Schizophrenia in males of cognitive performance: discriminative and diagnostic values

Esquizofrenia em homens pelo desempenho cognitivo: valor discriminativo e diagnóstico

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Keywords
Schizophrenia, diagnosis. Cognition disorders. Psychological tests. Diagnostic value.

Abstract

Objective
To evaluate the discriminative and diagnostic values of neuropsychological tests for identifying schizophrenia patients.
Methods
A cross-sectional study with 36 male schizophrenia outpatients and 72 healthy matched volunteers was carried out. Participants underwent the following neuropsychological tests: Wisconsin Card Sorting test, Verbal Fluency, Stroop test, Mini Mental State Examination, and Spatial Recognition Span. Sensitivity and specificity estimated the diagnostic value of tests with cutoffs obtained using Receiver Operating Characteristic curves. The latent class model (diagnosis of schizophrenia) was used as gold standard.
Results
Although patients presented lower scores in most tests, the highest canonical function for the discriminant analysis was 0.57 (Verbal Fluency M). The best sensitivity and specificity were obtained in the Verbal Fluency M test (75 and 65, respectively).
Conclusions
The neuropsychological tests showed moderate diagnostic value for the identification of schizophrenia patients. These findings suggested that the cognitive impairment measured by these tests might not be homogeneous among schizophrenia patients.

Descritores
Esquizofrenia, diagnóstico. Transtornos cognitivos. Testes psicológicos. Valor diagnóstico.

Resumo

Objetivo
Avaliar os valores discriminativos e diagnósticos de testes neuropsicológicos na identificação de pacientes com esquizofrenia.
Métodos
Estudo transversal com 36 pacientes ambulatoriais esquizofrênicos masculinos e 72 voluntários saudáveis pareados. Os testes neuropsicológicos usados foram o Wisconsin Card Sorting Test*, Fluência Verbal, teste de Stroop, Mini Exame do Estado Mental e Span de reconhecimento espacial. Valores diagnósticos dos testes foram estimados por sensibilidade e especificidade, com os pontos de corte obtidos através da curva ROC* (Receiver Operating Characteristic)*. O modelo de classe latente (diagnóstico de esquizofrenia) foi aplicado como padrão ouro.*
Resultados
Embora os pacientes tenham apresentado escores inferiores na maioria dos testes,

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a função canônica mais alta pela análise discriminante foi 0,57 (na fluência verbal com a letra M). Os melhores valores de sensibilidade e especificidade foram obtidos pelo teste de fluência verbal com a letra M (75 e 65, respectivamente).

Conclusões

Os testes neuropsicológicos demonstraram valores diagnósticos moderados na identificação de pacientes com esquizofrenia. Os achados sugerem que o prejuízo cognitivo, medido por esses testes, pode não ser homogêneo entre os pacientes esquizofrênicos.

INTRODUCTION

Significant cognitive impairment across multiple ability domains has been considered a core characteristic of schizophrenia and is not caused by chronic illness, treatment, or institutionalization.[1,10-13,15] Whether cognitive deficits in schizophrenia are general (impairment across multiple ability domains) or specific (reduced intellectual functions, such as attention, memory and executive functions) is a question still under debate.[4,13]

From a clinical point of view, if the cognitive impairment were a prominent characteristic of schizophrenia, a reliable neuropsychological evaluation would be an important instrument for the assessment of schizophrenia patients, as in the case of Alzheimer's disease. The neuropsychological examination is today considered an important part of the diagnostic procedure.[2] Recently, a neuropsychological battery was suggested as a cognitive screening test for schizophrenia and a useful prognostic indicator.[8]

Most studies on cognitive performance in schizophrenia have shown poorer average performances of patients compared to healthy volunteers. The studies applied statistical comparisons based on group variability, distribution and central tendency parameters, however, no clinical value has been carried out. The clinical application of this type of result remains poorly developed. How can any specific result of such test be interpreted? Which value identifies schizophrenia patients (i.e., cutoffs)? If a disrupted cognitive process may be seen as part of the disease symptoms, the application of specific neuropsychological tests should detect these changes and demonstrate efficiency in diagnosing the condition (i.e., the poor cognitive performance of schizophrenia). Further information on the prevalence and diagnostic values of the schizophrenia disrupted cognitive process is necessary to elucidate the practical use and the theoretical directions of this concept.

The main goal of this study was to evaluate the performance in neuropsychological tests of schizophrenia patients and healthy matched volunteers for discriminative and diagnostic values. There were selected neuropsychological tests commonly used for the assessment of cognitive functions of the frontal lobes, and for more diffuse functions to determine their clinical applicability in assessing schizophrenia patients.

METHODS

A cross-sectional study was designed for evaluating the ability of neuropsychological tests to identify cognitive pattern in schizophrenia. The diagnosis of schizophrenia itself (latent class for gold standard)[7] was applied in the diagnostic analysis.

Sample definition and subject selection

The group of schizophrenia patients comprised of 36 male outpatients, recruited from the Schizophrenia Outpatient Clinic of a large university hospital in Southern Brazil. Healthy volunteers were 72 male hospital employees, matched for age and educational level. All patients and volunteers signed an informed consent after the nature of all procedures and ethical guarantees were fully explained. Sample size was supported by the rate of the general population's cognitive deficit (5%), an estimated relative risk of 5 for schizophrenia, and a ratio unexposed: exposed of 2:1. Size estimation for cross-sectional studies was processed using the Epi-Info 6.4 software, with alpha and beta errors of 5% and 20%, respectively.

The corroboration of patients' diagnosis and ruling out psychiatric disorders among volunteers were performed using the semi-structured interviews of

Table 1 - Daily range of antipsychotic drugs and number of schizophrenic patients in use of.

Drugs	Daily dosage	N
Haloperidol	5-10 mg	10
Clozapine	300-700 mg	5
Chlorpromazine	300-400 mg	5
Sulpiride	600-1.000 mg	7
Risperidone	6-9 mg	3
Thioridazine	100-400 mg	2
Levomepromazine	300-400 mg	4

DSM IV by a certificate psychiatrist. Presence of other psychiatric disorder, neurological or medical conditions, use of psychoactive drugs and substance abuse, which affect cognition, were excluded. Patients kept their regular use of anti-psychotics (Table 1).

Demographic data presented no significant differences between groups. Mean ± SD age of schizophrenia patients was 33.14±6.53 years, and educational attainment was 9.83±2.88 years. Mean ± SD age of healthy volunteers was 32.75±6.95 years, and educational attainment was 10.18±3.61 years. Mean duration ± SD (range) of schizophrenia in years was 11.83±1.07 (2-31) (Table 2).

Neuropsychological tests

Each participant underwent neuropsychological tests administered by research assistants who were not aware of the clinical diagnosis of subjects at the time of evaluation (schizophrenia/healthy). The cognitive tests were as follows: Mini Mental State Examination – MMSE;[6] Spatial Recognition Span;[6] Verbal Fluency;[5] Stroop test A and B – abbreviated version;[12] and Wisconsin Card Sorting Test – computerized version (WCST).

The last three tests were selected for the inclusion of functions frequently attributed to the frontal lobes and widely used in the study of cognition in schizophrenia. The Mini Mental is a brief and more comprehensive examination measuring several cognitive areas (temporal and spatial orientation, memory acquisition and recall, attention and calculation, and language). The Mini Mental cutoffs were worldwide studied to screen cognitive deficit in several conditions. The Spatial Recognition Span measures attention and visual memory, and consists in the subject indicating the position of the last white circle consecutively placed on a black board out of the view of the examinee. In the abbreviated Stroop test, the subject is first asked to read, as quickly as possible, ten rows with the name of five colors printed with black ink on a white card (Stroop A). Afterwards, a second card containing ten rows of five names of colors printed with unmatched colors are presented and the subject is asked to name, as quickly as possible, the ink color of in print (Stroop B). Time (in seconds) to finish the reading and the number of incorrect ink color naming are the scores of Stroop test (time and error scores, respectively). Verbal fluency consists of free recall, as many as possible, of words beginning with letter "S" and "M" during a 1-minute period, and the score is the number of non-repeated words.

The computerized version of the Wisconsin Card Sorting test is the same test as the manual one. Cards in different shapes, colors and quantity are displayed one at a time in the middle of screen. Individuals have to identify the rule related to each new card, associating to one of the four fixed cards below. The main measures of this test are correct responses, perseverative errors, perseverative responses, responses of conceptual level, non-perseverative errors, number of categories reached, trials to complete the first category, total errors, learning-to-learn score, and failure to maintain set.

Table 2 - Demographic data of sample (mean scores and standard deviation in years).

Variables	Schizophrenia patients	Healthy volunteers
Age	33.14±6.53	32.75±6.95
Educational attainment	9.83±2.88	10.18±3.61
Duration of illness	11.83±1.07	

Table 3 - Mean scores and standard deviation of cognitive tests (Student's 't' test).

Test	Schizophrenia	Healthy	p value
MMSE total	26.75±2.83	28.07±1.89	0.015
Stroop A error score	0.36±0.96	0.36±0.66	1.000
Stroop A time score (sec)	33.78±8.79	27.79±10.4	0.002
Stroop B error score	3.91±5.79	3.76±4.14	0.891
Stroop B time score (sec)	85.51±30.2	70.05±23.3	0.010
Spatial Recognition Span	7.11±2.58	9.35±3.70	0.000
Verbal Fluency (S)	9.80±4.03	12.39±4.16	0.003
Verbal Fluency (M)	10.80±4.20	13.86±4.95	0.001
WCST Total Correct	70.89±19.9	85.61±19.1	0.000
WCST NP Error	24.86±12.7	19.76±9.98	0.040
WCST Perseverative Error	32.25±17.6	22.63±12.3	0.005
WCST Perseverative Response	37.75±24.20	25.44±15.50	0.008
WCST % Conceptual	39.89±21.30	57.10±20.83	0.000
WCST failure set	1.78±3.96	1.49±1.65	0.674
WCST 1rst category	33.65±27.60	15.76±11.30	0.001
WCST Total Error	57.11±19.90	42.39±19.10	0.000
WCST categories	3.22±2.70	4.90±3.09	0.005
WCST learning score	-3.20±6.12	-4.01±8.49	0.646
WCST % Perseverative	25.20±13.80	17.68±9.58	0.005

MMSE = Mini mental state examination
WCST = Wisconsin card sorting test

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Statistical analysis

All variables were submitted to a pegboard test (normal probability plot) before analyzing them using discriminant and Student's t Test for independent samples. Discriminative power and diagnostic values of cognitive tests were carried out using discriminant analysis and cutoff estimation from receiver operating characteristic (ROC) curves for sensitivity and specificity values. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS PC+) in a personal computer IBM-compatible.

RESULTS

The neuropsychological tests' scores of schizophrenia patients and healthy participants are displayed in Table 3. Patients presented significant lower scores of the Mini Mental Status, spatial recognition span, verbal fluency with letter S and M, the WCST correct answers, WCST responses of conceptual level, WCST categories. Duration, in seconds, to complete the Stroop test part A and B was longer among schizophrenia patients than healthy volunteers. Total error, perseverative error, perseverative response, first category, and percentage of perseverative answer of the WCST were higher among schizophrenia patients. Both groups showed similar performance only for the scores of the Stroop test A and B, and in the WCST failure to maintain set and learning score.

Correct classification for all neuropsychological tests was double checked using discriminant analysis. The canonical functions of the discriminant analysis for verbal fluency (M and S), Stroop test part B (duration), MMSE, Spatial Recognition Span, and the WCST response of conceptual level were higher (Table 4). The percent of grouped cases correctly classified was 83.5% for all tests in the analysis.

The diagnostic value of tests (for the cognitive pattern of schizophrenia) was measured by sensitivity and specificity, and cutoffs were obtained from the ROC curve procedure. Selected tests for this analysis were those presenting higher discriminant values. None of the tests showed adequate values for the identification of cognitive dysfunction for schizophrenia. The best result was that from the Verbal Fluency with letter M (Figure) that showed sensitivity and specificity values of 75 and 65 for the cutoff 11 (Table 5). False negatives were 25% and false positives 35%.

DISCUSSION

The study aimed the assessment of the clinical applicability (diagnostic value) of neuropsycho-

Table 4 - Discriminant values of all tests (% Correct Classification=83.54).

Canonical function	R
Verbal fluency M	0.574
Verbal fluency S	0.551
Stroop B duration	-0.468
MMSE	0.417
Spatial recognition span	0.302
WCST conceptual responses	0.301
WCST perseverative error	-0.292
WCST % perseverative	-0.292
Stroop A duration	-0.290
WCST perseverative response	-0.284
WCST failure set	-0.276
WCST error	-0.247
WCST correct	0.248
WCST trials for first category	-0.225
Stroop A error score	0.195
WCST category	0.158
WCST non-perseverative errors	-0.133
Stroop B error score	-0.086
WCST learning score	-0.061

Table 5 - Cutoff values for verbal fluency M and S, Stroop test B, WCST correct responses, perseverative errors, trials for first categories, responses of conceptual level, and MMSE.

Verbal fluency M											
Cutoffs (test score)	5	6	7	8	9	10	11	12	13	14	15
Sensitivity	11	22	39	44	53	58	75	75	75	78	86
Specificity	92	86	83	81	76	69	65	51	40	36	29
Verbal fluency S											
Cutoffs (test score)	2	3	4	5	6	7	8	9	10	11	14
Sensitivity	8	11	11	17	28	44	47	64	69	72	89
Specificity	100	99	93	90	90	86	79	65	51	46	21
Stroop B (duration)											
Cutoff (seconds)	88	85	80	78	75	72	70	68	64	60	58
Sensitivity	40	43	51	60	60	63	63	74	74	74	91
Specificity	83	83	79	75	75	64	64	56	49	46	36
MMSE total score											
Cutoff (test score)	19	20	21	22	23	24	25	26	27	28	29
Sensitivity	5	5	5	8	8	11	31	39	50	72	86
Specificity	100	100	100	100	97	94	89	78	67	56	26
Spatial recognition Span											
Cutoff (test score)	3	4	5	6	7	8	9	10	11	12	
Sensitivity	3	25	36	36	44	69	94	94	94	94	
Specificity	100	83	83	81	74	53	35	35	32	24	
WCST responses of conceptual level											
Cutoff (test score)	28	32	34	38	40	44	50	54	58	60	62
Sensitivity	36	44	47	50	53	56	61	69	78	81	89
Specificity	89	89	89	86	78	74	63	56	50	49	46

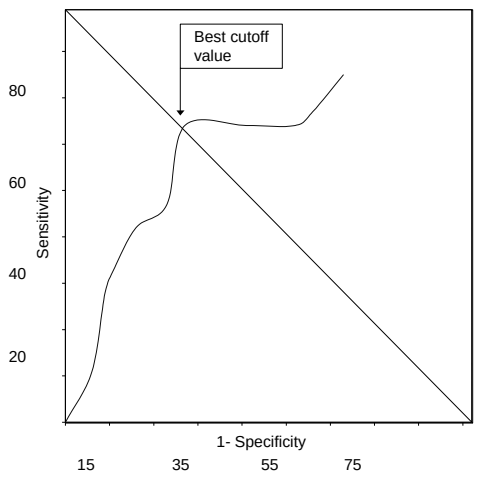

Figure - Receiver operator characteristic curve - Verbal fluency 'M'.

logical tests for the identification of schizophrenia patients because cognitive impairment has been recognized as a core characteristic of schizophrenia. Many studies in the last decades emphasized the cognitive deficit in schizophrenia, specially related to attention, memory and executive tasks,[9-13,15] although classification and discriminative power of the neuropsychological evaluation was rarely assessed.[4,10,14] These studies raised the hypothesis of cognitive impairment as a frequent clinical characteristic of disease and the cognitive evaluation has been considered a powerful tool for studying the brain and biological mechanisms in schizophrenia. It was intended to establish a correlation between measures of central tendency and variance of cognitive tests and frequency of patients whose test scores were below a cutoff point and differentiated them from the healthy participants. This approach was used to define the value of these instruments for undoubtedly differentiating schizophrenia patients from the age- and education-matched healthy subjects. The comparison of the neuropsychological tests scores between the groups showed lower performance of the schizophrenia group in the most tests. Although statistically significant, similar to the literature, a parallel clinical applicability of these tests was not achieved. The sensitivity of 75 and specificity of 65 for the Verbal Fluency "M" test were just intermediate for a diagnostic tool. The other tests showed poor clinical values (e.g., sensitivity 74 and specificity 56 for the Stroop test, 72 and 56 for the Mini Mental). The scores distribution analysis is based on the groups "central" parameters, which are strongly influenced by extreme values; however, they did not express either discriminative or clinical values.

The absence of a gold standard for cognitive deficit in schizophrenia required the application of the diagnosis itself as the gold standard (latent class).[7] The low sensitivity and specificity of various cutoffs and tests assessed in this study did not support the hypothesis of cognitive deficit as a core feature in schizophrenia. If this were a common condition, the tests would be able to identify the deficit or at least the different performance of schizophrenia patients and healthy participants. The cognitive impairment of schizophrenia patients may be of such a sort that is not assessable by these tests. Other neuropsychological tests for the detection of more generalized or specific impairment (e.g., verbal memory) could yield diagnostic efficiency. In the clinical practice today, neuropsychological examinations are often included in the diagnostic procedure, and their results also have an impact on the treatment planning.[2] However, this statement is true if the cognitive deficit was a frequent characteristic of the illness.

Identifying the nature, definition, and frequency of symptoms is crucial for the understanding and conceptualization of disease. Schizophrenia remains a disorder of great clinical heterogeneity with symptoms that vary within and between subjects. Some groups of schizophrenia patients may present higher frequency of cognitive deficit.[1,3,9,12] The study sample consisted of outpatients with probably less severe illnesses; however, most studies evaluated hospitalized, probably more severe, cases. Further studies for the evaluation of the discriminative power and clinical applicability of neuropsychological tests in sub-groups of illness, as well as older patients, patients presenting a different time course of disease or in the presence of more severe negative symptoms should be carried out.

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