## Original

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# An explanatory model of quality of life in schizophrenia: the role of processing speed and negative symptoms

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**Introduction.** Improving the quality of life of patients with schizophrenia is a major goal in managing this devastating disorder, but agreement is lacking about the factors that predict quality of life (QoL) over the course of the disorder.

**Methods.** We examined 165 hospitalized patients with schizophrenia in this study. We included measures for psychiatric (PANSS, insight and affective symptoms) and cognitive symptoms. Confirmatory factor analysis established a cognitive structure composed of the following six factors: attention, processing speed, verbal memory, fluency, working memory and executive functioning. Quality of life was assessed using the Heinrichs-Hanlon-Carpenter Scale.

**Results.** Age, duration of illness, presence of more severe negative symptoms and most cognitive factors correlated significantly with QoL indicators. Regression analysis showed that processing speed (PS) was by far the most important cognitive factor that predicted QoL. Moreover, the interaction between PS and negative symptoms, patient age and executive functions modified the effect of PS on QoL. Finally, positive symptoms and other socio-demographic data were not related to QoL in the current study.

**Conclusions.** Our findings suggest that PS and negative symptoms predict QoL in schizophrenia.

Key words:
Schizophrenia, Quality of life, Neurocognition, Processing Speed, Symptomatology, Confirmatory factor analysis

## Un modelo explicativo de la calidad de vida en la esquizofrenia: el papel de la velocidad de procesamiento y los síntomas negativos

**Introducción.** Mejorar la calidad de vida de los pacientes con esquizofrenia es un objetivo fundamental en una enfermedad que resulta devastadora, pero no hay acuerdo sobre qué factores predicen la calidad de vida (CV) en el curso de la enfermedad.

**Metodología.** En el presente estudio se examinaron a 165 pacientes hospitalizados con esquizofrenia. Se incluyeron medidas de síntomas psiquiátricos (PANSS, insight y síntomas afectivos) y cognitivas. Un análisis factorial confirmatorio estableció una estructura cognitiva compuesta de seis factores, que incluyen atención, velocidad de procesamiento, memoria verbal, fluidez, memoria de trabajo y funciones ejecutivas. La calidad de vida fue medida mediante la Escala de Calidad de Vida de Heinrichs-Hanlon-Carpenter.

**Resultados.** La edad, tiempo de duración de la enfermedad, mayor gravedad de síntomas negativos y la mayoría de factores cognitivos correlacionaron significativamente con los indicadores de CV. Los análisis de regresión mostraron que, muy por encima de los demás factores cognitivos, la velocidad de procesamiento (VP) es un importante predictor de la CV. Además, la interacción de la VP con los síntomas negativos, la edad del paciente y el nivel de deterioro en funciones ejecutivas modificaron el efecto de la VP sobre la CV. Finalmente, los síntomas positivos y otros datos socio-demográficos no guardaron relación con la CV en nuestro estudio.

**Conclusiones.** Nuestros hallazgos sugieren que la VP y los síntomas negativos predicen la CV en la esquizofrenia.

Palabras Clave:
Esquizofrenia, Calidad de Vida, Neurocognición, Velocidad de Procesamiento, Sintomatología, Análisis Factorial Confirmatorio

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## INTRODUCTION

The fact that patients with schizophrenia have impaired quality of life (QoL) has been widely documented.[1–3]

Improving the QoL of patients with this devastating disease is the ultimate goal of any intervention or therapy used in the management of the condition. In order to facilitate effective intervention to improve patient QoL, it is necessary to know what factors determine QoL in this disease. However, most of the recent literature on schizophrenia focuses on the prediction of functionality. Fewer studies include measures of QoL and/or an examination of the role of QoL in relation to the rest of the disease variables.

Aside from psychopathology, neurocognitive deficits contribute to the functional disability and impaired QoL,[2] including occupational capacity[4] and social status.[5, 6] Although the relation between some of the disease variables and QoL has been described in the literature, the pattern of interaction between the different factors and the specific contribution of each alteration to QoL remain to be clarified. Some authors have reported a relation between QoL and clinical variables such as general psychopathology,[7, 8] affective state,[9] negative symptoms and, to a lesser extent, positive symptoms.[10, 11] While there have been some negative findings,[2, 12, 13] most of these studies have described significant associations between clinical symptoms, generally the severity of negative symptoms, and QoL. In contrast, some recent studies have highlighted the central role of positive symptoms in the prediction of functionality and QoL.[14] Nonetheless, in a recent meta-analysis[15] it is suggested that the relationship between clinical symptoms and QoL is only modest. Therefore, other factors must be sought to explain the QoL in this population. However, the role of other variables, such as insight,[16, 17, 18] type of drug therapy,[19, 20] or occupational situation,[21] have not helped to significantly increase the variance.

On the other hand, patients with schizophrenia have a cognitive impairment ranging from 1 to 2 standard deviations below the mean in most of the samples studied.[22, 23-26] This deterioration can increase up to 3 standard deviations in the case of samples with chronic disease or older age.[27] Whereas the relation between cognition and functionality has been replicated repeatedly, the relation between cognition and QoL is more controversial.[28] Some of the studies that have examined the relation between cognitive deficit and QoL have confirmed that cognition contributes significantly to explaining QoL both objectively and subjectively,[2, 13, 28-30] while others have not found a positive relation between these variables.[7, 8, 31] One of the cognitive domains that has been related most consistently to QoL in the published literature[28] is processing speed (PS). While other cognitive abilities were related or not with QoL depending on the study, PS was positively related to QoL in schizophrenia in all the studies that measured the component.[15] Processing speed (PS) is defined as the parameter of the time needed to carry out a cognitive activity, both mental and psychomotor. Our group,[32, 33] among other authors, has found that this parameter is the best predictor of the functional capacity of patients with schizophrenia.[32-36] However, it is a cross-sectional skill common to all mental activity, so it is difficult to find other cognitive capacities that do not require PS to a greater or lesser degree. Thus, characterizing the specific contribution of each cognitive domain of PS separately would help to better understand the interactions between cognitive skills as well as their specific weight in the prediction of QoL in schizophrenia.

Finally, there are few studies in the literature in which the influence of cognitive symptoms and clinical symptoms and sociodemographic factors have been examined simultaneously.[13, 37] The team of Ritsner[37, 38] analyzed the role of socio-demographic variables, including age, sex and educational level, on QoL, along with clinical and cognitive factors. The authors concluded that better performance on executive function tasks, attention, memory and motor skill tasks was significantly associated with a higher QoL score, regardless of the sociodemographic characteristics of the sample and other disease-related factors. However, Sota and Heinrichs[13] found that cognitive performance in executive functions and memory predicted QoL in a sample of patients with chronic schizophrenia, but in this case, accompanied by sociodemographic variables, age and sex. Clinical symptoms, whether positive or negative, did not contribute significantly to explaining the variance in their sample.

Due to these contradictory findings, our team decided to study the predictive capacity of sociodemographic variables, clinical and cognitive, on the QoL of a sample of patients with chronic schizophrenia. To do this, an attempt was made to work with a confirmatory factor analysis (CFA) method to prevent the impact of the weight of each cognitive domain on performance in a single test and, at the same time, to work on a factorial structure of cognition as recommended by MATRICS.[39] Finally, we attempted to analyze the interaction between all the factors, particularly the cognitive domains, to isolate the specific contribution of the processing speed variable on the rest of the cognitive and clinical domains and the QoL.

## METHOD

### Sample

One hundred sixty-five patients hospitalized in the Psychiatric Hospital of Alava (HPA) who met the study inclusion criteria were recruited: 1) diagnosis of schizophrenia according to DSM-IV TR criteria based on a clinical interview with the patient's usual psychiatrist, 2) age range 18 to 65, 3) no current diagnosis of substance abuse according to DMV-IV TR criteria.[40] At the time of inclusion, all the patients were being treated with atypical antipsychotics.

The exclusion criteria included prior history of significant alteration of consciousness, mental retardation, absence of

| Table 1 | Sociodemographic, clinical and cognitive characteristics of patients with schizophrenia and their correlation with Quality of Life | | |
|---|---|---|---|
| | | Descriptive | Correlation with QoL |
| | | Mean + SD | Pearson R |
| Age (years) | | 33.78 + 10.82 | -0.34** |
| Education (years) | | 9.40 + 3.03 | 0.13 |
| Sex (n:%) | | | |
| Men | | 138 (83.6%) | |
| Women | | 27 (16.4%) | |
| Age at onset | | 22.42+6.21 | -0.07 |
| Duration of disease (years) | | 13.44+9.09 | -0.37*** |
| Number of hospitalizations | | 9.51+7.18 | -0.15 |
| DSM-IV (n;%) | | | |
| Paranoid | | 123 (78.3%) | |
| Disorganized | | 13 (8.3%) | |
| Catatonic | | 8 (5.1%) | |
| Unspecified | | 13 (8.3%) | |
| PANSS-P | | 24.09+10.84 | -0.12 |
| PANSS-N | | 26.97+10.70 | -0.63*** |
| PANSS-G | | 49.63+14.71 | -0.15 |
| Depression | | 3.21+4.53 | -0.05 |
| Mania | | 6.78+11.30 | 0.20* |
| QoL | | 38.66+26.50 | |
| Processing speed | | | 0.51*** |
| Verbal memory | | | 0.34*** |
| Working memory | | | 0.28** |
| Verbal fluency | | | 0.24** |
| Executive functions | | | 0.21* |
| Attention | | | 0.19 |
| Vocabulary | | | 0.31** |

DSM-IV = The Diagnostic and Statistical Manual of Mental Disorders-IV; PANSS-P = Positive symptoms of the Positive and Negative Symptom Scale; PANSS-N = Negative symptoms of the Positive and Negative Symptom Scale; PANSS-G = General Psychopathology of the Positive and Negative Symptom Scale; Depression= Calgary Depression Scale; Mania = Young Mania Rating Scale; QoL = Quality of Life Scale.
The scores of the cognitive factors are not shown in the descriptive column because, as standardized measures, all have a mean of 0 and standard deviation of 1.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

development disorder or relevant neurological or endocrine condition (cerebrovascular accident, hypertension), or significant sensory deficits. The sociodemographic characteristics of the resulting sample are detailed in Table 1.

All participants were volunteers and written informed consent to participate in the study was obtained. The study protocol was approved by the Ethics Committee of Deusto University.

## Evaluation

### *Psychopathology measures*

All patients were evaluated by means of a clinical interview and the following instruments: Positive and Negative Symptom Scale (PANNS),[41] Spanish version,[42] Calgary Depression Scale,[43] David Insight scale,[44] Young Mania Rating Scale[45] and the Clinical Global Impression (CGI).[46] The inter-examiner reliability ratio for scales was established at a minimum Kappa of 0.80. At the end of the training period, the reliability values obtained were between 0.83 and 0.91.

### *Neuropsychological assessment*

The neuropsychological assessment was carried out by a neuropsychologist blind to the patients' scores for psychiatric symptoms and QoL. The neuropsychological assessment included the Brief Test of Attention (BTA),[47] verbal memory (logical memory of the Weschler Adult Intelligence Scale-III (WAIS-III),[48] executive functions (Wisconsin Card Sorting Test-CV64),[49] working memory (forward digits, backward digits, letter-number sequencing of the WAIS-III),[50] verbal fluency (phonological and semantic fluency),[51] and processing speed (Stroop Color Test,[52] digit-symbol coding of the WAIS-III and Trail-Making Test Part A).[53]

### *Quality of life (QoL)*

QoL was assessed using the Heinrichs-Hanlon-Carpenter Quality of Life Scale. This semistructured clinical interview includes 21 items evaluated on a Likert type scale from 0 to 6 points. On this scale, higher score reflects better quality of life. Some of the domains explored include: interpersonal and social relationships, intrapsychic functions and instrumental role.

## Data analysis

According to the literature, grouping cognitive scores by domains rather than the isolated scores on each test contributes to a better definition of the weight of cognition in relation to the rest of the variables. For this reason, confirmatory factorial analysis (CFA) was used to examine the relations between the observed variables and the underlying hypothesized constructs. The proposed 6-factor model included processing speed, attention, verbal memory, working memory, verbal fluency and executive functions. This model was compared with a monofactorial model and with 5-factor and 4-factor models proposed in the literature. The 5-factor model grouped the verbal fluency tasks in the processing speed factor, maintaining the rest of the factors.

The 4-factor model, in addition to grouping fluency in the processing speed factor, also grouped the working memory and verbal memory tasks into a single memory factor. Finally, the monofactorial model grouped all the tests into a single general cognitive factor similar to the g factor.

The effect of processing speed (PS) on QoL was determined by means of multivariate analysis. All the direct scores of the cognitive tests were transformed into Z scores to create composite cognitive areas. Those variables in which a higher score implies worse performance were inverted so that a high score meant better performance on all the neuropsychological tests.

The large number of factors that influence the QoL of patients according to the literature were collected as variables. Those variables that presented a significant bilateral correlation with QoL, significance being established in 0.05, were selected for the subsequent analyses (interaction and multiple regression analyses).

The significance of the set of interactions was then evaluated by means of a global significance test (Chunk Test) on the basis of the decrease of $R^2$ produced on estimating the maximum model without interactions. The significant interactions were selected and included in the model with the confounding variables that were considered influential in the previous step in order to obtain a more accurate estimate of the effect of processing speed on QoL. Multiple regression analyses were performed using the PASW statistical package for Windows (SPSS), version 15.0.

## RESULTS

### Confirmatory factorial analysis (CFA) of the cognitive structure

The goodness of fit statistics indicate that the monofactorial model (g model) does not fit the data observed for the sample ($\chi^2$=893.1; Chi-square/df=7.5; RMSEA=0.20; NNFI=0.63; CFI=0.68). Therefore, the single factor model is far from being an adequate latent structure that fits the data obtained. The 5-factor model, which combined fluency and processing speed, did not show adequate fit indices ($\chi^2$=115.9, $\chi^2$/df=2. 11, RMSEA 0.09, NNFI=0. 92, CFI=0.94). Finally, the 4-factor model (which included fluency and processing speed in a single factor and additionally combined verbal memory and working memory into a single factor) did not properly fit the data obtained ($\chi^2$=162.7, $\chi^2$/df=2.76, RMSEA=0.11, NNFI=0.89, CFI=0.91). Instead, the results indicate that the hypothetical 6-factor model yields a very good fit for the sample ($\chi^2$=95.6; Chi-square/df=1.2; RMSEA=0.04; NNFI=0.99; CFI=0.99). All the factorial loads were significant, indicating that the variables were loaded in the factor whose measurement was intended. Overall, the

majority of the tests showed high factorial loads on the respective factors, from -0.68 to 0.99. Finally, the mean factorial load for the complete sample was 0.83.

## Influence of PS on QoL

All the variables that correlated significantly with the dependent variable were selected to determine the influence of processing speed on QoL. These variables were: patient age, duration of disease, PANSS score on the negative symptom subscale, observed performance in fluency, verbal memory, working memory, executive functions and vocabulary (Table 1). The first step was to evaluate significance of the set of eight possible interactions of all these variables with PS. Addition of the set of interactions produced an increase in $R^2$ of 9.5%, which was significant (F=2.28; p=0.03), so the significance of each of the terms of interaction was determined and the statistically non-significant terms were removed from the model. According to this criterion, three interactions with PS were selected, age (p<0.02), negative symptoms (p<0.02) and executive functions (p<0.02), respectively.

Once the final model was determined and the confounding variables and interactions were selected, multiple regression analysis was performed to determine the influence of PS on QoL. The results of this analysis are shown in Table 2. The model explains 60% of the variability of the QoL in our sample and is globally significant (F=9.12; p<0.001). After controlling the confounding variables and taking into account the action of the variables that are modifying the effect of PS, it was evident that in the sample studied each unit of improvement in PS in the patients was accompanied by an average improvement in QoL of 49.11 points on the QoL scale (CI 95%: 20.13 to 78.08).

## The role of age, the severity of negative symptoms and the deterioration of executive functions in modifying the effect of PS on QoL.

The method followed to estimate the interaction between each of these three variables (age, severity of negative symptoms and severity of the deterioration of executive functions) was based on the method proposed by Figueiras, Domenech and Cadarso[37] applied to multiple regression using the PASW program. For each of the three estimates, three values were chosen: minimum, maximum and mean scores obtained by the sample on each of the scales studied. The results are presented in Table 3. The same phenomenon is reproduced with the three variables. There was a clear interaction between age, severity of negative symptoms and the severity of the deterioration of the executive functions with PS in relation to the effect of PS on QoL in schizophrenia. The effect of PS on improved QoL was

potentiated in patients who were younger (40.22 points), with no negative symptoms (43.22 points) or better executive function (71.68 points). Conversely, the positive effect of PS on QoL is attenuated in older patients (17.02 points), patients with extremely severe negative symptoms (15.03 points) and patients with more deteriorated executive functions (25.95 points). In every case, the size of the effect was up to three-fold greater when the minimum and maximum scores on the scales studied were compared. Nonetheless, it should be noted that this effect tended to disappear in older patients and in patients with a greater presence of negative symptoms. For more detail of these interactions, see Figure 1.

## CONCLUSIONS

The results obtained in this study confirm that QoL is associated with more than one disease factor in patients with schizophrenia. Our data are also consistent with the previous literature that demonstrates that neuropsychological impairment and negative symptoms are the best predictors of QoL in this pathology.[7, 55-58] However, the existence of complex interactions that need to be analyzed and explained is added.

In contrast with some previous studies,[14, 15] but consistent with other more recent studies,[2, 13, 28, 56, 59] the model that took into account patient age, educational level, and the severity of negative and cognitive symptoms explained 60% of the variance in QoL in our sample. In our case, the years of evolution of the disease also contributed significantly to the model, possibly because it was a chronic sample with a mean disease duration of 10 years.

As was hypothesized, PS had special relevance in the model. Responding in part to the question posed by Voruganti[60]
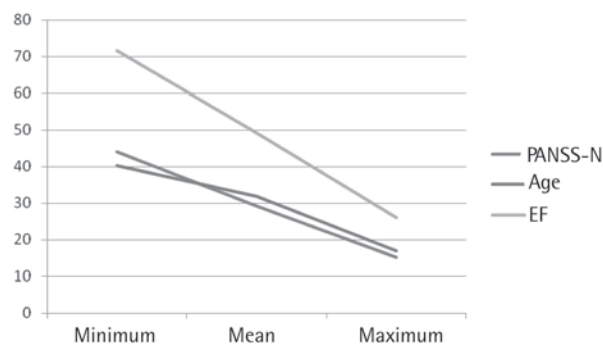


PANSS-N: Negative symptoms of the Positive and Negative Symptom Scale; EF = Executive Functions

| Figure 1 | Interaction between Processing Speed, Quality of Life, Negative Symptoms, Age and Executive Functions |

| Table 2 | Effect of Processing Speed on Quality of Life: multiple regression analysis. |
|---|---|

| Model | B | β | t | Sig. | Confidence interval of 95.0% for B | |
|---|---|---|---|---|---|---|
| PS | 49.10 | 1.39 | 3.37 | 0.001 | 20.13 | 78.08 |
| Age | –0.43 | –0.16 | –0.92 | 0.356 | –1.35 | 0.493 |
| Duration of disease | –0.26 | –0.08 | –0.55 | 0.579 | –1.19 | 0.67 |
| PANSS-N | –1.60 | –0.61 | –5.94 | 0.000 | –2.14 | –1.06 |
| Working memory | –0.70 | –0.02 | –0.19 | 0.843 | –7.75 | 6.34 |
| Verbal memory | 2.78 | 0.10 | 0.99 | 0.322 | –2.77 | 8.34 |
| Verbal fluency | –12.06 | –0.38 | –3.74 | 0.000 | –18.49 | –5.64 |
| Executive functions | –4.27 | –0.13 | –1.44 | 0.152 | –10.14 | 1.60 |
| Vocabulary | –0.07 | –0.03 | –0.23 | 0.812 | –0.69 | 0.54 |
| PSxAge | –0.49 | –0.58 | –1.51 | 0.135 | –1.14 | 0.15 |
| PSxPANSS-N | –0.74 | –0.62 | –2.18 | 0.032 | –1.41 | –0.06 |
| PSxEF | –11.75 | –0.28 | –2.40 | 0.019 | –21.51 | –2.00 |

Models' properties for predicting scores of Quality of Life: R2 = 0.77, F = 9.12, df = 12.73, P < 0.001.
PS = Processing speed; PANSS-N = Negative symptoms of the Positive and Negative Symptoms Scale; EF = Executive Functions; PSxAge = Processing Speed and Age Interaction Term; PSxPANSS-N = Processing Speed and Negative Symptoms Interaction Term; PSxEF = Processing Speed and Executive Functions Interaction Term

| Table 3 | Analysis of the Interaction between Processing Speed and the variable Age, Negative Symptoms and Executive Functions on Quality of Life in patients with schizophrenia |
|---|---|

| | Size of effect and 95% confidence intervals | | |
|---|---|---|---|
| PANSS-N values | Minimum=7 | Mean=26.97 | Maximum=46 |
| Size of effect | 43.92 (17.53-70.31) | 29.13 (6.02-52.23) | 15.03 (-11.76-41.81) |
| Age values | Minimum=18 | Mean=35.12 | Maximum=65 |
| Size of effect | 40.22 (18.28-62.17) | 31.77 (11.87-51.67) | 17.02 (-12.0-46.04) |
| EF values | Minimum=-1.92 | Mean=-0.0077 | Maximum=1.97 |
| Size of effect | 71.68 (28.96-114.40) | 49.20 (20.18-78.22) | 25.95 (2.33-49.57) |

Minimum = minimum score obtained in the study sample for each scale.
Mean = mean score obtained in the study sample for each scale.
Maximum = maximum score obtained in the study sample for each scale.
PANSS-N = Negative symptoms of the Positive and Negative Symptom Scale; EF = Executive Functions

regarding the most important cognitive functions in the improvement of social functioning, the results of our study showed that PS had a very important effect on QoL in schizophrenia, much more than the role of the rest of cognitive factors. Although all cognitive factors resulting from CFA except attention initially correlated with QoL, this effect disappeared in regression analysis once the weight of PS was considered. The absence of a relation between attention and QoL is not surprising because it was one of the main findings of the meta-analysis of Tolman et al. in 2010,[22] thus reaffirming that each cognitive factor can play a different role in the pathology. However, in this review the deterioration of the patients in terms of executive function was considered relevant for the prediction of QoL in most of the studies. In our CFA results, some tests that other researchers often labeled as executive functions (e.g. FAS), were grouped as an independent factor, causing the executive functions variable to lose its weight in the final regression model. Our results

also suggest that the analysis of correlation used in some previous studies has limitations and may overestimate the influence of some variables. When the data are analyzed with more detailed methodology, such as that offered by multiple regressions, the effect of some variables disappeared, allowing a more cautious approach to the data.

Another of the relevant findings of this study is the potentiating effect of the interaction of PS with other variables (patient age, severity of negative symptoms and severity of the deterioration of executive functions) on QoL. Patients with a greater presence of negative symptoms had a poorer QoL, regardless of their PS. However, in patients with few negative symptoms, the effect of PS on QoL tripled compared to the patients with the most severe negative symptoms. The relation between negative symptoms and PS seems to be very complex and is still far from being fully understood and explained. The same phenomenon repeats with age and the severity of the deterioration of executive functions. In younger patients and in patients with better preserved executive functions, the effect of greater processing speed on QoL tripled in magnitude in relation to older patients and patients with poorer executive function performance.

On the other hand, QoL was not associated with positive symptoms in our sample, confirming previous data suggesting a smaller contribution of positive symptoms to QoL.[7, 56] Our results were also inconsistent with those of Ristner[38] on the effects of socio-demographic variables on QoL, but confirmed the findings of Sota and Heinrichs[13] and the meta-analysis of Tolman et al.,[22] who emphasized the role of variables such as patient age for understanding the interactions between cognition, psychopathology and QoL. However, in our case the years of education completed by the patient did not modify the interaction model found.

Our results were clinically relevant. The influence of PS on QoL was of large magnitude: for each z-score unit of improvement in processing speed, QoL improved an average of 49 points. Although it is true that a unit of the z score (one standard deviation) is a lot when referring to PS, the magnitude of its effect on the QoL scale is surprising (the Heinrichs-Hanlon-Carpenter QoL scale), ranging from a minimum of 0 to a maximum of 126. If other studies confirm this finding, any intervention on PS, whether pharmacological or rehabilitative, can be expected to generate large benefits for the QoL of people with schizophrenia.

Another finding of great interest is the variation in the magnitude of this effect depending on the patient characteristics: in younger people, in people with very few negative symptoms and in people with less impairment of their executive functions, the effect of PS on QoL is even more evident. These findings allow us to predict that interventions on PS would be effective in any patient, but would be much more marked on the QoL of people with

these characteristics, for example, in patients suffering from their first psychotic episodes.

Once the role of neuropsychological deficits in QoL is recognized, we suggest that neuropsychological deficits be included in the routine assessment of patients with schizophrenia. It may yield useful information for predicting the future status of the patients and, as a result, help to establish treatment planning strategies. Consequently, cognitive rehabilitation programs might be added to complement new drug treatments. As proposed by the MATRICS initiative,[39] treatment strategies that enable cognitive improvement may be a particularly relevant and innovative contribution in the improvement of QoL in patients with schizophrenia. In fact, evidence of the effectiveness of cognitive rehabilitation programs in patients with schizophrenia has begun to be published, with benefits that are not limited to cognitive functioning, but also extend to overall function and clinical symptoms.[61] As cognitive and negative symptoms are differentially related to QoL, compared to positive symptoms, they could be understood as treatment objectives with specific intervention characteristics and needs.

Despite these interesting findings, our study had some limitations. Firstly, the model of latent cognitive structure differs slightly from the model proposed by the MATRICS initiative[39] and other studies, because our study incorporates the verbal fluency factor instead of visual memory. The solidity of the data that confirm the presence of verbal fluency as an independent factor in our sample supports the hypothesis of Szoke et al.[62] about the relevance of verbal fluency as possible endophenotypes of the disease. Secondly, the present study is cross-sectional. A longitudinal design is undoubtedly preferable in the literature, but in the context of current knowledge of the subject, cross-sectional studies help to understand the relations between such complex variables. Thirdly, only one QoL measure is included: the Heinrichs-Hanlon-Carpenter Quality of Life Scale,[54] a tool based on clinician criterion. It would have been ideal to have an additional subjective QoL measure to be able to contrast the information obtained with both types of instrument.

To summarize, a better understanding of the predictors and processes that underlie QoL will help to improve treatment in patients with schizophrenia, including drug treatment, cognitive rehabilitation and psychosocial interventions. Given that the predictors of the QoL differ in nature, we suggest interdisciplinary interventions to improve the QoL of both patients and their caregivers.

## REFERENCES

1. Saleem P, Olié JP, Loo H. Social functioning and quality of life in the schizophrenic patient: Advantages of amisulpride. Int Clin Psychopharmacol. 2002;17(1):1-8.

2. Alptekin K, Akvardar Y, Kivircik Akdede BB, Dumlu K, Isik D, Pirincci F, et al. Is quality of life associated with cognitive impairment in schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry. 2005 Feb;29(2):239-44.

3. Sweers K, De Schepper E, De Hert M. La capacidad de marcha está asociada a la calidad de vida (relacionada con la salud) y nivel de actividad física en pacientes con esquizofrenia: estudio preliminar. Actas Esp Psiquiatr. 2011;39(4):211-6.

4. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996;153(3):321-30.

5. Dickerson FB, Ringel NB, Parente F. Subjective quality of life in out-patients with schizophrenia: clinical and utilization correlates. Acta Psychiatr Scand. 1998 Aug;98(2):124-7.

6. Jones PB, Bebbington P, Foerster A, Lewis SW. Premorbid social underachievement in schizophrenia: Results from the Camberwell Collaborative Psychosis Study. British Journal of Psychiatry. 1993;162(1):65-71.

7. Heslegrave RJ, Awad AG, Voruganti LN. The influence of neurocognitive deficits and symptoms on quality of life in schizophrenia. J Psychiatry Neurosci. 1997 Jul;22(4):235-43.

8. Wegener S, Redoblado-Hodge MA, Lucas S, Fitzgerald D, Harris A, Brennan J. Relative contributions of psychiatric symptoms and neuropsychological functioning to quality of life in first-episode psychosis. Aust N Z J Psychiatry. 2005 Jun;39(6):487-92.

9. Tomida K, Takahashi N, Saito S, Maeno N, Iwamoto K, Yoshida K, et al. Relationship of psychopathological symptoms and cognitive function to subjective quality of life in patients with chronic schizophrenia. Psychiatry Clin Neurosci. 2010 02;64(1):62-9.

10. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: A 2.5 year follow-up study. Schizophr Res. 2000 07;44(1):47-56.

11. Bow-Thomas CC, Velligan DI, Miller AL, Olsen J. Predicting quality of life from symptomatology in schizophrenia at exacerbation and stabilization. Psychiatry Res. 1999 May 31;86(2):131-42.

12. Hansson L, Middelboe T, Merinder L, Bjarnason O, Bengtsson-Tops A, Nilsson L, et al. Predictors of subjective quality of life in schizophrenic patients living in the community. A Nordic multicentre study. Int J Soc Psychiatry. 1999 Winter;45(4):247-58.

13. Sota TL, Heinrichs RW. Demographic, clinical, and neurocognitive predictors of quality of life in schizophrenia patients receiving conventional neuroleptics. Compr Psychiatry. 2004 Sep-Oct;45(5):415-21.

14. Wittorf A, Wiedemann G, Buchkremer G, Klingberg S. Prediction of community outcome in schizophrenia 1 year after discharge from inpatient treatment. Eur Arch Psychiatry Clin Neurosci. 2008 02;258(1):48-58.

15. Eack SM, Newhill CE. Psychiatric symptoms and quality of life in schizophrenia: A meta-analysis. Schizophr Bull. 2007 09;33(5):1225-37.

16. Segarra Echebarría R, Ojeda dP, Zabala Rabadán A, García Ormaza J, Peña Lasa J, Eguíluz Uruchurtu I, et al. Insight in first episode psychosis. Conceptual and clinical considerations. The European Journal of Psychiatry. 2010 04;24(2):78-86.

17. Nakamae T, Kitabayashi Y, Okamura A, Shibata K, Iwahashi S, Naka F, et al. Insight and quality of life in long-term hospitalized Japanese patients with chronic schizophrenia. Psychiatry Clin Neurosci. 2010 Aug;64(4):372-6.

18. Rocca P, Castagna F, Mongini T, Montemagni C, Bogetto F. Relative contributions of psychotic symptoms and insight to quality of life in stable schizophrenia. Psychiatry Res. 2010 15;177(1-2):71-6.

19. Nuss P, Tessier C. Antipsychotic medication, functional outcome and quality of life in schizophrenia: Focus on amisulpride. Curr Med Res Opin. 2010;26(4):787-801.

20. Puschner B, Angermeyer MC, Leese M, Thornicroft G, Schene A, Kikkert M, et al. Course of adherence to medication and quality of life in people with schizophrenia. Psychiatry Res. 2009 Feb 28;165(3):224-33.

21. Priebe S, Reininghaus U, McCabe R, Burns T, Eklund M, Hansson L, et al. Factors influencing subjective quality of life in patients with schizophrenia and other mental disorders: A pooled analysis. Schizophr Res. 2010 08;121(1-3):251-8.

22. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. Neuropsychology 1998 07;12(3):426-45.

23. Ojeda N, Sanchez P, Pena J, Elizagarate E, Yoller AB, Larumbe J, et al. Verbal fluency in schizophrenia: does cognitive performance reflect the same underlying mechanisms in patients and healthy controls? J Nerv Ment Dis. 2010 Apr;198(4):286-91.

24. Peña J, Ojeda N, Segarra R, Eguiluz JI, García J, Gutiérrez M. Executive functioning correctly classified diagnoses in patients with first-episode psychosis: Evidence from a 2-year longitudinal study. Schizophr Res. 2011 03;126(1-3):77-80.

25. Simões do Couto F, Queiroz C, Barbosa T, Ferreira L, Firmino H, Viseu M, et al. Caracterización clínica y terapéutica de un muestreo portugués de pacientes con esquizofrenia. Actas Esp Psiquiatr. 2011;39(3):147-54.

26. Sánchez P, Ojeda N, Elizagárate E, Peña J, Ballesteros J, Yoller AB, et al. Déficit atencionales y respuesta al tratamiento farmacológico en pacientes con esquizofrenia resistente al tratamiento: Resultados mediante análisis factorial confirmatorio. Revista de Psiquiatría y Salud Mental. 2010 6;3(2):40-9.

27. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, et al. Neuropsychology of first-episode schizophrenia: Initial characterization and clinical correlates. Am J Psychiatry. 2000;157(4):549-59.

28. Tolman AW, Kurtz MM. Neurocognitive Predictors of Objective and Subjective Quality of Life in Individuals With Schizophrenia: A Meta-Analytic Investigation. Schizophr Bull. 2010 Jul 11.

29. Aksaray G, Oflu S, Kaptanoglu C, Bal C. Neurocognitive deficits and quality of life in outpatients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2002 Oct;26(6):1217-9.

30. Matsui M, Sumiyoshi T, Arai H, Higuchi Y, Kurachi M. Cognitive functioning related to quality of life in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jan;32(1):280-7.

31. Hofer A, Baumgartner S, Bodner T, Edlinger M, Hummer M, Kemmler G, et al. Patient outcomes in schizophrenia II: The impact of cognition. European Psychiatry. 2005 08;20(5-6):395-402.

32. Sánchez P, Ojeda N, Peña J, Elizagárate E, Yoller AB, Gutiérrez M, et al. Predictors of longitudinal changes in schizophrenia: The role of processing speed. J Clin Psychiatry. 2009;70(6):888-96.

33. Ojeda N, Peña J, Sánchez P, Elizagárate E, Ezcurra J. Processing speed mediates the relationship between verbal memory, verbal fluency, and functional outcome in chronic schizophrenia. Schizophr Res. 2008 04;101(1):225-33.

34. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry. 2007;64(5):532-42.

35. Gold JM, Goldberg RW, McNary SW, Dixon LB, Lehman AF. Cognitive correlates of job tenure among patients with severe mental illness. Am J Psychiatry. 2002;159(8):1395-402.

36. Rodriguez-Sanchez JM, Crespo-Facorro B, Gonzalez-Blanch C, Perez-Iglesias R, Vazquez-Barquero JL, PAFIP Group Study. Cognitive dysfunction in first-episode psychosis: the processing speed hypothesis. Br J Psychiatry Suppl 2007 Dec;51:s107-10.

37. Ritsner MS. Predicting quality of life impairment in chronic schizophrenia from cognitive variables. Qual Life Res. 2007 Aug;16(6):929-37.

38. Ritsner MS, Blumenkrantz H. Predicting domain-specific insight of schizophrenia patients from symptomatology, multiple neurocognitive functions, and personality related traits. Psychiatry Res. 2007;149(1):59-69.

39. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res. 2004 12;72(1):29-39.

40. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th, text revision ed. Washington, DC: American Psychiatric Association; 2000.

41. Kay SR, Flszbein A, Opfer LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull. 1987;13(2):261-76.

42. Peralta Martín V, Cuesta Zorita MJ. Validación de la escala de los síndromes positivo y negativo (PANSS) en una muestra de esquizofrénicos españoles. Actas Luso Esp Neurol Psiquiatr Cienc Afines. 1994 07;22(4):171-7.

43. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res. 1990 07;3(4):247-51.

44. David AS. Insight and psychosis. British Journal of Psychiatry. 1990 06;156:798-808.

45. Colom F, Vieta E, Martinez-Arán A, García-García M, Reinares M, Torrent C, et al. Versión española de una escala de evaluación de la manía. Validez y fiabilidad de la escala Young. Medicina Clinica. 2002;119:366-71.

46. Guy W. CGI: Clinical Global Impressions. Manual for the ECDEU Assessment Battery. Chevy Chase: National Institute of Mental Health; 1970.

47. Schretlen DJ. Brief test of attention. Odessa, FL.: Psychological Assessment Resources; 1996.

48. Wechsler D. The Wechsler Memory Scale-Revised. New York: Psychological Corporation; 1987.

49. Heaton RK, Chelune GJ, Talley JL, Talley JL, Kay GG, Curtiss G. Wisconsin card sorting test. Revised and expanded. Odessa, FL: Psychological Assessment Resources; 1993.

50. Wechsler D. WAIS-III Manual: Wechsler Adult Intelligence Scale-III. New York: Psychological Corporation; 1997.

51. Peña-Casanova J. Programa integrado de exploración neuropsicológica. Manual. Barcelona: Masson; 1990.

52. Golden CJ. Stroop color and word test: A manual for clinical and experimental uses. Chicago: Stoelting Co; 1978.

53. Reitan R, Wolfson D. The Haldstead-Reitan Neuropsychological Test Battery. Tucson: Neuropsychology Press; 1985.

54. Heinrichs DW, Hanlon TE, Carpenter WT,Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984;10(3):388-98.

55. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. Am J Psychiatry. 1998 Sep;155(9):1196-201.

56. Savilla K, Kettler L, Galletly C. Relationships between cognitive deficits, symptoms and quality of life in schizophrenia. Aust N Z J Psychiatry. 2008 Jun;42(6):496-504.

57. Ojeda N, Sánchez P, Elizagárate E, Yoller AB, Ezcurra J, Ramírez I, et al. Course of cognitive symptoms in schizophrenia: a review of the literature. Actas Esp Psiquiatr. 2007;35(4):263-70.

58. Haro JM, Ciudad A, Alonso J, Bousoño M, Suárez D, Novick D, et al. Remisión y recaída en el tratamiento ambulatorio de los pacientes con esquizofrenia. Resultados a 3 años. Actas Esp Psiquiatr. 2008 ;36(4):187-96.

59. Herman M. Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. Int J Ment Health Nurs. 2004 Dec;13(4):282-91.

60. Voruganti LP, Awad AG, Parker G, Forrest C, Usmani Y, Fernando ML, et al. Cognition, functioning and quality of life in schizophrenia treatment: results of a one-year randomized controlled trial of olanzapine and quetiapine. Schizophr Res. 2007 Nov;96(1-3):146-55.

61. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry. 2007 Dec;164(12):1791-802.

62. Szöke A, Trandafir A, Dupont M, Méary A, Schürhoff F, Leboyer M. Longitudinal studies of cognition in schizophrenia: Meta-analysis. British Journal of Psychiatry. 2008;192(4):248-57.