Research Article

Neuropsychological screening for schizophrenia: A brief tool to assess subtypes of schizophrenia

Screening neuropsicológico para la esquizofrenia: una breve herramienta para el estudio de los subtipos de esquizofrenia

Ezequiel Uribe[1,2*], María Torres[1]

[1]*Centro de Biofísica y Neurociencias. Laboratorio de Neurobiología Conductual. Escuela de Ciencias Biomédicas, Universidad de Carabobo. Valencia, Venezuela.* [2]*Programa Doctoral en Ciencias Médicas, Universidad de Carabobo.*

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Abstract
Schizophrenia generates neuropsychological deficit related to prefrontal functions, but there no existent batteries capable to identify different patterns of neuropsychological affectation. Therefore, we developed a brief neuropsychology battery which encompasses the most frequent cognitive deficits in every clinical subtype of the disease. In line with this, an internal consistency of Schizophrenia´s Neuropsychological Screening (SNS) was determined with Cronbach's alpha coefficient. The SNS total score was correlated with MATRICS Consensus Cognitive Battery (MCCB) and with Brief Assessment of Cognition in Schizophrenia (BACS). The ability of the SNS to discriminate neuropsychological profile of healthy controls from patients diagnosed with schizophrenia was determined using a receiver operating characteristic (ROC) curve analysis. The results of this study showed that Internal consistency of the SNS (Cronbach's alpha) was 0.868, and most subtests correlated significantly between themselves. SNS did not correlate with classic neuropsychological batteries for schizophrenia MCCB (p:0,937) neither with BACS (p:0,496). The ROC curve analysis on the SNS total score between healthy controls and schizophrenic patients generated a cutoff score of 17 points with a sensitivity of 96.6% and specificity of 95.0%. Area under the ROC curve was 0.990 (CI: 95%; 0,490; $p < 0.0001$). Moreover, the SNS showed neuropsychological clustering properties for every clinical subtype of schizophrenia. In conclusion, SNS is a new kind of neuropsychological battery which is capable of identifying specific patterns of neuropsychological affectation in all the clinical presentations of schizophrenia.

Keywords: Catatonia, Biological psychiatry, Hebephrenia, Paranoid delusion, Prefrontal cortex, Endophenotype.

Resumen
La esquizofrenia genera un deficit neuropsicologico relacionado con funciones frontales, pero en la actualidad no existen baterías capaces de discriminar los diferentes patrones de afectación neuropsicologica. Debido a esto, desarrollamos una batería neuropsicologica que involucra las afectaciones cognitivas más comunes en cada subtipo clínico de la esquizofrenia. Para su validación, se determinó la consistencia interna de la batería mediante el coeficiente alfa de Cronbach. Los resultados de la batería fueron correlacionados con la MCCB (MATRICS Consensus Cognitive Battery) y BACS (Brief Assessment of Cognition in Schizophrenia). La habilidad de la batería para discriminar entre controles y pacientes con esquizofrenia fue determinada mediante la curva ROC (Receiver Operating Characteristic). La consistencia interna fue de 0,868 y la mayoría de los test de la batería correlacionan significativamente entre ellos. Nuestra batería no tuvo correlaciones con MCCB (p:0,937) y BACS (p:0,496). La curva ROC generó un punto de corte entre controls y esquizofrénicos de 17 puntos, con una sensibilidad de 96,6% y especificidad de 95,0%. El área bajo la curva ROC fue 0,990 (CI: 95%; 0,490; $p < 0.0001$). Además, nuestra batería puso en evidencia propiedades de agrupación para cada subtipo clínico de la esquizofrenia. En conclusión, nuestra batería es capaz de identificar diferentes patrones de afectación neuropsicológica en todos los subtipos clínicos de la enfermedad.

Palabras clave: Catatonia, Psiquiatría biologica, Hebefrenia, Delirio paranoide, Cortex prefrontal, Endofenotipo.

*Corresponding Author: Ezequiel Uribe, MD. Apartado postal 3798. El Trigal, Valencia 2001, Venezuela. Tel: +58-241-8666259, Fax: +58-241-8685321. E-mail: euribe@uc.edu.ve, ezequiel.uribe@hotmail.com

1. Introduction

Schizophrenia is a disabling disorder which affects 1% of the world population; involving several brain areas and mental functions like thought, mood, perception, and cognition.[1] Schizophrenic patients have marked differences in the clinical symptoms as well as an extremely variable pattern of brain damage, involving frequently frontostriatal circuits;[2] giving rise at least three neuropsychological deficit patterns, matching with those occurring in dorsolateral, orbitofrontal and anterior cingulated syndrome.[3] Furthermore, those patterns of neuropsychological deficits probably occur separately, in every clinical subtype of schizophrenia. For example, paranoid schizophrenia which is the most common subtype of the disease and frequently presents the better prognosis,[4] shows alterations in reversal learning and theory of mind, both related to the orbitofrontal cortex.[5,6] Besides, orbitofrontal cortex of patients with paranoid schizophrenia reveals activation abnormalities in functional Magnetic Resonance Imaging (fMRI) during the presentation of images of sad, furious and cheerful faces,[7] a pattern of neuropsychological deficit that does not match with another clinical subtypes of schizophrenia.[3]

On the other hand, catatonic schizophrenia shows prominent motor alterations and its prognosis is unfavorable and highly disabling.[8] The performance of patients with catatonic schizophrenia in the visual and perception object-space tests is deficient,[9] often associated with the reduction of cerebral blood flow in the left anterior cingulated circuit during the brain Single Photon Emission Computed Tomography (SPECT) with Tc-99mECD.[10] In contrast, patients with paranoid schizophrenia don't show a remarkable deficit in those tasks.[11] This circuit regulates spatial processing of movement, which is required for the correct performance of motor activity and lesions of these brain regions generate abnormalities in the cognitive component of movement control,[12] being associated to catatonia because of damage in this area generates akinetic mutism; consisting in a remarkable apathy with indifference to pain, hungry or thirst, lack of motor initiative, abnormal movements, echopraxia and echolalia,[13] mimicking at least eight (8) DSM V catatonia's diagnosis criteria.[14]

Patients with simple and residual schizophrenia have the highest degree of cerebral atrophy,[15] more severe in dorsolateral prefrontal cortex in MRI, associated to a prominent social retraction[16,17] and deficit in working memory,[13] exhibiting also impairments on a number of neurocognitive measures that are purportedly partly subserved by dorsolateral prefrontal basal ganglia-thalamocortical circuit,[18] involving disexecutivity with disturbances in planning, monitoring, sustained attention, learning disabilities and poor logical thinking.[12] Finally, hebephrenic schizophrenia is associated with a blood flow reduction in the right frontal lobe during SPECT, especially in Broca's area; a situation not manifested in patients with others subtypes of the disease. Disorganized thinking in schizophrenia is associated with a reduction of fractional anisotropy in medial longitudinal fasciculus, which connects all the language regions,[19] justifying the alterations in the verbal fluency[20] and semantic in the hebephrenic patient.[21] This subtype also presents orbital, cingulated[22] and dorsolateral circuits dysfunction,[23] indicating a frontal multi-circuit deterioration, aiming a dark prognosis, even when psychotic symptoms have been controlled.[24]

The subtypes of schizophrenia were recently eliminated by Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DMS-V),[14] due to the fact that almost all patients developed criteria for more than one subtype of schizophrenia during the illness course and generally are less used by psychiatrists.[25] However, clinical research is obligated to develop characterizations of the disease, attempt the developing of endophenotypes.[26-28] Recent neuropsychological researches about schizophrenia have found the presence of at least four well-defined groups,[3,29] but the currents neuropsychological and cognitive batteries widely used in clinical research,

MATRICS Consensus Cognitive Battery (MCCB) and with Brief Assessment of Cognition in Schizophrenia (BACS) do not gather all neuropsychological deficit present in all the clinical subtypes of the disease. In these order of ideas, we developed a brief tool for the characterization of neuropsychological groups of schizophrenia including patients of all the clinical subtypes of the disease for its validation.

2. Methods

2.1. Participants

A total of 120 participants were included in this study, 61 who were healthy controls and 59 who were diagnosed with schizophrenia through DSM V criteria.[14] Within the schizophrenia group, 16 patients presented paranoid subtype, 9 of them had catatonic subtypes, 12 of them simple subtypes, 10 of them residual subtypes and finally, 12 of them had hebephrenic subtypes, all of which were diagnosed through DSM IV criteria.[30] Schizophrenic patients had no evidence of neurological or other medical condition, have between 25 to 50 years of age and have not others psychiatric diagnosis. There were 24 female patients and 35 male patients, and results were no separated by gender. All the patients were medicated with psychotropic drugs at the moment of the evaluations. Healthy controls were examined with a comprehensive neuropsychological and neuropsychiatry evaluation and had no history of either neurological or psychiatric disorder. To avoid circularity, specialists determining diagnoses of patients included in the analysis were blind to their performance on the tool introduced in this study, the SNS.

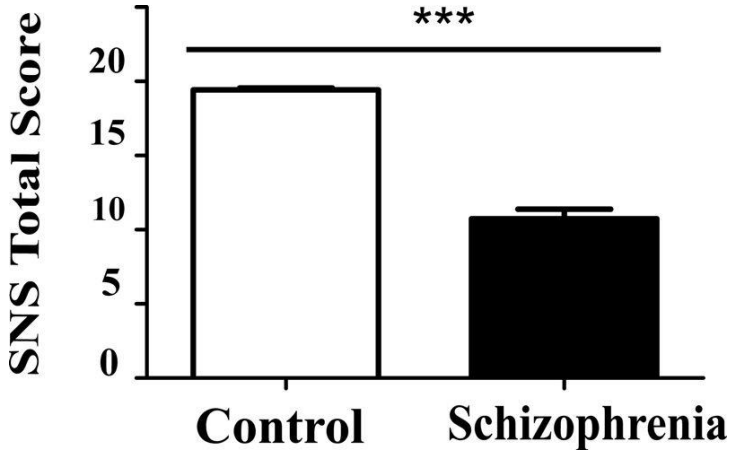

Figure 1: SNS total score between controls vs schizophrenic patients. ***p<0,005 for different between groups. (non-parametric Mann-Whitney tests).

2.2. Selection of the battery's subtest

Subtest of SNS was selected by an extensive review of scientific literature through Pubmed, choosing the five most cited test with positive results for each schizophrenia subtype.

2.3. Procedure

The study was initially approved by the ethics committee at the Biophysics and Neurosciences Center, following international regulations established for human research subjects. All participants were evaluated with MATRICS Consensus Cognitive Battery (MCCB) and with Brief Assessment of Cognition in Schizophrenia (BACS). The SNS score is calculated as the sum of each of the twenty subtest scores (one point for each one). Subtests are grouped in four blocks, each one with five subtests (Table 1). Overall average

administration time is approximately 40 minutes.

Table 1. Blocks of SNS and the neuropsychological function mesuered.

Items of the SNB	Mesurement
Block 1	
Identification of composite faces (Part 1)	Identification of emotional expressions
Identification of composite faces (Part 2)	Identification of emotional expressions
Conflicting Instructions	Working memory, interference sensitivity
Go-NoGo	Motor inhibitory control
Stroop effect abbreviated	Visual inhibitory control
Block 2	
Motor Luria series	Motor Programming
BCoS complex figure copy task	Visuo-spatial capacity
BCoS complex figure memory task	Visual memory
Three-dimensional object recognition task	Three-dimensional visual recognition
Poppelreuter-Ghent's overlapping figures test	Bi-dimensional visual recognition
Block 3	
Word list learning	Short term memory
Trail making test part B	Working memory
Delayed recall of word list learning	Mediate term memory
Zoo Map test modified, part 2	Planning
Zoo Map test modified, part 1	Planning and working memory
Block 4	
Words by letters	Letter fluency
Words by family	Semantic fluency
Proverb interpretation	Abstraction capacity
Picture naming	Semantic capacity
Months of the year backward	Verbal working memory

2.4. The SNS subtests

Identification of emotional expressions from composite faces, part 1[31] Nine pictures of emotional composites expressions were exhibited in the center of the paper. Every picture consisted of the combination of the upper and lower halves, showing each one different emotional expression. The patient was asked to mark out for the upper half of the face where the expression should be classified; the other half of the face had to be ignored. Six labeled words (from left to right: "happiness," "surprise," "anger," "fear," "sadness," "disgust") were aligned in a horizontal row on the paper below the picture. After the instruction and three practice trials, 15 experimental trials were performed. The trial sequence was random across the nine different emotion composites. If subjects made from zero to two errors the score was 1; for more than two errors the score was 0.

Identification of emotional expressions from composite faces, part 2.[31] The same nine pictures of emotional composites expressions were presented in the center of the paper, following the same rules of part 1. The patient was asked to mark out the lower half of the face in which the expression should be classified. If subjects made no errors, one or two -errors the score was 1; for more than two errors the score was 0.

Conflicting Instructions and interference.[32] Subjects were asked to hit the table once when the administrator hit it twice, or to hit the table twice when the administrator hit it only once. To ensure the subject had clearly understood the task, a practice trial was performed. After that, the examiner completed the following series: 1-1-2-1-2-2-2-1-1-2. If subjects made no errors, one or two errors, the score was 1; for more than two errors, the score was 0.

Go–No Go.[32] This task was administered immediately after conflicting instructions test. Subjects were told that this time when the test administrator hit the table once, they should hit it twice as well; but when the examiner hit it twice, they should do nothing. To ensure the subject had clearly understood the task, a practice trial was performed. After that, the examiner completed the following series: 1-1-2-1-2-2-2-1-1-2. If subjects made no errors, one or two errors the score was 1; for more than two errors the score was 0.

Stroop effect abbreviated.[33] Four colors were employed in this experiment: red, green, blue, and yellow. The congruent stimuli consisted of each of the four-color names printed in its own color. The incongruent stimuli consisted of each of the four-color names printed in the three other ink colors. The neutral stimuli consisted of squares printed in one of the four colors of ink. There were three blocks of trials, each one composed of 72 stimuli: 24 neutrals, 24 congruent, and 24 incongruent. Subjects were asked to say aloud as rapidly and accurately as possible the ink color that the words were printed in while ignoring the word itself. Just for the incongruent block; if subjects made no errors, one or two errors, the score was 1; for more than two errors the score was 0.

Motor Programming.[34] This subtest asks the patient to perform the Luria series, "fist, edge, palm" by initially copying the administrator, and by subsequently doing the series on his or her own then by repeating the series five times alone. If subjects achieved at least three consecutive series on their own, the score was 1; if they failed at achieving at least three consecutive series the score was 0.

BCoS complex figure copy task.[35,36] This subtest asks the patient to copy the figure the best they can. Each patient is given a maximum of 3 min to complete the task. Each end rectangle was evaluated on the presence of seven elements (left rectangle: diagonal end/three bars, circle, horizontal bar, top square, bottom square, top left diagonal bar, and the parallel bar below it; right rectangle: left and right lines of the triangle shape, double dot, horizontal bar, top square, bottom square, and right diagonal end/one curved line with an "S" shape). If subjects do not omit elements the score was 1; if they commit one or more omissions the score was 0.

BCoS complex figure memory task.[36] This subtest asks the patient to memorize in 2 minutes the figure and then draw it in 3 min or less. If they do not omit or omit just one or two elements of the figure, the score was 1. For the omission of three or more elements of the figure, the score was 0.

Three-dimensional object recognition task.[37] This subtest shows one target 3D figure and bellow, nine figures (30° rotations around a horizontal or vertical axis), three of which are the same figure at different orientations and six distractors. Subjects were asked to identify the three target images based on its shape and rotation angle as accurately as possible. If subjects achieved to select the three figures correctly, the score was 1; if not, the score was 0.

Poppelreuter-Ghent's overlapping figures test.[38] Consist of test-chart with four, overlapping, two-dimensional line-drawings of common objects: Jar, hammer, iron, and knife. The patient was instructed to name each element of the picture separately. If subjects achieved to name the four elements, the score was 1; if they did not it, the score was 0.

Word list learning and short-term memory.[39] This subtest asks the subject to learn a list of 12 common words, 3 from each of four categories. Words are read to the subject at an approximate rate of 1 each second. The subject is then asked to recall the elements listed in any order. The process is repeated for six trials or until the subject reports all 12 words. If subjects achieved to recall the twelve elements in any order, the score was 1; if they weren't able to do it, the score was 0. It was advised that the same list of words would be asked later.

Trail making test part B.[40] This test consisted of 25 circles distributed over a sheet of paper. Circles include both numbers (1–13) and letters (A–L). The patient draws lines to connect the circles in an ascending pattern, alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. If the patient made an error, it was necessary to point it out immediately and allow the patient to correct it and start again. If subjects achieved to complete the line correctly in less than 3 minutes the score was 1; if they did it in more than 3 minutes the score was 0.

Delayed recall of word list learning.[39] The patient was asked to repeat all twelve words previously learned. If subjects achieved to recall the twelve elements in any order, the score was 1; if they did not it, the score was 0.

Zoo Map test modified, part 1.[41] This task involves plotting or following a route through a map that does not contravene a set of rules. The patient was asked to prepare a cup of tea, obeying the following rules: 1) you must use the teapot and the spoon 2) add milk and sugar. Previously, the patient was warned to look carefully at all the objects below and plan a route on the map from start to finish in two minutes. After that, the patient had one minute to draw correctly the choose in the map. If subjects achieved to prepare the teacup without breaking the rules, the score was 1; if they did not it, the score was 0.

Zoo Map test modified, part 2.[41] The patient was asked to prepare a cup of coffee, obeying the following rules: 1) you must use the coffee pot and the spoon 2) add just sugar. Previously, the patient was warned to look carefully at all the objects below and plan a route on the map from start to finish in two minutes. If subjects achieved to prepare the coffee cup without breaking the rules, the score was 1; if they didn't do it, the score was 0.

Words by letters.[42] This subtest asks the patient to say any words which begin with one letter of the alphabet, letter previously determined by the administrator, as quickly as he or she can, in just one minute. If subjects achieved to say at least 15 words in 1 min, the score was 1; if they did not it, the score was 0.

Words by family.[42] This subtest asks the patient to say all the animals they can in just one minute. If subjects achieved to say at least 15 animals in 1 min, the score was 1; if they did not it, the score was 0.

Abstraction Capacity (Proverb interpretation).[43] Three proverbs were read to the subjects and they were asked to explain their meaning. For the three proverbs, a score of 1 was given when the subject gave an adequate explanation for each one. Otherwise, the score was 0. The three proverbs were chosen specifically for this demographic population based on their high frequency in oral speech.

Picture naming.[44] This task consisted of 36 pictures. These 36 pictures were divided into six different semantic categories, with six items in each category. The semantic categories

represented in the test were animals, fruits, plants, vehicles, furniture, and clothing. If subjects achieved to name all the 36 pictures, the score was 1, otherwise, the score was 0.

Months of the year backward.[43] The patient was asked to list the months of the year backwards, starting with December, as quickly as he or she can, in just two minutes. If the subjects made one or more errors, they had to start again from December. If subjects completed correctly the months backward without errors in two minutes or less, the score was 1; otherwise, the score was 0.

3. Statistical Analysis

Internal consistency was determined with Cronbach's alpha coefficient. To analyze concurrent validity with other tasks shown to be sensitive to schizophrenia, the SNS total score was correlated with MATRICS Consensus Cognitive Battery (MCCB) and with Brief Assessment of Cognition in Schizophrenia (BACS) through nonparametric Spearman's correlation coefficient. The ability of the SNS to discriminate neuropsychological profile of healthy controls from patients diagnosed with schizophrenia was determined using a receiver operating characteristic (ROC) curve analysis. Demographic and clinical information, as well as neuropsychological test performance, were compared between the groups using non-parametric Kruskal Wallis test analyses of variance with Dunn post hoc analyses when appropriate. Non-parametric Mann-Whitney tests were used to compare two groups at a time. To further analyze differentiating subtypes of schizophrenia, K-means cluster analysis was made. Statistical analyses were performed using PAST3 software package.

4. Results

Fifty-nine schizophrenic patients were evaluated with the prefrontal neuropsychology battery; 16 were paranoids, 9 were catatonics, 12 were simples, 10 were residuals and 12 were hebephrenics. Besides, 61 controls were evaluated with the same instruments. In order to submit our battery to validation, all the patients and controls were evaluated with MCCB and BACS. From the 59 schizophrenic patients, 27 were females and 32 were males. The mean age was 36,1 years, the mean disease time was 6,3 years. The mean total score of SNS in schizophrenic patients was 10,44 points, and the mean in the control group was 18,79 points (p:0,0001) (Fig.1). Moreover, there were significant differences in SNS total score between every subtypes of schizophrenia and controls (Fig.2). The mean time of responding the battery in schizophrenics was 63,5 minutes, and in the control group was 43,2 minutes.

4.1. Results of sub groups

Control group (n: 61): The total median score was 19 points (25 percentile: 18; 75 percentile: 20). In block 1 the median was 5, for block 2 was 5, for block 3 was 4 and finally, for block 4 was 5. There were no differences between blocks of the test (KW: 0,98).

Paranoid group (n: 16): The total median score was 14 points (25 percentile: 12,25; 75 percentile: 15). In block 1 the median was 1, for block 2 was 5, for block 3 was 4 and for block 4 was 4. Block 1 was significantly different with respect to block 2 (KW: 0,0002), block 3 (KW: 0,001) and block 4 (KW: 0,0004). Moreover, block 3 was significantly different with respect to block 2 (KW:0,024) and with respect to block 4 (KW: 0,041).

Catatonic group (n: 9): The total median score was 14 points (25 percentile: 11; 75 percentile: 15,5). In block 1 the median was 4, for block 2 was 1, for block 3 was 4 and for block 4 was 5. Block 2 was significantly different with respect to block 1 (KW: 0,0001), with respect to block 3 (KW: 0,0019) and with respect to block 4 (KW: 0,0001).

Simple group (n: 12): The total median score was 11 points (25 percentile: 10; 75 percentile: 12,75). In block 1 the median was 3,5; for block 2 was 5, for block 3 was 0 and for block 4 was 2,5. Block 3 was significantly different with respect to block 1 (KW: 0,0009), with respect

to block 2 (KW: 0,0001) and with respect to block 4 (KW: 0,0010). Moreover, block 1 was significantly different with respect to block 2 (KW:0,024) and block 2 with respect to block 4 (KW: 0,041).

Residual group (n: 10): The total median score was 13 points (25 percentile: 11,75; 75 percentile: 15,25). In block 1 the median was 4; in the block 2 was 5, in the block 3 was 1 and in the block 4 was 4. Block 3 was significantly different with respect to block 1 (KW: 0,0031), with respect to block 2 (KW: 0,0001) and with respect to block 4 (KW: 0,0043). Moreover, block 2 was significantly different with respect to block 4 (KW:0,039).

Hebephrenic group (n:12): The total median score was 2 points (25 percentile: 1,25; 75 percentile: 3). In block 1 the median was 0,5, for block 2 was 0, for block 3 was 0 and finally for block 4 was 0. There were no significant differences between blocks of the test (Fig.3).

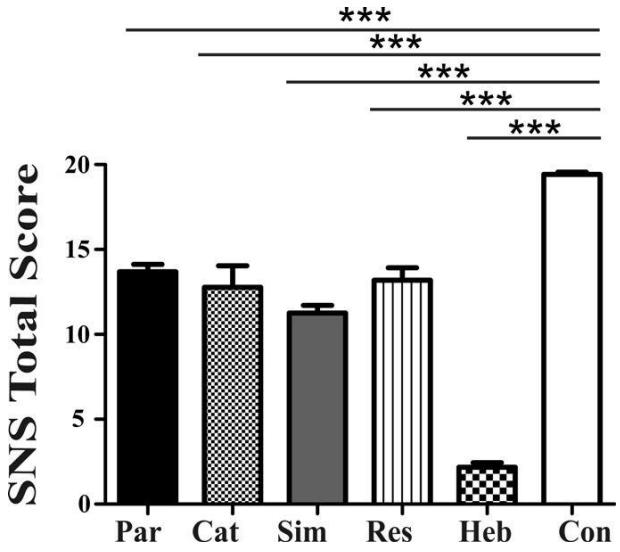

Figure 2: SNS total score between controls and every sub type of schizophrenia (Par: Paranoid, Cat: Catatonic, Sim: Simple, Res: Residual, Heb: Hebephrenic, Con: Control). ***p<0,005 for differences between groups. (Kruskal Wallis test analyses of variance with Tukey post hoc analyses).

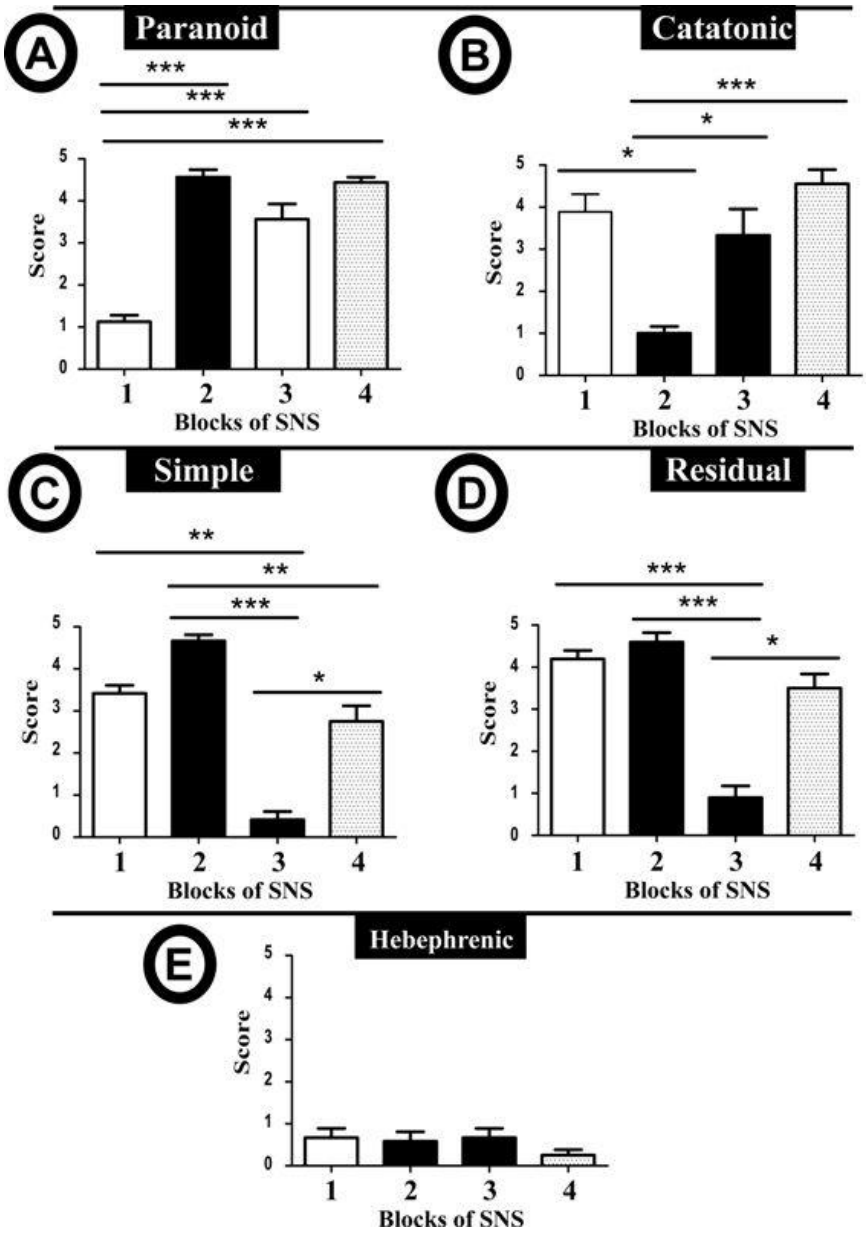

Figure 3: SNS score by blocks (1: orbitofrontal, 2: anterior cingulated, 3: Prefrontodorsolateral, 4: language) in every sub type of schizophrenia. *p<0,05, **p<0,01, ***p<0,005 for differences between groups. (Kruskal Wallis test analyses of variance with Tukey post hoc analyses).

Validation: Internal consistency of the SNS was very good (Cronbach's alpha = 0.868), and most subtests correlated significantly between themselves (Table 2). SNS did not correlate with classic neuropsychological batteries for schizophrenia MCCB (p:0,937) neither with BACS (p:0,496) (Fig.4). Test-Retest Reliability (intraclass correlation coefficient) which takes into account changes in mean level, were generally good, considering an r value of 0.70 to be acceptable test-retest reliability for clinical trials. Most of the tests achieved at least that level. Test-retest reliability data are summarized in Table 3.

Table 2. Cronbach´s alpha by ítem of SNS

Item of SNS	Mean of the SNS if the ítem is removed	Variance of the SNS if the ítem is removed	Correlation ítem-total corrected	Cronbach´s alpha if the ítem is removed
Item1	9,95	25,428	,234	,870
Item2	9,85	25,235	,283	,868
Item3	9,92	24,493	,428	,863
Item4	10,05	25,463	,233	,870
Item5	10,08	25,493	,232	,870
Item6	9,81	23,913	,577	,858
Item7	9,85	24,442	,450	,862
Item8	9,81	24,258	,501	,860
Item9	9,81	23,947	,570	,858
Item10	9,76	25,219	,309	,867
Item11	10,05	24,118	,516	,860
Item12	10,07	24,168	,509	,860
Item13	10,15	24,580	,451	,862
Item14	10,14	24,981	,354	,866
Item15	10,15	24,821	,397	,864
Item16	9,95	24,222	,483	,861
Item17	9,90	24,058	,522	,860
Item18	9,76	23,046	,810	,849
Item19	9,83	23,316	,705	,853
Item20	9,80	23,234	,741	,852

Table 3. Test-Retest Reliability of the 20 Tests in the SNS

Items of the SNB	Test Scores Used	Interclass Correlation Coefficient
Identification of emotional expressions	Total number corrects	0,71
Identification of emotional expressions	Total number corrects	0,74
Conflicting Instructions	Total number corrects	0,80
Go-NoGo	Total number corrects	0,78
Stroop effect abbreviated	Number of correct responses	0,72
Motor Luria series	Total number corrects	0,81
BCoS complex figure copy task	Total number of elements drawed	0,83
BCoS complex figure memory task	Total number of elements drawed	0,70
Three-dimensional object recognition task	Correct response	0,65
Poppelreuter-Ghent's overlapping figures test	Total number corrects	0,58
Word list learning	Total number of words learned	0,88
Trail making test part B	Time to completion	0,66
Delayed recall of word list learning	Total number of words learned	0,82
Zoo Map test modified, part 2	Time to completation	0,71
Zoo Map test modified, part 1	Time to completation	0,67
Words by letters	Total number of words named in 60 seconds	0,74
Words by family	Total number of words named in 60 seconds	0,80
Proverb interpretation	Total number corrects	0,77
Picture naming	Total number corrects	0,89
Months of the year backward	Total number corrects	0,86

The ROC curve analysis on the SNS total score between healthy controls and schizophrenic patients generated a cutoff score of 17 points with a sensitivity of 96.6% and specificity of 95.0% (Fig.5). Area under the ROC curve was 0.990 (CI: 95%; 0,490; $p < 0.0001$). Furthermore, when patient groups were separated based on their type of schizophrenia, a ROC curve analysis between paranoid subgroup and control generated a cutoff score of 17 points, with a sensitivity of 93,3% and a specificity of 95,0%, with an area under the curve of 0.984 (CI: 0.435–0.533; $p < 0.0001$). Block 1 of the SNS had the lower average with 1,125 points in the paranoid subtype. ROC curve analysis between catatonic subgroup and control generated a cutoff score of 17 points, with a sensitivity of 100% and a specificity of

95,0%, with an area under the curve of 0.985 (CI: 0.417–0.554; p < 0.0001). Block 2 of the SNS had the lower average with 1 point. For simple and residual subgroups, the cutoff score was 17 points, with a sensitivity of 95,2% and a specificity of 95,0%, with an area under the curve of 0.989 (CI: 0.450–0.528; p < 0.0001). Block 3 of the SNS had the lower average with 0,636 points. For hebephrenic subgroup, the cutoff score at ROC curve analysis was 15 points, with a sensitivity of 100% and a specificity of 100%, with an area under the curve of 1 (CI: 0.448–0.552; p < 0.0001). All Blocks of the SNS had less than 1 point of average (Block 1: 0,66; Block 2: 0,58, Block 3: 0,08; Block 4:0).

To further analyze the superiority of the SNS in differentiating subtypes of schizophrenia, K-means cluster analysis was made where the percentage of match between clinical subtypes of schizophrenia and the SNS score was: paranoid group matching with SNS Block 1: 75%; catatonic group matching with SNS Block 2: 55,5%; simple and residual groups matching with SNS Block 3: 50%; hebephrenic group matching with SNS Block 4: 100%. Control group did not match with one specific SNS Blocks (Fig.6). The same analysis was made with the data obtained from the application of MCCB and BACS to all subgroups of schizophrenia, but there were not cluster distribution. Clustering NJ and KlustaWin 3D were made but did not produce adequate data.

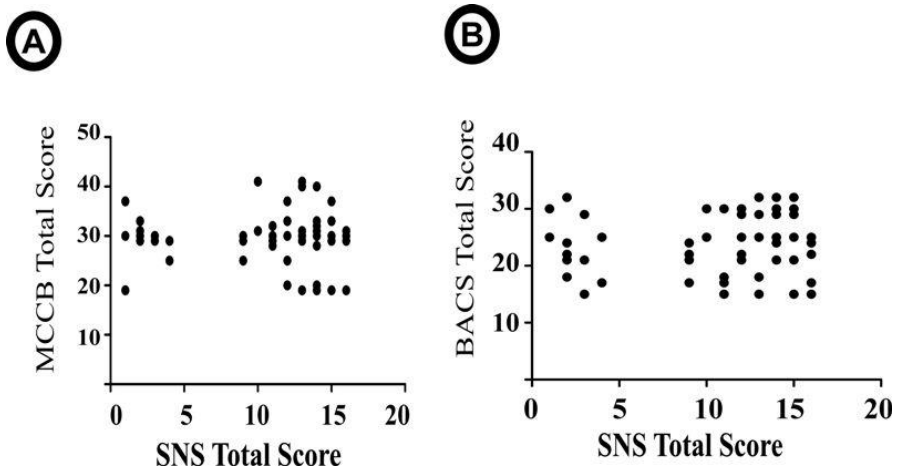

Figure 4. SNS total score correlated with MCCB and BACS through nonparametric Spearman's correlation coefficient.

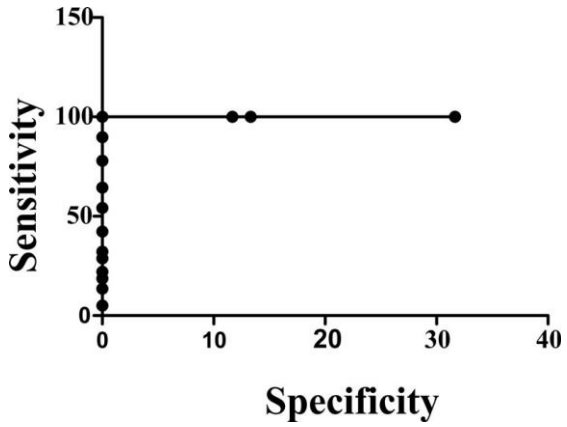

Figure 5: ROC curve analysis on the SNS total score between controls and schizophrenic patients, showing the sensitivity and specificity.

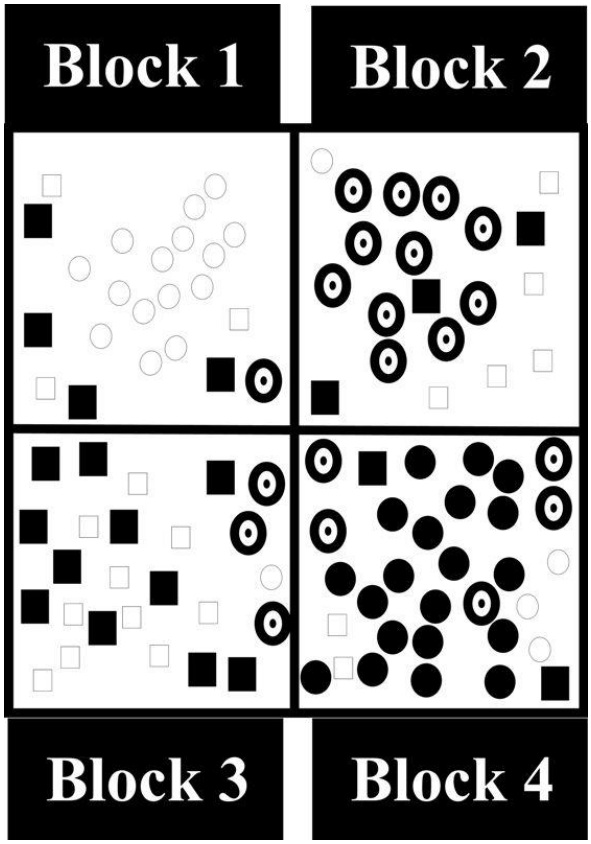

Figure 6: K-means cluster analysis showing the percentage of match between clinical subtypes of schizophrenia and blocks of SNS score. White circles: paranoid, circles with point in the middle: catatonic, black squares: simple, white squares: residual, black circles: hebephrenic.

5. Discussion

In our study, the SNS has demonstrated interesting psychometric properties: very good internal consistency and a cutoff between schizophrenics and control with high sensitivity and specificity. In our opinion, the best contribution of SNS is its tendency to group neuropsychological patterns to clinical symptoms, which is not possible with any of the cognitive instruments currently available. For example, in paranoid schizophrenia the SNS Block 1 had the lower score, with a neuropsychological deficit mainly circumscribed to emotional faces recognition, inhibitory control and working memory, suggesting preferential dysfunction of medial prefrontal cortex.[45,46] Catatonic subtype showed deficit specifically in the cognitive component of movement control and object-space perception, circumscribed to SNS Block 2, and suggesting anterior cingulated circuit damage.[12] The same occurred with simple and residual subtypes of schizophrenia, who had a deficit in SNS Block 3 performance, with an affectation of short-term memory, working memory, planning and logical thinking, a neuropsychological deficit linked with dorsolateral prefrontal circuit dysfunction.[47] Hebephrenic subgroup presented the lower total score of SNS, with a prominent language deficit (Block 4), and a poor performance in the rest SNS blocks, clustering all the neuropsychological deficits of all schizophrenia subtypes.

Evidently, SNS is capable of identifying neuropsychological patterns of affectation in the different clinical presentation of schizophrenia, which is no possible applying the classic available batteries. MCCB for example, was validated with "schizophrenic" patients without naming its subtype, and part of the sample were depressed type schizoaffective patients,[48] a condition comparable with schizophrenia concerning neuropsychological impairment, but not completely similar.[49,50] Furthermore, 14 of 20 items of the MCCB battery addresses dorsolateral prefrontal deficits (Working memory, attention, problem solving and processing), being this way just one of many cognitive abnormalities present in all the clinical subtypes of the disease (Table 4). In addition, the neuropsychological function of dorsolateral prefrontal circuit seems to show an age-related impairment[51,52] and the sample average age for the validation of MCCB was 44 years.[48] Maybe those are the reasons why this battery cannot determine neuropsychological groups in schizophrenia and consequently, there is no statistical correlation with SNS. On the other hand, BACS evaluates just the neurocognitive deficit related to executive functions, but not all the schizophrenic patients show this type of impairment.[53] Even more, BACS, just like MCCB, addresses dorsolateral prefrontal déficits with different neuropsychological subtests (table 4) and included for its validation patients with a schizoaffective and schizophreniform disorder.[54] Another limitation of the SNS was the selection of each subtest, based in high impact scientific publication related to neuropsychological abnormalities in subtypes of schizophrenia, but most of them are made just with paranoids or did not specify the subtype of schizophrenic patients.

Table 4. Neurocognitive items evaluated in SNS, MCCB and BACS

SNS	MCCB	BACS
Identification of emotional expressions	Category fluency test	List learning
Conflicting Instructions	Trail making test, part A	Digit sequencing task
Go-NoGo	Digit symbol-coding sut test of WEIS III	Token motor task
Stroop effect abbreviated	Symbol-coding sut test of BACS	Category instances
Motor Luria series	3-7 continuous performans test, shortenet version	Controlled oral worl association test
BCoS complex figure copy task	Continuous performance test, identical pairs version	Symbol coding
BCoS complex figure memory task	Digit secuencing subtest of BACS	Tower of London
Three-dimensional object recognition task	Letter number secuencing sub test of WAIS III	
Poppelreuter-Ghent's overlapping figures test	Letter-number spam test	
Word list learning	Spatial span subtest of Wechsler memory scale	
Trail making test part B	Spatial delayed response task	
Delayed recall of word list learning	Daily living memory sub test of Neuropsychological assessment batery	
Zoo Map test modified, part 2	Inmediate recall of Hopkins verbal learning test	
Zoo Map test modified, part 1	Shape learning subtest of Neuropsychological assessment batery	
Words by letters	Brief visuospatial memory test	
Words by family	Block design subtest of WAIS-III	
Proverb interpretation	Tower of London	
Picture naming	Maze of Neuropsychological assessment batery	
Months of the year backward	Perceiving emotions branch of Mayer-Salovey-Caruso Emotional Intelligence Test	
	Managing emotions branch of Mayer-Salovey-Caruso Emotional Intelligence Test	

6. Conclusion

With the apparition of DSM V, were removed the clinic subtypes of schizophrenia and the general criteria for the diagnosis of the disease has not changed significantly since DSM III, making of schizophrenia a condition in which exist more questions than answers.[25] Biological

psychiatry has made efforts in standardizing neurobiological correlation of every mental disorder, but in the particular case of schizophrenia has not been possible yet, mainly because schizophrenia is a heterogenic condition with a wide spectrum of symptoms and brain impartment which will not reach the standardization obeying the current scientific framework that governs it.[29] Neuropsychology is a good candidate for its inclusion in the diagnosis criteria, beyond the simple clinical observation, but the neuropsychological batteries currently worldwide used (MCCB and BACS) are determined to propose the dorsolateral prefrontal deficit how the only and more frequent for schizophrenia, although recent scientific evidence suggests another neuropsychological pattern which is even linked with clinical symptoms of the disease.[3]

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8. Interest conflicts

Authors declare no conflict of interest.

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