it has adjustment statistics for the determination of the number of subtypes and permits the use of variables having a different nature.[18] This statistical technique has been used previously in studies on cognitive subtypes of other neuropsychiatric disorders.[19,20]

METHODS

This is a cross-sectional study forming a part of an investigation on neuropsychological endophenotypes in schizophrenia performed by the Universities of Antioquia, Pontificia Bolivariana and Nacional of Colombia. Convenience sampling was performed with subjects having schizophrenia between 2009 in 2012 from the outpatient departments of the University hospitals San Vicente Fundación, Mental of Antioquia and SAMEIN of Medellín (Colombia); and the Hospitals Santa Clara and Victoria of Bogotá (Colombia). A sample of subjects was collected from the community who were not affected by psychotic or affective disorders. This was used to establish the performance measurements in the neuropsychological tests in the population without mental disorders. The ethics committee of all the participating institutions approved the research protocol.

Inclusion criteria of the group of patients with schizophrenia were: age between 18 and 65 years, diagnosis of schizophrenia according to the fourth revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[21] and who had not been hospitalized in the last month. Exclusion criteria were those patients with characteristics that could hinder the performance of the tests or alter their results, as: analphabetism, visual or hearing limitations, use of benzodiazepines in the last months, disorders due to psychoactive substance abuse in the previous six months (except nicotine), electroconvulsive therapy, significant encephalocranial trauma (loss of consciousness for more than 15 minutes or neurological sequels) or neurological diseases such as epilepsy, mental retardation, dementia or other neurodegenerative disorders.

Procedures

Before initiating the collection of the information, training workshops and standardization of instruments were performed for the neuropsychologists and psychiatrists who evaluated the subjects.

All the participants were evaluated by a psychiatrist, after signing the informed consent. The psychiatrist used the Diagnostic Interview for Genetic Studies (DIGS)[22] and applied the Scale for the Assessment of Negative Symptoms (SANS),[23] Positive Symptoms (SAPS)[24] and Global Assessment of Functioning Scale (GAFs).[25] After, the subject was evaluated by a neuropsychologist who applied a protocol of verbal working memory, semantic memory, sustained attention, executive function and recognition of emotions from facial expression. The final diagnosis of schizophrenia was

established using a strategy of better estimation with the participation of two expert psychiatrists who independently evaluated the patient's material (DIGS and clinical history). If there was no agreement between them, a third expert psychiatrist was called. If consensus was still not reached, the patient was excluded from the study.

Information collecting instrument

- *DIGS:* Instrument designed for genetic studies on schizophrenia and affective disorders including sections on other mental disorders to establish comorbidities and differential diagnosis.[22] It was translated and validated in Colombia and showed high test-retest and inter-rater reliability.[26]
- *SAPS and SANS:* Complementary instruments for the evaluation of schizophrenia used for the study of their clinical phenomenology and severity.[23,24] The SAPS contains 30 items and is organized into the subscales of hallucinations, delusions, bizarre behaviors, formal thought disorders and inappropriate affect disorders. The SANS contains 20 items organized in the subscales of affective flattening, alogia, abulia, anhedonia, associality and attentional impairment. Both scales were validated in Colombian population and showed convergent construct validity, test-retest and inter-rater reliability and sensitivity to change.[27]
- GAFS: It evaluates global assessment of the individual during a specific period on a continuum from the disease to psychological or psychiatric health. Values on the scale go from 1, representing the hypothetically sicker subject to 100, representing the most healthy one.[25]
- *DS-CPT: Degraded Stimulus - Continuous Performance Test:* This test was developed to measure sustained attention or vigilance.[28] The participant should monitor a series of digits going from zero to nine presented every 40 ms. The objective of the subject is to press a button on the computer mouse when a zero is identified. The digits are blurry, which increases the test difficulty and thus it has been considered more appropriate for researching the endophenotypes of schizophrenia. The hit rate and false alarm rate is recorded and used to calculate sensitivity (d') as the principal measurement.
- LNST: *Letters and numbers sequencing test:* Obtained from the Weschler Adult Intelligence Test (WAIS-III).[29] This is a working memory test in which groups of numbers mixed with letters are presented to the individuals. The task is to mentally order the numbers in ascendant order and the letters alphabetically. Seven trials are performed, each one having three sequences. The numbers and letters increase when the subject passes on the next trial. If the subject makes a mistake in the three sequences forming a part of the trial, the test is interrupted.
- *Wisconsin Card Sorting test, modified version of the neurosciences group of the University of Antioquia:*[30] This evaluates the executive function of strategic planning, use of environmental feedback, orientation of behavior towards achieving goals and modulation of impulsive responses. It has 48 cards, as the Nelson version, but does not permit the subject to choose a category to begin the test but rather begins with color.[30,31]
- *Verbal Learning Test- Spain-Complutence (TAVEC):* This was developed considering the principals of the Verbal Learning Test of California (CVLT).[32] Five trials of 16 words comprising four semantic groups are presented. Recall is evaluated immediately after each trial, then after a second list of 16 words and a 20-minut wait.
- *MTEET: Multiple transformation of Emotional Expression Task:* This is a dynamic emotional expressions recognition test designed in the Neurosciences Center of Cuba consisting in a series of images demonstrating the progressive transformation of a neutral facial image (0% of expression) into a complete emotional expression (100% of the expression).[33] The Ekman models were used for the study. This test represented seven basic emotional expressions: neutral, happiness, surprise, sadness, anger, disgust and fear. The neutral emotional expression was only used for the beginning of each sequence. Sensitivity (average number of intermediate expressions before identifying an emotion) and accuracy (percentage of correct recognitions for each emotion) was measured.

Statistical analysis

To describe the trial's participating subjects, central tendency and dispersions for quantitative variables and frequencies and percentages for the qualitative measurements were used.

To identify the neurocognitive subtypes of schizophrenia, an analysis of latent classes was performed with the statistical program Latent Gold 4,5 using the neuropsychological variables of the tests that had been used in previous studies on endophenotypes in schizophrenia,[34] and that did not have high statistical correlation with other variables taken from the same test. Similarly, sensitivity (d') of DS-CPT, total score in the LNST, total correct in the five short term memory trials of the TAVEC, number of categories and perseverations of the card sorting test and accuracy and sensitivity of the MTEET were obtained. Due to the requirements of the latent class analysis, it was necessary to perform dichotomic measures of the scores in the neuropsychological tests. To do so, cutoffs were established, considering age and schooling, according to the quartile corresponding to the lowest performance on the score obtained by the non-affected subject group. After, ten models were calculated. For each one of them, the goodness of fit was calculated using the index of the "Akaike information criterion" (AIC) and the Bayesian Information Criterion

(BIC). The model having the lowest AIC and BIC was selected and a Bootstrap re-sampling method was performed to obtain an adjusted p value, which was considered adequate if it was greater than 0.05. Compliance with the supposition of local independence and relationship of sample size and number of parameters estimated was verified, which should be greater than 5.

The possible association between the neurocognitive subtypes and demographic and clinical variations was studied. The clinical variables were: previous depressive episodes, suicide attempts, background of substance dependence, age of onset of the schizophrenia, duration of the disorder (in years), severe deterioration (incapacity to maintain employment and social dysfunction), hallucinations and delusions (score on subscales corresponding to the SAPS), disorganization (score on subscales of the SAPS), disorganization (score on the subscales of the SAPS: "bizarre behaviors," "formal thought disorders" and "inappropriate affect"), negative symptoms (total score on the SANS), global functioning during the last months (score on the GAFs) and "pharmacological treatment adherence (use in the last month of the antipsychotic medications with the dose as prescribed). The neurocognitive subtypes in their categoric characteristics were compared using the Odds Ratio (OR) calculation and regarding quantitative characteristics using the Kruskal-Wallis test. The significant level was 0.5 and all the analyses were made with the SPSS 20.0 statistical program.

RESULTS

A total of 333 subjects with possible schizophrenia were recruited, 38 of whom were ruled out because they did not fulfill the eligibility criteria and 42 more because they had not performed one or more of the neuropsychology tests. Thus, 253 patients were included. Their demographic and clinical characteristics are shown in table 1. Among the causes for incomplete neuropsychological evaluation, incapacity to understand or finish the test or refusal of the patient to perform any tests were recorded. When the subjects who did not finish the tests were compared with those enrolled in the study, we found that the former had higher medians in age (44.03 *vs* 36.17; Mann-Whitney U Test=3398.00, p=0.014), duration of the disorder (20.91 *vs* 13.76; Mann-Whitney U test =3291.50, p=0.07), disorganization (12.00 *vs* 4.00; Mann-Whitney U Test=2512.00, p<0.001) and negative symptoms (59.50 *vs* 39.00; Mann-Whitney U=2813.00, p<0.001), They also had lower medians for: schooling (6.50 *vs* 11.00; Mann-Whitney U=2538.00, p<0.001) and global functioning during the last month (35.00 *vs* 40.00; Mann-Whitney U=3030.50, p=0.002). No differences were found in age at onset of the disease (22.00 *vs* 20.00; Mann-Whitney U test=3985.50, p=0.413) or in hallucinations and delusions (12.00 *vs* 7.00; Mann-Whitney U=3591.50, p=0.159).

The non-affected group was initially made up of 433 subjects, 37 of whom were excluded as they did not fulfill the inclusion criteria. In this group, 139 (35.1%) individual were male, and mean age and schooling was 24.9 years (Interquartile range: 21.5-34.4) and 14 years (Interquartile range: 12-16), respectively. From these, the quartiles representing the worse performance in each one of the scores of the tests were established (Table 2). Based on these quartiles, it was established that subjects with schizophrenia had deficient performance and it was observed that 90.7% had deficient performance in at least one of the tests performed.

Neurocognitive subtypes

In the latent classes analysis, the model having the best goodness of fit according to the BIC (2595.88) and AIC (2472.21) values was chosen, this being the one having four subtypes. When the neuropsychological characteristics of each one were evaluated, they were called as follows: "global cognitive deficit," "without cognitive deficit," "with memory and executive deficit" and with memory and emotional recognition deficit (Table 3).

Association between cognitive subtypes and demographic and clinical characteristics

When subjects without cognitive deficit were compared, those with "executive function and memory deficit" and "global cognitive deterioration" had the greatest possibility of being male. Subjects with "global cognitive deficit" were younger, and all the subtypes had greater frequency of being unemployed (Tables 4 and 5).

Regarding the clinical characteristics, the subjects with global cognitive deterioration had more negative symptoms and less global functioning in the last month than the other neurocognitive subtypes. No differences were found in age of onset, duration of disorder, hallucinations and delusions or disorganization (Tables 4 and 5).

When comparisons were made with the subtype without cognitive deterioration, it was found that: 1) the subtypes of global cognitive deterioration "with memory and emotional recognition deficit" had less possibility of previous depressive episodes; 2) the subtypes "with memory and executive function deficits" and "global cognitive deterioration" had greater frequency of adherence to treatment and being a male; 3)the three subtypes with some deficits showed greater likelihood of being classified as having "severe deterioration" and being unemployed. We did not find significant differences in the background of substance dependency (without nicotine) or suicide attempts (Tables 4 and 5).

Table 1 Demographic, clinical and neuropsychological characteristics of the subjects with schizophrenia

Characteristics	Median	Interquartile Range	Minimum	Maximum
Demographics				
Age (years)	38.99	27.95 - 48.81	18.00	65.00
Schooling (years)	10.00	7.00 - 11.00	1.00	20.00
Symptoms and scores on scales				
Duration of disorder (years)	14.39	7.66 - 24.65	1.08	47.36
Age at onset of the schizophrenia (years)	20.00	17.00 - 26.00	4.00	49.00
Hallucinations and delusions (SAPS)	7.00	1.75 - 23.00	0.00	73.00
Disorganization (SAPS)	4.00	0.00 - 10.50	0.00	44.00
Negative symptoms (SANS)	40.00	23.00 - 56.75	0.00	86.00
GAFS in the last month	40.00	31.00 - 55.00	11.00	80.00
Neuropsychological tests				
DS-CPT – d'	1.59	0.91 - 2.21	0.02	4.90
Letters and numbers sequencing test	6.00	4.00 - 8.00	1.00	13.00
TAVEC* – Total correct	31.00	24.00 - 39.00	8.00	62.00
TAVEC* – Semantic strategies	1.00	1.00 - 2.00	0.00	9.00
Executive function* – Categories	2.00	1.00 - 3.00	0.00	6.00
Executive Function * – Perseverations	20.00	16.00 - 25.00	2.00	47.00
MTEET – % of correct (accuracy)	56.60	44.59 - 67.31	20.00	90.57
MTEET – Mean trials (sensitivity)	15.45	14.03 - 16.44	10.03	18.96

Characteristics	Frequency	Percentage
Demographics		
Male gender	208	70.5
Unemployed	181	61.4
Symptoms		
Course		
· Episodic course	151	51.2
· Continuous course	131	44.4
· Without data	13	4.4
Deterioration		
· Severe deterioration	110	37.3
· Mild and moderate deterioration	172	58.3
· Without data	13	4.4
Adherence to drug treatment	196	66.4
Background of major depressive episode	45	15.3
Background of suicide attempt	67	22.7
Background of substance abuse (non-nicotine)	73	24.7
Deficient performance on neuropsychological tests		
Sustained attention	102	34.6
Letters and numbers sequencing test	191	64.7
Verbal memory - total correct	242	82.0
Verbal memory - Semantic strategies	120	40.7

Table 1 Continuation

Characteristics	Frequency	Percentage
Executive Function – Categories	178	60.3
Executive Function * – Perseverations	132	44.7
Recognition of Emotions – Total correct	176	59.7
Recognition of Emotions - Mean trials	173	58.6

SAPS: Scale assessment of positive symptoms, SANS: Scale assessment of negative symptoms, PAS: Premorbid adjustment scale, GAFS: Global Assessment of functioning scale, DS-CPT: Degraded Stimulus - Continuous Performance Test. MTEET: Multiple transformation of Emotional Expression Task. TAVEC: Spanish version of the California Verbal Learning Test

*Measured with the Wisconsin Card Sorting test, modified version of the neurosciences group of the University of Antioquia

Table 2 Scores corresponding to the worse quartile of performance on the neuropsychological tests in the unaffected population

Groups	Neuropsychological Variable						
	d' (DS-CPT)	Total Correct (TAVEC)	Percentage Correct (MTEET)	Mean Trials (MTEET)	Total Score (LNST)	Number of categories (WSCTm)	Perserverative Errors (WSCTm)
18 to 40 years of age							
Schooling							
0 to 5 years	1.67	33	28	15.69	4	2	21
6 to 11 years	1.36	42	38	15.01	8	2	22
More than 11 years	1.82	49	37	14.62	9	3	15
41 to 50 years of age							
Schooling							
0 to 5 years	0.75	38	30	15.49	4	1	19
6 to 11 years	0.89	39	31	14.75	5	0	23
More than 11 years	1.38	43	42	13.92	7	2	16
51 to 65 years of age							
Schooling							
0 to 5 years	0.74	34	25	14.98	4	0	27
6 to 11 years	0.80	33	31	16.32	5	1	25
More than 11 years	1.39	43	37	15.46	6	1	21

DS-CPT: Degraded Stimulus - Continuous Performance Test. TAVEC: Spanish version of the California Verbal Learning Test. MTEET: Multiple transformation of Emotional Expression Task. LNST: Letters and numbers sequencing test. WSCTm: Wisconsin Card Sorting Test, modified version of the neurosciences group of the University of Antioquia

DISCUSSION

We identified four neurocognitive subtypes in schizophrenia that varied from global cognitive deficit to absence of cognitive deficits. This type of neurocognitive "spectrum," in which a proportion of patients from 15 to 30 percent is detected, which is considered as having normal cognitive functioning, has been previously reported.[6,35,36]

The subtypes were identified empirically according to the statistical criteria defined in the analysis of latent classes. Other studies with other empirical methods (as cluster analysis) or classifications *a priori* have determined different amounts of subtypes, varying from two to five.[9,11,36,37] In spite of these differences, the presence of alterations of working and verbal memory and executive function as variables has been described, this allowing for the typing of patients with

Table 3 Neurocognitive subtypes of schizophrenia

Neuropsychological Function	Neurocognitive subtypes			
	With memory and executive deficit	Global cognitive deficit	With memory and emotional recognition deficit	Without cognitive deficit
	n = 75	n = 74	n = 60	n = 44
	Probability*	Probability*	Probability*	Probability*
Sustained attention	0.373	0.600	0.284	0.170
Working memory	0.642	0.993	0.668	0.391
Verbal memory (Total Correct)	0.954	0.921	0.890	0.471
Verbal memory (Semantic Strategies)	0.330	0.608	0.449	0.210
Executive function	0.717	0.996	0.120	0.462
(Categories)	0.645	0.656	0.070	0.269
Executive Function (Perseverations)	0.293	0.952	0.868	0.052
Recognition of emotions from facial expressions (Total correct)	0.515	0.787	0.806	0.080

* Probability of being affected in the neuropsychological test given that one belongs to the category.

schizophrenia, and especially to differentiate those individuals with "intermediate" neurocognitive subtypes.[6] Although the use of recognition of emotions from facial expressions for subtyping is not common, our study made it possible to discriminate one of the profiles of intermediate functioning. Given that this variable is an important candidate for neuropsychological endophenotype,[33,38,39] its inclusion in the creation of new subtypes may help to improve their diagnostic validity, as other authors have suggested.[40]

We were able to determine that those subjects classified in subtypes with greater cognitive deterioration also had a higher amount of negative symptoms. However, we did not find differences between subtypes in the severity of disorganization, hallucinations and delusions. The association with negative symptoms agrees with the findings of other studies, but lack of differences in positive symptoms has had divergent results. Some have observed that the subjects with greater cognitive deficit have more disorganized symptoms and others have not found this association.[6,41,42] It is possible that the lack of association may be due to the clinical stability required for admission into the research that results in the fact that the subject of our sample having less positive symptoms compared with the patients in the usual practice in the participants another investigations.

In the present study, we have observed greater presence of affective psychopathology in the group without cognitive deficit. This has been reported previously and has been seen not only associated with greater cognitive preservation but also independently with higher intelligence quotient.[43] This disagrees with other findings in which those having greater cognitive capacity and introspection have worse perception of their disease, more demoralization and greater risk of depression and suicide.[44] Even so, other explanations may exist. For example, the presence of less adherence to treatment observed in the subtype in our study, which has shown to be associated with risk of depression and suicide.[45] According to this, the subjects with cognitive functioning close to normal could face other psychopathological difficulties and less adherence to antipsychotic treatment, this representing a different clinical challenge. However, the lower adherence to pharmacological treatment that we have found in subjects without cognitive deficit compared with the subtypes "with global cognitive deficit" and "memory and executive function deficit," is a finding that seems to contradict previous studies. It has been reported that the greater the cognitive deterioration, the lower the adherence to medical treatment, possibly related with poor introspection;[46] and that deficiencies in memory and conceptualization are associated with less skills in the

Table 4 Association of demographic and quantitative clinical characteristics with neurocognitive subtypes of schizophrenia

Characteristics	Neurocognitive subtypes					
	With memory and executive deficit	Global cognitive deficit	With memory and emotional recognition deficit	Without cognitive deficit	Chi^2 4 GI*	p value
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)		
Age (years)	37.98 (29.47 to 46.93)	31.66 (26.22 to 46.39)	41.73 (28.97 to 49.99)	39.56 (24.78 to 50.18)	7.410	0.060
Schooling (years)	9.00 (5.00 to 12.50)	10.00 (7.00 to 11.00)	11.00 (7.00 to 11.00)	11.00 (9.50 to 12.75)	5.323	0.150
Age of onset of Schizophrenia (years)	21.00 (17.50 to 27.50)	18.00 (16.00 to 24.00)	20.00 (17.00 to 29.00)	21.00 (17.25 to 29.00)	6.246	0.100
Duration of the Disease (years)	13.62 (7.61 to 24.65)	11.75 (6.70 to 22.76)	14.93 (8.39 to 26.01)	13.71 (7.23 to 23.41)	2.577	0.461
Hallucinations and Delusions (SAPS)	5.50 (2.00 to 18.50)	9.00 (0.00 to 22.00)	7.00 (2.00 to 25.00)	5.00 (0.00 to 20.50)	1.674	0.643
Disorganization (SAPS)	4.00 (0.00 to 8.00)	4.00 (0.00 to 11.00)	3.00 (0.00 to 13.00)	3.00 (1.00 to 7.00)	2.078	0.556
Negative Symptoms (SANS)	35.50 (18.25 to 49.50)	47.50 (32.00 to 61.00)	37.50 (22.00 to 55.75)	26.00 (13.25 to 37.00)	25.703	< **0.0001**
Global Functions during the last month (GAFS)	50.00 (35.00 to 60.00)	40.00 (31.00 to 55.00)	40.00 (31.00 to 55.00)	45.00 (40.00 to 57.50)	8.385	**0.039**

* Non-parametric comparisons by mean of the Kruskal-Wallis test. IQR: InterQuartile Range, EF: Executive Function, RFE: Recognition of Emotions from Facial Expressions, SAPS: Scale assessment of positive symptoms, SANS: Scale assessment of negative symptoms, GAFS: Global Assessing of Functioning Scale

management of the medication.[47] However, in a follow-up study of subjects with a first psychotic episode, those with greater cognitive performance had less likelihood of abandoning treatment during the course of one year.[48] One explanation for our findings is the definition of adherence as intake of medicines as prescribed, without evaluating if the patient did so actively and voluntarily. Thus, there may be an influence of the family members supervising that the patients with greater cognitive deterioration take the medication, but this influence does not occur in those who do not seem to have alterations.

The subtypes identified in our study may be associated with dysfunctions of certain neural zones or networks. As noted, verbal working memory is a neuropsychological function affected in several subtypes and is a candidate to endophenotype of schizophrenia.[49-51] Its involvement can be secondary to alterations in the prefrontal activity, especially in dorsolateral regions.[52] Semantic memory, which has a high frequency of alterations in two of the subtypes, is associated with a possible dysfunction of the cingulate, upper temporal gyrus and precuneus.[53] Recognition of emotions from facial expressions seems to be associated with dysfunction of the amygdala and fusiform gyrus.[54,55] Sustained attention has been associated with subtle alterations in the gray matter in the left thalamic nucleus, angular gyrus, supramarginal gyrus, inferior frontal and left post-central gyri.[56] In regards to executive function, a high correlation with other neurocognitive disorders has been reported,[49,57] so that it can be stated that failures in attention, recognition of emotions or memory can depend on its performance, and may even share brain areas with other functions such as the dorsolateral prefrontal cortex, ventrolateral cortex, anterior cingulate and thalamus.[58] In spite of this, in our investigation, one of the groups did not show alterations in this function, but did so in working memory and recognition of emotions, which could suggest some grade of independence between these functions. This suggests that our subtypes have a predominance of prefrontal, temporal, cingulate and thalamus involvement and that those in which there are alterations in recognition of emotions have dysfunction of the amygdala. However, new studies are needed to validate and

Table 5 Association of categoric demographic and clinical characteristics with neurocognitive subtypes of schizophrenia

Variable	Neurocognitive Subtypes*					
	With memory and executive deficit		Global cognitive deficit		With memory and emotional recognition deficit	
	OR	(CI 95%)	OR	(CI 95%)	OR	(CI 95%)
Male gender	**2.50**	**(1.09 to 5.74)**	**3.00**	**(1.33 to 6.76)**	1.77	(0.77 to 4.04)
Background of Depressive Episode	0.65	(0.27 to 1.57)	**0.39**	**(0.16 to 0.97)**	**0.21**	**(0.07 to 0.66)**
Substance Dependence (non-nicotine)	1.52	(0.60 to 3.88)	1.51	(0.61 to 3.76)	1.46	(0.56 to 3.81)
Adherence to drug treatment	**2.75**	**(1.19 to 6.38)**	**3.66**	**(1.58 to 8.47)**	1.26	(0.56 to 2.86)
Severity						
Severe Deterioration	**3.40**	**(1.17 to 9.85)**	**4.81**	**(1.71 to 13.58)**	**5.52**	**(1.89 to 16.14)**
Mild and Moderate Deterioration**						
Suicide Attempts	0.91	(0.61 to 1.35)	0.93	(0.64 to 1.34)	0.90	(0.59 to 1.37)
Unemployment	**3.00**	**(1.33 to 6.77)**	**5.23**	**(2.33 to 11.80)**	**2.43**	**(1.06 to 5.55)**

*Odds ratio, using those without cognitive deficit versus each neurocognitive subtype as comparator group

**Comparator category for the factors in the variable

correlation the neurocognitive subtypes with neurophysiological and neuroanatomical characteristics to corroborate these hypotheses.

The present study has several limitations: 1) When the analysis of latent classes was performed for the identification of the subtypes, the cognitive performance variables which were continuous became dichotomic, using the worst performance quartile of a group of non-affected subjects. This was done to facilitate the performance of the latent classes analysis and the interpretation of the subtypes, although we are aware that this entails loss of information. 2) There was significant heterogeneity in the duration of the schizophrenia. Furthermore, it was not possible to evaluate the cumulative effect of the psychopharmaceuticals and there was no adjustment for the dose and medication consumed. 3) Although we included those neuropsychological variables reported most frequently in the tests applied, it is still possible that the inclusion of other variables of these tests can generate cognitive subtypes other than those reported. 4) The intelligence quotient was not measured, this having been used in other investigations to make adjustments in the results and to exclude subjects with mild mental retardation in a more reliable way than the use of the symptoms.[59] 5) Differences between subtypes in several clinical and demographic characteristics were evaluated. This introduces the problem of the multiple tests leading to greater likelihood of spurious associations due to type I errors. For this reason, this analysis should be considered as exploratory and its results should be confirmed in future studies. 6) We should consider that given that this is a cross-sectional study, we could not establish if the associations between the subtypes and demographic or clinical characterizes are causal, nor the changes that could occurring during the course of the disorder. It is necessary to perform similar studies in other populations to determine if the findings are replicable and perform investigations with longitudinal designs to make it possible to establish causality and evaluate other variables of interest as relapses, response to treatment and stability of the neurocognitive subtypes. 7) We found a group of patients who had clinical stability during the last month, but in spite of this, could not perform the neuropsychological tests. In some of them, their cognitive condition did not permit evaluation because they did not understand the instructions or the results were not valid, and therefore, it would be possible that they made up a group of subjects with greater cognitive deficit compared with those being able to complete all the tests. However, it is possible that their clinical condition, represented in greater negative and disorganized symptoms, would hinder the performance of the test, in spite of the stability. Consequently, many of the subjects who were not evaluable could have a more serious course of the disorder, as suggested by the association with greater time of disease, worse global functionality and less schooling.

CONCLUSION

Subjects with schizophrenia had a cognitive deterioration spectrum divided into four subtypes according to grade and type of involvement, this agreeing with the findings of

previous studies. The subtypes with worse cognitive performance were associated with variables indicating worse functional deterioration and, on the contrary to that expected, those with better cognitive functioning level showed an association with greater frequency of suicide attempts and depressive episodes, and less drug treatment adherence. The subtyping based on neurocognitive characteristics can provide additional information that could improve the validity in the clinical and investigational approach to schizophrenia.

CONFLICT OF INTERESTS

None of the authors have conflict of interest regarding the subject presented in the article.

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