Verbal working memory in individuals with schizophrenia and their first degree relatives: relationship with negative and disorganized symptoms

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Objective: To determine whether there are differences in verbal working memory amongst subjects with schizophrenia, their first degree relatives and controls, and to evaluate the influence of symptoms on these differences, as an initial step to assess whether this cognitive function is an endophenotype.

Methods: We examined 197 cases with schizophrenia, 197 first degree relatives and 200 controls through psychiatric interviews and the Letters and Numbers Sequencing test (LNS). Performance was compared among the three groups adjusting for age, sex and education level. Adjustment for "negative symptoms" and "disorganization" was performed afterwards.

Results: Subjects with schizophrenia showed lower performance in the LNS than their first degree relatives and the healthy controls; the effect sizes were 0.75 and 1.18 respectively. There was a small difference between relatives and controls (effect size =0.38). These differences were significant after adjustment for negative and disorganized symptoms, but the effect sizes became smaller: 0.26 for relatives vs. subjects with schizophrenia, 0.56 for controls vs. subjects with schizophrenia and 0.33 for relatives vs. controls. Among individuals with schizophrenia, performance in the LNS was not associated with disorder duration, disease onset age, antipsychotics, history of depressive episodes or substance use disorders.

Conclusion: Results suggest verbal working memory may be considered as an endophenotype in schizophrenia.

Key words: Schizophrenia, Endophenotype, Verbal working memory, Negative symptoms, Disorganized symptoms

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Memoria de trabajo verbal en individuos con esquizofrenia y sus familiares de primer grado: Relación con los sintomas negativos y desorganizados

Objetivo: Determinar si hay diferencias en la memoria de trabajo verbal entre sujetos con esquizofrenia, familiares de primer grado y controles, y evaluar la influencia que pueden tener en estas diferencias los síntomas del trastorno, como un paso para establecer si esta función cognitiva es un endofenotipo.

Métodos: A 197 sujetos con esquizofrenia, 197 familiares de primer grado y 200 controles comunitarios, se les hizo evaluación psiquiátrica y se les aplicó la prueba sucesión de letras y números (SLN). Se comparó el desempeño de los tres grupos ajustando por edad, sexo y escolaridad, y luego se ajustó también por síntomas negativos y desorganizados.

Resultados: Los sujetos con esquizofrenia mostraron un menor desempeño en la SLN con respecto a sus familiares de primer grado no-afectados y los controles, con tamaños de efecto de 0,75 y 1,18 respectivamente. Hubo una diferencia

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pequeña pero significativa entre familiares y controles (tamaño de efecto =0,38). Estas diferencias siguieron siendo significativas después de ajustar por síntomas negativos y desorganizados, pero los tamaños de efecto disminuyeron a: 0,26 para familiares vs sujetos con esquizofrenia, 0,56 para controles vs sujetos con esquizofrenia y 0,33 para familiares vs controles. Entre los sujetos con esquizofrenia, el desempeño en la SLN no se asoció significativamente con duración del trastorno, edad de inicio, uso de antipsicóticos, ni historia de episodios depresivos o trastornos por uso de sustancias.

Conclusión: Los resultados sugieren que la memoria de trabajo verbal puede ser considerada un endofenotipo de la esquizofrenia.

Palabras clave: Esquizofrenia, Endofenotipo, Memoria de trabajo verbal, Síntomas negativos, Síntomas desorganizados

INTRODUCTION

It has been demonstrated that schizophrenia has genetic factors within its etiology. However, up to now, genes that are clearly associated with susceptibility for this disorder have not been identified.[1,2] One of the reasons for this is the current definition of the schizophrenia phenotype. This is based on signs and symptoms, which may be the final outcome of different etiopathological conditions.[2-4] This has implied the search for phenotypes that are different from the clinical definition of the disorder and that may be more useful for the genetic research.[5] Among these new phenotypes are the endophenotypes. These endophenotypes are measurable traits that would be in an intermediate position between the genotype and the diagnosis. [5,6] In other words, if the person has genetic vulnerability for the disorder, there would be physiopathological alterations that manifest as endophenotypes, even though the signs and symptoms have still not developed. The following criteria should be met for a trait to be considered an endophenotype:[6] to be associated with the disorder of interest when comparing those affected and not affected, the finding of higher rates in the nonaffected relatives of the person suffering the disorder that in the general population, being present independently of the fluctuations of the clinical condition of the individual and the use of medications, being inheritable and showing segregation with the disorder.

Biochemical, neurophysiological, neuroimaginological and neurocognitive characteristics have been studied, among others, as possible endophenotypes for schizophrenia.[7,8] Its neurocognitive characteristics have stimulated interest for research because they are easier to apply in large-sized samples, as those required for molecular genetic studies.[9] One of the candidates for the neurocognitive endophenotype of schizophrenia is verbal working memory. This is a storage system with limited capacity that maintains and manipulates the information in a temporal way. It is necessary for the carrying out of complex tasks as reasoning, language understanding and learning.[10] It has been proposed that verbal working memory has two processes, one storage and another that also involves manipulation of the information.[11] Using tests that evaluate both processes, it has been observed in different populations (including Latin American) that subjects with schizophrenia have lower performance than persons without personal or family backgrounds of the disorder.[12-15] Furthermore, it has been found that when the unaffected relatives of subjects with schizophrenia are compared with the latter, the unaffected relatives of the subjects with schizophrenia have lower performance, principally when using manipulation tests.[16-19]

In subjects with schizophrenia, a negative correlation has been demonstrated between performance on verbal working memory tests and negative symptoms.[17,20-22] These symptoms tend to remain even if the psychosis has disappeared and they have also been observed in some nonaffected relatives.[23] In addition, positive symptoms, such as hallucinations, delusions and disorganization, could be related as well with performance on cognitive function tests.[24,25] It has also been demonstrated that disorganized symptoms may be present in an attenuated way in unaffected relatives of subjects was schizophrenia.[25,26] It is possible that the differences that have been reported regarding performance on verbal working memory tests among subjects with schizophrenia, relatives and controls may be explained by the relationship that this cognitive function may have with negative and disorganized symptoms. It is important to clarify the influence of the symptoms because the independence of the clinical condition is one of the criteria to consider that a trait is an endophenotype.

Based on the above, it was decided to perform this study in order to determine if there are differences in performance on a verbal working memory test that involves manipulation processes among subjects affected by schizophrenia, their first degree relatives and healthy controls and to evaluate the influence that the symptoms of the disorder may have in these differences.

METHODS

Subjects

This is a cross-sectional study that included subjects with schizophrenia together with one of their first degree relatives (parents or brothers) who were not affected by the disorder and unaffected individuals from the community

(control group). This study is part of an investigation on several neuropsychological endophenotypes in schizophrenia conducted by the University of Antioquia, Pontificia Bolivariana University and National University of Colombia.

The schizophrenia subjects were obtained between July 2009 and December 2011 from the outpatient consultation of the following hospitals: Hospital Universitario San Vicente Fundación, Hospital Mental de Antioquia and Samein of the city of Medellín and Hospitals Santa Clara and La Victoria of the city of Bogota, in Colombia. The ethics committees of these hospitals together with those of the participating Universities approved the research protocol.

In the three groups, persons aged 18 to 65 years were included. Exclusion criteria were illiteracy, being physically incapable of participating in a neuropsychological evaluation due to systemic, visual, or hearing problems, use of benzodiazepine in the last month, having undergone electroshock therapy in the last six months, substance abuse or dependency without remission in the last six months, having suffered significant traumatic brain injury (with loss of consciousness over 15 minutes or neurological sequels), epilepsy, dementia or other neurodegenerative disorders and mental retardation.

In addition to the above criteria, the individuals with schizophrenia should have been diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised (DSM-IV-TR)[27] and have more than one month of psychiatric stability. The relatives of the subjects with schizophrenia and the controls should not have any background of bipolar disorder or psychiatric disorders according to the DSM-IV-TR; and the control should not have any family history of schizophrenia or other psychotic disorders.

Procedures

Before initiating the study, training workshops were carried out for the neuropsychologists and psychiatrists who evaluated the subjects on the application of the instruments. After, a pilot study including 26 subjects was performed. In this study, each neuropsychologist separately evaluated the same subject with a difference of one week in order to determine the interrater reliability. Based on the results, an intraclass correlation coefficient was calculated. This was 0.85 (95% CI: 0.65-0.94), with which interrater reliability was considered adequate.

Clinical and neuropsychological evaluations

The subjects with schizophrenia who could participate in the study were identified from the list of outpatients of the participating hospitals and clinics. The control group was made up of volunteers from the community. Once identified, each one of the possible participants was contacted by a nurse who explained the study objectives and procedures. The subject was invited to participate in the study and was given an appointment to sign the informed consent after they had read and understood it. If the subject accepted, he/she entered into the research. After, both subjects with schizophrenia and relatives and control individuals were evaluated by a psychiatrist who used the Diagnostics Interview for Genetic Studies (DIGS)[28] to establish the diagnosis according to the DSM-IV-TR criteria, and the Scales for Assessment of Negative (SANS) and Positive Symptoms (SAPS)[29,30] were applied. After, the Best Diagnostic Estimation procedure was carried out by two expert psychiatrists, different from those who had made the interview. They separately reviewed the available information (DIGS, scales and clinical history) of each subject in order to corroborate the diagnosis. If there was disagreement between the psychiatrist, a third evaluator was used, and if the disagreement continued, the three psychiatrists met and reached the diagnosis by consensus. If no consensus was reached, the subject was excluded from the study.

After being interviewed by the psychiatrist, the subject was evaluated by a neuropsychologist for the application of a protocol that included working memory tasks, attention, verbal memory, executive function and facial recognition of emotions. The neuropsychological tests were identical for both the subject with schizophrenia as well as for the relatives and control group.

Information collection instruments

Diagnostics Interview for Genetic Studies (DIGS). It was developed by the National Health Institute of the United States for genetic studies of schizophrenia and mood state disorders. It provides a detailed evaluation of psychosis, mood state disorders and those related with substances for a reliable differential diagnosis.[28] It was translated and validated for Columbia and demonstrated understandability, validity of appearance and contents, and high test-retest and interrater reproducibility for all the diagnoses.[31]

Scales for the assessment of positive symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS).[29,30] These are complementary instruments that are mainly used to study clinical phenomenology, severity and response to treatment of schizophrenia. The SANS contains 20 items organized into the following subscales: affective flattening and blunting, alogia, avolition-apathy, anhedonia-asociality and attention deterioration. The SAPS contains 30 items organized into the following subscales: hallucinations, delusions, bizarre behaviors, positive formal thought and inappropriate affect disorders. Each subscale includes items to evaluate specific symptoms and an item of global score

Table 1 Demographic and clinical characteristics of the subjects with schizophrenia, their first relatives and controls

Characteristics	Subjects with schizophrenia n = 197		Familiares de primer grado n=197		Controles n=200		p Value
	Freq.	%	Freq.	%	Freq.	%	
Male gender	147	74.6	37	18.8	102	51.0	<0.0001
Previous depressive episodes	31	15.8	45	23.1	26	13.1	0.03
History of substance abuse or dependence	68	34.5	23	11.7	38	19.0	<0.0001

	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean (SD)	Min	Max	
Age (years)	37.09 (11.57)	18	64	49.57 (10.31)	18	65	31.38 (13.34)	18	64	<0.0001
Schooling (years)	9.54 (3.36)	1	20	9.57 (4.95)	1	23	10.97 (3.29)	1	21	<0.0001
Onset age (years)	21.57 (7.86)	4	49							
Duration of schizophrenia (years)	15.41 (9.69)	1.09	40.8							
SANS	40.52 (20.03)	0	86	4.13 (1.64)	0	46	1.64 (3.96)	0	31	<0.0001
SAPS	19.64 (19.45)	0	91	1.05 (2.38)	0	14	0.55 (2.13)	0	14	<0.0001
Hallucinations and delusions	13.03 (15.66)	0	73	0.08 (0.37)	0	2	0.06 (0.49)	0	6	<0.0001
Disorganization	6.88 (7.88)	0	33	0.96 (2.31)	0	14	0.49 (1.93)	0	14	<0.0001

Note: SD = Standard Deviation, Freq. = Frequency, % = Percentage, SANS = Scale for Assessment of Negative Symptoms, SAPS = Scale for Assessment of Positive Symptoms.

that represents the view of the evaluator on the global severity of the symptoms in this subscales. The scores are assigned based on the clinical interview, behaviors observed during it, review of the clinical material and information provided by the family and caregivers of the patient. These scales were already validated in Columbia where high internal consistency, sensibility to change and test retest and interrater reproducibility were found.[32] In the present investigation, three groups of symptoms were used: "negatives," "hallucinations and delusions" and "disorganization." These were measured as follows: the "negative ones" with the total score on the SANS, "hallucinations and delusions" with this subscales of the SAPS that have the same name and "disorganization" with this subscales of the SAPS called "bizarre behaviors," "formal thought disorders" and "inappropriate affective disorders."

Succession of Letters and Numbers Test (SLN). This was obtained from the Wechsler Adult Intelligence Scale (WAIS-III).[33] In this verbal working memory test, the participants are presented groups of numbers mixed with letters. The participants mentally reorganize the order of the letters and numbers presented, in such a way that all the number should be first said in ascending order and then in alphabetical order. Seven trials are made, each one of the sequences. When they go from one trial to the next, the numbers of digits and letters increase. If the subject makes a mistake in the three sequences forming a part of the test, the test is interrupted. This test is chosen because it evaluates the working memory involving information manipulation process, which have been shown to be more affected in schizophrenia according to previous studies.[13] Furthermore, due to its reliability and utility, it has been included in other neuropsychological batteries that have been specifically designed for schizophrenia, as, for example, that of the program "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS)[34].

Statistical analysis

All the analysis was done using the SPSS 20.0 program. Measures of central tendencies and of dispersion for quantitative variables, and frequencies and percentages for the qualitative were used to describe the subjects participating in the study. After, it was determined if there were differences between subjects with schizophrenia, relatives and controls in the demographic and clinical characteristics, using the Chi Square test for qualitative variables and ANOVA (F) for the quantitative ones.

The association of the score of the SLN with onset age, duration of the disorder and scores on the SANS and SAPS was evaluated within the schizophrenia subjects group. Pearson's correlation coefficient was used followed by the multiple linear regression in order to adjust for the covariables

of age, gender and schooling. Furthermore, the association of the use of antipsychotics, background of substance use disorders and depressive disorders with the performance on the test was evaluated by covariance analysis (ANCOVA), using age, gender and schooling as covariables.

To establish if there were differences in the score on the succession of letters and numbers test between subjects with schizophrenia, their relatives and controls, a regression analysis of effects mixed with a non-structured covariance structure matrix was carried out. The following were used in this analysis: family as randomized effect, since the relatives are not independent; the group (schizophrenia vs relative vs control) as fixed effect; the research site (Bogotá *vs* Medellín), age, gender and schooling as covariables, and score on the SLN as dependent variable. Prior to the analysis, it was evaluated if there were interactions of the "group" variable with each one of the covariables and no significance was found. Bonferroni correction was used to compare the pairs. In addition, in order to evaluate effect size in the differences by pairs, Cohen's D was calculated, dividing the difference between the adjusted means by the weighted standard deviation. This was calculated using the number of persons and standard error of each group.[35] It was considered a negligible effect when it was less than 0.15, small between 0.15 and 0,40, median between 0.40 and 0.75, large between 0.75 and 1.10, very large between 1.10 and 1.45 and extremely large when greater than 1.45.

To establish the effect that the symptoms could have on the differences between groups with the SLN scores, a new regression analysis of mixed effects was carried out. This was similar to that described in the previous paragraph, but adding the scores of the SANS and "disorganization" to the covariables.

A significance level of 0.05 was used for all the tests.

RESULTS

A total of 197 subjects with schizophrenia and one of their first degree relatives participated: 105 with one of their siblings and 92 with one of their parents. The demographic and clinical characteristics can be seen in table 1. There was a greater proportion of men and history of substance abuse or dependence in the schizophrenia subjects group. In the relatives group, there was a slightly higher frequency of background of previous depressive episodes was found. Furthermore, significant differences were found in age and schooling among the three groups. Age was higher in the relatives and lower in the controls, and the latter had more schooling. Regarding the symptoms evaluated with the SANS and SAPS scales, as was expected, the score was higher in the subjects with schizophrenia than in the relatives and controls.

The average score on the SLN was slightly greater in men than in women without statistically significant differences [7.63 (SD=3.39) *vs* 7.19 (SD=2.84), t=-1.74, p=0.08]. In addition, a statistically significant correlation was found in the SLN score with age (r=-0.42; p<0.0001) and schooling (r=0.59; p<0.0001). There were no differences in the averages of the scores on the test between those having a background of substance abuse and those who did not [7.16 (SD=3.05) *vs* 7.47 (SD=3.14); t=0.98, p=0.33], or between those who had backgrounds of major depressive episodes and those who did not [7.61 (SD=3.01) *vs* 7.36 (SD=3.15); t=-0.74, p=0.46].

Clinical characteristics of subjects with schizophrenia or performance on the SLN

Within the group of subjects with schizophrenia, 14 were not taking antipsychotics. It was observed that there were differences on the SLN score between the subjects who did and did not take antipsychotics [7.36 (SD=2.87) *vs* 5.78 (SD=2.66); (t=2.13, p=0.03]. However, this difference was no longer statistically significant when adjusted by age and schooling (F_1=1.20, p=0.27).

In the bivariate analysis, a statistically significant association was observed between the score on SLN and duration of the schizophrenia (r =-0.27, β=-0.07, t=-3.98, p<0.0001). However, when adjusting for age, gender and schooling, the association was no longer significant (β=-0.02, t=-0.92, p=0.36).

With the negative symptoms, measured with the SANS scale, a statistically significant association was found in the bivariate analysis with the score on the SLN (r=-0.26, β=-0.03, t=-3.69, p<0.0001). This association continued to be significant after adjusting for age, gender and schooling (β=-0.02, t=-2.45, p=0.01). Something similar occurred with the disorganized symptoms: in the bivariate analysis, a significant association was observed with SLN (r=-0.24, β=-0.08, t=-3.48, p=0.001). This to be significant after adjusting for age, gender and schooling (β=-0.06, t=-2.93, p=0.004). Regarding the "hallucinations and delusions" symptoms, no association was found with the score on the SLN (r=-0.03, β=-0.006, t=-0.44, p=0.66).

Performance on the SLN test in subjects with schizophrenia, their relatives and controls

The means and standard deviations in the scores of the SLN were: 5.89 (SD=2.69) in subjects with schizophrenia, 6.99 (SD=2.72) in relatives and 9.3 (SD=2.93) in controls. Table 2 shows that the subjects with schizophrenia had significantly lower performance than the controls and relatives. In addition, the effect sizes were large for both, although greater in comparison to the controls. Furthermore, the controls have better performance than the relatives but the effect size was small. This was observed after adjusting for the covariables which, in this analysis, demonstrated that they were

Table 2 Score on the Succession of Letters and Numbers test in subjects with schizophrenia, their first degree relatives and controls

	Group		Control *vs* Schizophrenia			Relative *vs* schizophrenia			Control *vs* relative		
	Statistics	P Value	Difference of means (95% CI)	P Value	Effect size§	Difference of means (95% CI)	P Value	Effect size	Difference of means (95% CI)	P Value	Effect size
Without adjusting for negative and disorganized symptoms*	$F_{2;458}$=78.48	<0.0001	2.78 (2.21-3.34)	< 0.0001	1.18	1.82 (1.26-2.38)	< 0.0001	0.75	0.96 (0.30-1.61)	0.003	0.38
Adjusted for negative and disorganized symptoms**	$F_{2;520}$=12.42	<0.0001	1.72 (0.85-2.59)	< 0.0001	0.56	0.81 (-0.03-1.64)	0.06	0.26	0.91 (0.27-1.56)	0.002	0.33

* Results based on mixed effects regression analysis that included family as a random effect; the group as fixed effect, and age, schooling and site as covariables. Bonferroni's correction was performed for the paired comparisons.
** Results based on mixed effects regression analysis that included family as a random effect; the group as fixed effect, and age, schooling, site, negative and disorganization symptoms as covariables. Bonferroni's correction was performed for the paired comparisons.
§ Effect size was calculated with Cohen's D, dividing the different of means by weighted standard deviation. It was considered negligible effect when it was less than 0.15, small between 0.15 and 0,40, median between 0.40 and 0.75, large between 0.75 and 1.10, very large between 1.10 and 1.45 and extremely large when greater than 1.45.

significantly associated with the score on the SLN: age ($F_{1;587}$=55.27, p<0.001), schooling ($F_{1;561}$=165.02, p<0.0001) and site ($F_{1;432}$=8.13, p=0.005). The gender variable did not have a significant effect on the score. The interactions between the "group" variable and each one of the covariables also did not have a significant effect on the score.

Effect of the symptoms on the differences in scores between subjects with schizophrenia, their relatives and controls

When covariables "negative symptoms" given by the scores on the SANS and "hallucinations and delusions" and "disorganization" of the SAPS were added to the regression analysis of mixed effects, they did not show an effect on the score in the performance of the test ($F_{1;503}$=0.04, p=0.84), but they did so in "disorganization" ($F_{1;535}$=4.49, p=0.03) and "negative symptoms" ($F_{1;512}$=7.56, p<0.0001). Previously, it was shown that there was no significant interaction of the group with the SANS ($F_{2;506}$=0.49, p=0.61) and "disorganization" ($F_{2;532}$=0.73, p=0.48). It was observed that significant differences continued to exist among the three groups, but the effect size decreased. Between the controls and subjects with schizophrenia, there was a median effect size and a small effect between the latter and their relatives. The effect size of the differences between relatives in controls was small and similar to that found in the first analysis (Table 2).

DISCUSSION

It was observed that patients diagnosed with schizophrenia perform worse on the SLN then their unaffected relatives and the healthy controls of the community. These differences are independent of gender, age, schooling and negative and disorganized symptoms. Thus, it can be stated that verbal working memory is related with the disorder in question and fulfills the first necessary characteristic to be an endophenotype. Other studies have demonstrated the deficit in verbal working memory and have added that performance is worse when manipulation of the information is evaluated and when the burden is progressively increased.[12,13] This probably reflects the dysfunction of the frontal system, medial, temporal and diencephalic regions that have been proposed as part of the pathophysiological bases of schizophrenia.[36]

In this study, it was also observed that performance on the SLN was less in first degree relatives of patients with schizophrenia than in the healthy controls of the community, although the effect size was small. The greater discrepancy initially observed between relatives and healthy controls decreased after adjusting by age, schooling, and negative and disorganized symptoms, which are related with performance. This is coherent with the results found in other studies that also use manipulation tests.[16-18] However, in the other studies, except for that of de Horan et al., the effect sizes were greater. These discrepancies could be explained by the characteristics per se of the control and relatives of each

one of the studies and because the lack of independence between the members of the same family was not taken into account in the analysis. The small effect size does not rule out working memory as an endophenotype because it is likely that there are persons with and without the deficit in the relative group. Furthermore, when an average is obtained for the performance of all of them, the differences with the general population are clinically unimportant. This statement is supported by the findings of previous studies. These previous studies have demonstrated that the percentage of relatives whose performance is less than one standard deviation of the mean is between 15 to 38%.[37] In addition, the research that has demonstrated that inheritability of verbal working memory is between 36 and 42% and the functional magnetic resonance investigations that have shown increases in right prefrontal cortex activity with working memory test in unaffected relatives of subjects with schizophrenia support the fact that this neurocognitive function can be considered an endophenotype. I

Regarding the relation of verbal working memory with schizophrenia symptoms, we have observed that hallucinations and delusions do not show a correlation with performance on the test, this being coherent with other studies.[16,24] However, we have observed that when performance is lower on the SLN, the score is higher for "negative symptoms" and for "disorganization." However, the magnitude of this correlation was low. The association with negative symptoms has also been found by several authors that these authors explain by the relation that these symptoms and working memory have with prefrontal function.[17,20-22] The correlation of verbal working memory with "disorganization" has also been observed in other studies. However, it has not been found that it has a significant effect on the differences observed in cognitive characteristics between subjects with schizophrenia and healthy controls.[24] Nonetheless, we observed that both negative as well as disorganized symptoms had an effect on the differences in score on the SLN. When adjusting for them, we observed that individuals with schizophrenia and their relatives continued showing significantly worse performance than the performance of the controls on the working memory test, although the difference was minor. This indicates that in spite of the influence of the symptoms, working memory deficits has some independence from them. This also supports that this is an endophenotype.

It was not observed that performance on the SLN would be affected by onset age of the disorder. This agrees with the results of other studies that have shown that onset age does not have a significant effect on working memory, even after adjusting for age, gender, chronicity and number of affected relatives.[41] The duration of the disorder seemed to be associated with performance on the SLN. However, this association disappeared when adjusting for age, gender and schooling. This indicates that these variables explained the association. It was also observed that performance on this test was not altered by previous history of depression or psychoactive substance consumption and that it seemed to be independent of the use of medications. This is consistent with functional neuroimaging studies that have found deficit in working memory in patients who have never taken antipsychotic medications.[42,43]

The great heterogeneity in the duration of the schizophrenia in the subjects included could be a limitation of the present study. This makes it difficult to establish to what degree the findings are due to deterioration because the disorder or to cumulative effects of the antipsychotics. However, some studies have not found differences between chronic and first episode patients and low performance on the verbal working memory tests.[44] Another limitation is that in spite of not finding differences between persons who either took or did not take antipsychotics, the possibility that the deficit may have been influenced by the dose and type of antipsychotic cannot be completely ruled out.

CONCLUSION

This study suggests that verbal working memory evaluated with the SLN fulfills the following criteria to be considered an endophenotype of schizophrenia: 1) Performance is lower in subjects with schizophrenia and their relatives than in the controls of the community. 2) The differences between the groups continue to be observed after adjusting for the presence of negative and disorganized symptoms, which affects the performance on the SLN. 3) Within the group of subjects with schizophrenia, performance does not seem to be altered by onset age, duration of the disorder, use of antipsychotic medications, and history of depressive episodes or psychoactive substance use disorders.

CONFLICT OF INTERESTS

None of the authors has a conflict of interest in the subject presented in the article.

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