Predictors of Longitudinal Changes in Schizophrenia: The Role of Processing Speed

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Background: The main objective was to identify variables that predict functional disability in chronic schizophrenia over time.

Method: We examined 95 hospitalized patients with schizophrenia (DSM-IV criteria) in a long-stage unit and 53 healthy controls (matched for age, gender, and years of education). Neuropsychological battery included tests for verbal memory, working memory, executive functioning, and processing speed. Functional disability was assessed at 6-month follow-up with the Disability Assessment Schedule after the neuropsychological and clinical assessment. The study was conducted from September 2005 to July 2008.

Results: Patient performance was significantly lower than that of the healthy comparison subjects on all neurocognitive variables ($p < .001$). Most, but not all, neurocognitive measures were significantly correlated with the patients' functional disability shown 6 months after admission to the study, including self-care management, vocational outcome, family contact, and social functioning. Results suggest that processing speed has a significant influence in these relationships.

Conclusions: Processing speed plays an outstanding role in the relationship between neurocognitive symptoms and self-care, vocational outcome, and social functioning. Our data support the possibility of processing speed as the best longitudinal predictor of the level of autonomy in patients with chronic schizophrenia.

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Poor functional outcome in patients with schizophrenia is a core characteristic of the disease, and its public sector costs are high.[1] Several studies have shown that positive symptoms are weakly associated with functional outcome.[2,3] Although some studies have nevertheless shown negative results,[4–6] negative symptoms have been found more often to be significantly related to poor functional performance.[2,7,8] Additionally, some authors suggest that negative symptoms and neurocognitive deficits are unrelated domains and predict functional outcome independently in schizophrenia.[9,10]

There is accumulating evidence that neurocognitive abilities predict functional outcome.[9,11–14] More specifically, Dickerson et al.[15] found that verbal memory and verbal fluency predicted changes in social and community outcome. Bryson and Bell[4] described the relationship between verbal memory, executive functioning, and significant improvement in work performance. In a similar way, Jaeger et al.[6] observed that verbal fluency, attention, and verbal memory predicted work and school performance and independent living skills, even after controlling for negative symptoms. Daily problem-solving skills have also been found to depend on verbal memory abilities, verbal fluency, and processing speed.[13,16] On the other hand, some studies have demonstrated processing speed to be strongly related to verbal memory[17,18] in chronic schizophrenia.

The parameters in functional outcomes that have generated a higher volume of literature include social and community functioning, work-school outcome, independent living skills, and daily problem solving. The relevance of identifying determinants or predictors for functional capability in patients with schizophrenia is evident due to the clinical, financial, and quality-of-life impact. In a recent study, Bowie et al.[19] described brilliantly the relationship between cognitive domains, symptoms, depression, and different functional outcomes. Their data suggested that attention and working memory are both related to work skills and executive functioning is related to interpersonal behaviors, whereas processing speed is associated with both outcome domains. Nevertheless, the authors did not consider processing speed to have a possible mediator effect

among additional cognitive variables and specific functional outcomes in the illness.[19]

Considering previous literature and the recent increasing relevance provided to processing speed in schizophrenia,[14,20] we hypothesized that processing speed could play a differential mediating role between the cognitive domains (verbal memory, working memory, and executive functioning) and functional disability over time and has predictive power over functional disability parameters in chronic schizophrenia. That is to say, the association among cognitive domains (verbal memory, working memory, and executive functioning) and resulting functional disability (self-care management, family contact, vocational outcome, and social functioning) could be at least partially attributed to the mediating effect of processing speed.

Therefore, we analyzed first the role played by verbal memory, working memory, and executive functioning in specific disability domains such as self-care management, family contact, vocational outcome, and social functioning. Second, we explored the possible interaction between processing speed and other cognitive domains (verbal memory, verbal fluency, working memory, and executive functioning) as predictors of specific functional abilities observed in schizophrenia.

METHOD

Participants

Ninety-five patients hospitalized in a long-stage unit were recruited from the Psychiatric Hospital of Alava, Vitoria, Spain. Subjects met diagnostic criteria for schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) using the Structured Clinical Interview for DSM-IV.[21] After admission, clinical interview by the psychiatrist and psychologist was used to evaluate the level of collaboration and effort at the assessment protocol. All patients were taking antipsychotic medication at the time of recruitment. The patients ranged in age from 18 to 65 years. The mean time since first diagnosis was 14.03 (SD = 9.01) years. Exclusion criteria included previous history of lack of consciousness (> 1 hour), mental retardation, relevant neurologic condition including cerebrovascular disease, hypertension, and significant sensorial deficits.

In the 10 days after admission, all participants underwent a general medical evaluation and cognitive assessment described here. Patients additionally completed psychiatric interview and psychiatric evaluation including Positive and Negative Syndrome Scale,[22] Brief Psychiatric Rating Scale,[23] Calgary Depression Scale,[24] and Young Mania Rating Scale.[25] Psychiatrists who carried out the psychiatric evaluation were blind to the neuropsychological results.

Fifty-three healthy control participants were recruited and screened to rule out past or current history of severe psychiatric disorder, medical conditions relevant to the central nervous system, or significant sensorial deficits. Patients and controls did not significantly differ in age ($t = -0.69$, $p = .49$), gender distribution ($\chi^2 = 0.92$, $p = .34$), or years of education ($t = 0.89$, $p = .43$).

All subjects were voluntary and gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee at the Health Department (Vitoria, Spain). The study was conducted from September 2005 to July 2008.

Measures

The same neuropsychologist performed the cognitive evaluation for both groups. The assessment included tests of verbal memory, executive functioning, working memory, and processing speed. The 4 cognitive domains were obtained as follows: verbal memory was acquired from performance on the Logical Memory I & II section of the Wechsler Memory Scale-Revised.[26] Wisconsin Card Sorting Test-CV64[27] results were considered as executive functioning measures, while working memory included Letter and Number Sequencing and Digits Backward from the Wechsler Adult Intelligence Scale-III[28] (WAIS-III). For the processing speed index, measures included Stroop Color and Word Test,[29] Digit Symbol Substitution Test from WAIS-III,[28] and Trail Making Test-Part A.[30] We made composite scores with the tests described above for the 4 domains (verbal fluency, verbal memory, working memory, and processing speed).

All cognitive measures were converted to z scores on the basis of the mean and standard deviation of the control group, and the sign of some measures was adjusted so that higher scores indicated better neurocognitive performance. The internal consistency of these composite scores was very high: processing speed (Cronbach's $\alpha = .94$), executive functioning ($\alpha = .98$), working memory ($\alpha = .92$), and verbal memory ($\alpha = .98$).

Functional disability was assessed by a psychiatrist blind to neuropsychological results at 6-month follow-up after clinical and neuropsychological assessment using the Disability Assessment Schedule[31] (DAS-WHO). The DAS-WHO offers indicators of functional disability in 4 characterized domains: self-care management, social functioning, vocational outcome, and family contact. The DAS-WHO is a Likert-type scale; scores range from 0 (no disability) to 5 (maximum). A score of 1 means there is already a degree of disability. As the scale has 4 items, 20 is the maximum disability possible. Every score above 12 is usually interpreted in the literature as severe functional impairment.

Data Analyses

Normality of data was tested with the Kolmogorov-Smirnov test. All scales created resembled the normal distribution. The χ^2 test was used to analyze any differences

Table 1. Demographics, Cognitive Profiles, and Clinical Characteristics by Group[a]

Variable	Schizophrenia Patients (N = 95)	Healthy Control Group (N = 53)	Test of Group Differences	p	Effect Size, η^2
Age, mean ± SD, y	35.75 ± 10.46	34.45 ± 11.88	t = –0.69	.49	
Education, mean ± SD, y	10.40 ± 2.95	10.75 ± 1.86	t = 0.89	.43	
Gender, N (%)			χ^2 = 0.92	.34	
Male	78 (82.1)	40 (75.5)			
Female	17 (17.9)	13 (24.5)			
Executive functioning score, mean ± SD	–1.23 ± 1.43		F = 51.57	< .001	0.28
Verbal memory score, mean ± SD	–1.53 ± 0.84		F = 87.29	< .001	0.40
Working memory score, mean ± SD	–1.22 ± 0.99		F = 52.52	< .001	0.29
Processing speed score, mean ± SD	–2.17 ± 1.49		F = 106.10	< .001	0.45
Time since diagnosis, mean ± SD, y	14.03 ± 9.01				
Age at onset, mean ± SD, y	21.74 ± 5.93				
DSM-IV diagnosis, N (%)					
Paranoid	74 (77.9)				
Disorganized	7 (7.4)				
Catatonic	4 (4.2)				
Nonspecified	10 (10.5)				
BPRS total score, mean ± SD	27.02 ± 11.58				
PANSS-Positive score, mean ± SD	24.27 ± 10.68				
PANSS-Negative score, mean ± SD	27.52 ± 10.79				
PANSS-General Psychopathology score, mean ± SD	49.58 ± 14.43				
Calgary Depression Scale score, mean ± SD	3.29 ± 4.17				
Young Mania Rating Scale score, mean ± SD	5.61 ± 9.89				
DAS-WHO score, mean ± SD	13.25 ± 4.15				
Self-care management	2.12 ± 1.55				
Vocational outcome	3.54 ± 1.55				
Family contact	3.38 ± 1.32				
Social functioning	3.62 ± 1.55				

[a]Cognitive measures were converted into z scores on the basis of the mean and standard deviation of the control group. Internal consistency of these composite scores was very high: processing speed (Cronbach's α = .94), executive functioning (α = .98), working memory (α = .92), and verbal memory (α = .98).

Abbreviations: BPRS = Brief Psychiatric Rating Scale, DAS-WHO = Disability Assessment Schedule, PANSS = Positive and Negative Syndrome Scale.

between the 2 groups for gender, and t tests were used for age and years of education. Multivariate analysis of variance was used as the primary test of group differences, with group as a between-subjects factor and the neuropsychological scales as dependent variables. Data were analyzed using Pearson product moment correlations and multiple regressions in order to determine the relationships among variables.

To test the hypothesis that processing speed mediates the effect of predictor variables (verbal memory, executive functioning, and working memory) on functional disability, we followed previously published and recommended criteria.[32–34] In a first step, the predictors (executive functioning, verbal memory, and working memory) must be significantly associated with functional disability. In the second step, predictors must be significantly associated with the potential mediating variable, in our case, processing speed. In the third step, the mediator (processing speed) must be related to the outcome variable (functional disability).

The final step is to show that the strength of the association between predictors and functional disability is significantly reduced when the mediator is added to the model. If perfect mediation is obtained, the predictor effect will become zero, showing that processing speed fully mediates the relation. If the path between the predictors (verbal memory, executive functioning, and working memory) and functional disability remains significant, it suggests that the processing speed variable is a partial mediator. Separate analyses were performed with executive functioning, verbal memory, and working memory as predictor variables. The significance level was set at .05. All tests were 2-tailed.

RESULTS

Differences Between Patients With Schizophrenia and the Control Group

As expected, patients performed worse in all cognitive domains compared to controls. The most impaired domain in the patient group was processing speed (η^2 = 0.45), followed by verbal memory (η^2 = 0.40). These results, as well as demographics and characteristics of the samples, are described in Table 1.

Correlations Between Neurocognition and Functional Outcome

As measured by the DAS-WHO, the level of disability in our sample was severe (mean ± SD = 13.25 ± 4.15). The most impaired area was social functioning

Table 2. Correlations Between Neurocognitive Measures and Disability Domains in Chronic Schizophrenia Patients

Measure	Self-Care Management	Vocational Outcome	Family Contact	Social Functioning	DAS-WHO
Processing speed	–0.39[a]	–0.39[a]	–0.35[b]	–0.46[a]	–0.45[a]
Working memory	–0.28[b]	–0.30[b]	–0.36[a]	–0.21[c]	–0.41[a]
Verbal memory	–0.28[b]	–0.42[a]	–0.12[d]	–0.34[a]	–0.31[b]
Executive functioning	–0.10[d]	–0.23[c]	0.03[d]	–0.12[d]	–0.20[c]

[a]$p < .001$.
[b]$p < .01$.
[c]$p < .05$.
[d]Nonsignificant.
Abbreviation: DAS-WHO = Disability Assessment Schedule.

(3.62 ± 1.55), followed by vocational outcome (3.54 ± 1.55) and family contact (3.38 ± 1.32), as indicated in Table 1.

As described in Table 2, performance on cognitive domains was significantly correlated with both the total score on the DAS-WHO and all 4 specific domains of functional disability (self-care management, vocational outcome, family contact, and social functioning). On the other hand, results of these correlations indicated that processing speed and working memory were significantly related to all 4 functional disability domains (self-care management, social functioning, vocational outcome, and family contact). Similarly, verbal memory was significantly correlated with most domains except family contact. Surprisingly, however, executive functioning showed a significant relationship with vocational outcome ($r = –0.23$) but not with the other outcome dimensions analyzed. Therefore, regarding executive functioning, further mediation analysis was only possible for vocational outcome.

Tests of Processing Speed Mediation

Tests of mediation were conducted separately for the 4 dimensions of functional disability: self-care management, vocational outcome, family contact, and social functioning.

Test of processing speed mediation for verbal memory and working memory on the DAS-WHO: self-care management. Table 3 shows the results of the analyses for self-care management. In the first step, verbal memory significantly predicted self-care management. In the second step, the potential mediator (processing speed) was regressed on verbal memory to estimate the path between verbal memory and processing speed. In the third stage, processing speed predicted self-care management. Finally, verbal memory and processing speed were entered simultaneously in the equation as predictor variables. At this point, the regression coefficient was significant, showing that processing speed could act as a mediator between verbal memory and self-care management.

Sobel's equation was used to further clarify the significance of the mediating pathway.[35] The result of this test was significant at $p < .05$ for processing speed ($z = –2.06$), suggesting full mediation. The unstandardized regression coefficient for verbal memory on self-care management decreased from –0.54 to –0.26 in the third step. The same procedure was used to test whether processing speed accounted for working memory differences on self-care management. The result of this test was significant at $p < .05$ for processing speed ($z = –2.18$), suggesting full mediation.

Test of processing speed mediation for verbal memory, executive functioning, and working memory on the DAS-WHO: vocational outcome. Table 4 shows the results of the analyses for vocational outcome. Sobel's equation for verbal memory was significant at $p < .05$ for processing speed ($z = –2.06$). This was a partial mediation because the path between verbal memory and vocational outcome remained significant. In the case of executive functioning, a test of significance of the mediating pathway showed that processing speed accounted for the influence of executive functioning on vocational outcome ($z = –2.50$ and $p < .01$), meaning a full mediation. In the case of working memory, processing speed also appeared as a full mediator. Sobel's equation for verbal memory was significant at $p < .05$ for processing speed ($z = –2.28$).

Test of processing speed mediation for working memory on the DAS-WHO: family contact. The path between processing speed and family contact was not significant in the fourth step, when the potential mediator (processing speed) and the predictor (working memory) were entered simultaneously in the regression ($p = .11$), so no mediating effect was found.

Test of processing speed mediation for verbal memory and working memory on the DAS-WHO: social functioning. The same procedure was used to test whether processing speed accounted for verbal memory and working memory differences on social functioning. The results are shown in Table 5. Sobel's equation for verbal memory was significant at $p < .01$ for processing speed ($z = –3.01$). The results for working memory showed that processing speed acted as a mediator, and Sobel's equation was significant at $p < .01$ ($z = –2.86$). All mediation analyses for social functioning suggested full mediation as shown in Table 5.

DISCUSSION

As expected, our patients with schizophrenia showed severe impairment in all cognitive measures when compared to controls matched for age, gender, and years of education (showing large effect sizes according to

Table 3. Regression Analyses Testing Processing Speed Mediation of Verbal Memory and Working Memory on Self-Care Management

					Statistic			
Predictor Variable	B	SE	β	t	R^2	F	df	Criterion Variable
Verbal Memory								
Step 1					0.08	6.99	1,90[a]	
Verbal memory	–0.54	0.20	–0.28	–2.64[a]				Self-care[b]
Step 2					0.22	21.92	1,90[c]	
Verbal memory	0.49	0.10	0.46	4.68[c]				Processing speed
Step 3					0.10	9.26	1,90[a]	
Processing speed	–0.62	0.20	–0.32	–3.04[a]				Self-care
Step 4					0.19	9.69	1,90[a]	
Verbal memory	–0.26	0.22	–0.14	–1.19[d]				Self-care
Processing speed	–0.50	0.23	–0.26	–2.16[e]				Self-care
Working Memory								
Step 1					0.08	6.88	1,90[a]	
Working memory	–0.51	0.19	–0.275	–2.62[a]				Self-care
Step 2					0.34	42.70	1,90[c]	
Working memory	0.51	0.08	0.58	6.54[c]				Processing speed
Step 3					0.10	9.26	1,90[a]	
Processing speed	–0.62	0.20	–0.32	–3.04[a]				Self-care
Step 4					0.13	5.65	1,90[a]	
Working memory	–0.16	0.24	–0.08	–0.67[d]				Self-care
Processing speed	–0.61	0.26	–0.29	–2.29[e]				Self-care

[a] $p < .01$.
[b] Self-care management from the Disability Assessment Schedule.
[c] $p < .001$.
[d] Nonsignificant.
[e] $p < .05$.

Cohen's criteria).[36] Consistent with previous literature,[20,37] performance in processing speed index was the more severely impaired cognitive domain, followed by verbal memory. Our data indicate that most cognitive measures were related to the functional outcome domains after 6 months' admission to the study. Results obtained support our initial hypothesis: processing speed acts as a pathway through which verbal memory, executive functioning, and working memory predict the course of patients' functional ability over time. These results reveal a pattern of relationships that is mostly consistent with previous findings,[12,16,38] in which authors described some, but not all, of these associations in their samples.

In our study, the relationship between self-care management and verbal memory was consistent with our mediation hypothesis. The relevance of this finding is strong considering the increasing literature supporting the relationship between verbal memory and functional outcomes in schizophrenia. Holthausen et al.[18] reported that both processing speed and semantic organization were associated with verbal memory efficiency in schizophrenia. However, the specific pattern of prediction or mediation for functional outcome was not analyzed in this study. Although measures of processing speed were administered to the outpatient sample, the authors found only a very limited relationship between processing speed and the need for rehabilitation.[18] Despite the initially expected predictive value of verbal memory,[12] in our study, once processing speed was entered in the model, significance of verbal memory disappeared completely.

The relationship between self-care management and working memory was also consistent with full mediation by processing speed in our sample, and, therefore, our results question past literature supporting the relationship between activities of daily living and working memory. One major finding by Dickerson et al.[15] was an inverse relationship between perseverative errors in the Wisconsin Card Sorting Test and scores on a scale of self-care management in a sample of 72 outpatients with schizophrenia over a 2-year follow-up period. That is to say, a lower ability to keep track of the test was inversely related to improvement in patients' self-care abilities.[15] There are other studies reporting the link between self-care management and working memory.[16,19] However, none of them have further analyzed processing speed in their samples and therefore the possible mediation effect.

Vocational outcome showed a slightly differential pattern of interaction with verbal memory, with processing speed only partially mediating the relationship between variables. The potential value of cognition as predictor of vocational outcome in competitive employment was also reported by Holthausen et al.[39] Similarly, this group found a very limited effect of processing speed influencing the relation with vocational outcome. Additionally, our results are consistent with our hypothesis of full mediating effect for both working memory and executive functioning.

Table 4. Regression Analyses Testing Processing Speed Mediation of Verbal Memory, Working Memory, and Executive Functioning on Vocational Outcome

Predictor Variable	B	SE	β	t	Statistic R^2	F	df	Criterion Variable
Verbal Memory								
Step 1					0.17	17.66	1,90[a]	
Verbal memory	–0.76	0.18	–0.42	–4.20[a]				Vocational[b]
Step 2					0.22	21.92	1,90[a]	
Verbal memory	0.49	0.10	0.46	4.68[a]				Processing speed
Step 3					0.13	12.66	1,90[a]	
Processing speed	–0.67	0.19	–0.36	–3.56[a]				Vocational
Step 4					0.21	10.70	1,90[a]	
Verbal memory	–0.54	0.20	–0.30	–2.64[c]				Vocational
Processing speed	–0.45	0.22	–0.54	–2.14[d]				Vocational
Working Memory								
Step 1					0.09	8.35	1,90[c]	
Working memory	–0.58	0.20	–0.30	–2.89[c]				Vocational
Step 2					0.34	42.70	1,90[a]	
Working memory	0.51	0.08	0.58	6.54[a]				Processing speed
Step 3					0.13	12.66	1,90[a]	
Processing speed	–0.67	0.19	–0.36	–3.56[a]				Vocational
Step 4					0.14	6.93	1,90[c]	
Working memory	–0.22	0.24	–0.12	–0.93[e]				Vocational
Processing speed	–0.66	0.27	–0.30	–2.40[d]				Vocational
Executive Functioning								
Step 1					0.05	4.93	1,90[d]	
Executive functioning	–0.38	0.17	–0.23	–2.22[d]				Vocational
Step 2					0.14	13.75	1,90[a]	
Executive functioning	0.32	0.08	0.38	3.71[a]				Processing speed
Step 3					0.13	12.66	1,90[a]	
Processing speed	–0.67	0.19	–0.36	–3.56[a]				Vocational
Step 4					0.15	7.00	1,90[c]	
Executive functioning	–0.20	0.18	–0.12	–1.13[e]				Vocational
Processing speed	–0.60	0.21	–0.32	–2.87 [c]				Vocational

[a]$p < .001$.
[b]Vocational outcome from the Disability Assessment Schedule.
[c]$p < .01$.
[d]$p < .05$.
[e]Nonsignificant.

These results are consistent with Gold et al.,[40] who emphasized that the total number of hours worked by patients in a supervised job was related to a variable labeled as attention.

Bowie et al.[19] found similar findings with working memory having both a direct and indirect effect on work skills through functional competence, while verbal memory and executive functioning had only an indirect effect on work skills through functional competence. Processing speed had a direct effect on overall work skills. The authors[19] entered all these cognitive domains together into the model, but they did not consider processing speed as a putative mediator through which working memory, executive functioning, and verbal memory could predict work skills as predicted in our data.

With regard to social functioning, processing speed appeared as a full mediator for cognitive measures that initially appeared as predictors (executive functioning did not predict this domain). The results suggest that when processing speed is considered in the analyses, the rest of the cognitive indicators lose great power of explanation on functional outcome. These results are compatible with McClure et al.,[41] who found in a sample of older patients that everyday living skills (including social functioning) were predicted by Trail Making Test-A (one of the processing speed measures used in our study), accounting for 17% of the variance, followed by verbal memory (6%) and Trail Making Test-B, often included as a measure of executive functioning (3%).

Both our[14] and McClure and colleagues' results[41] contrast with those of Revheim et al.,[13] who found that working memory was the cognitive variable that strongly predicted daily problem-solving skills. These differences could be partially explained by methodological issues such as the instrument to evaluate functional disability. These contributions may suggest again the need to

Table 5. Regression Analyses Testing Processing Speed Mediation of Verbal Memory and Working Memory on Social Functioning

Predictor Variable	B	SE	β	t	Statistic R^2	f	df	Criterion Variable
Verbal Memory								
Step 1					0.11	10.90	1,90[a]	
Verbal memory	–0.51	0.16	–0.34	–3.30[a]				Social[b]
Step 2					0.22	21.92	1,90[a]	
Verbal memory	0.49	0.10	0.46	4.68[a]				Processing speed
Step 3					0.18	18.24	1,90[a]	
Processing speed	–0.67	0.16	–0.42	–4.27[a]				Social
Step 4					0.22	11.14	1,90[a]	
Verbal memory	–0.26	0.17	–0.17	–1.52[c]				Social
Processing speed	–0.58	0.18	–0.37	–3.25[d]				Social
Working Memory								
Step 1					0.05	4.01	1,90[e]	
Working memory	–0.41	0.20	–0.21	–2.02[e]				Social
Step 2					0.34	42.70	1,90[a]	
Working memory	0.51	0.08	0.58	6.54[a]				Processing speed
Step 3					0.18	18.24	1,90[a]	
Processing speed	–0.67	0.16	–0.42	–4.27[a]				Social
Step 4					0.14	6.81	1,90[d]	
Working memory	–0.04	0.24	–0.02	–0.17[c]				Social
Processing speed	–0.83	0.27	–0.39	–3.10[d]				Social

[a]$p < .001$.
[b]Social functioning from the Disability Assessment Schedule.
[c]Nonsignificant.
[d]$p < .01$.
[e]$p < .05$.

revise recent cross-sectional studies that did not include processing speed measures in their analysis and concluded that cognitive domains predicted social functioning and interpersonal problem solving in patients with schizophrenia.[42–44]

Family contact was in the present study the functional outcome index that had the weakest relationship with neurocognition. Patients' family contact was related to processing speed and working memory but not to verbal memory and executive functioning. Additionally, processing speed did not contribute to explain deficits in this domain, not even the interaction with other variables. The lack of predictive value of most neurocognitive disorders on family contact is not surprising in our Spaniard culture, given the protected environment in which these relationships are displayed in contrast to social, community, and vocational functioning. In other words, the patient's family will be more tolerant to the patient's deficits due to their personal relationship (especially when behavior disorders are not present) than will people who are not relatives. Familial support usually acts as an ameliorator of the deficits when the patient with schizophrenia is living in the family home. Additionally, in our hospitalized sample, family contact is limited and filtered by the hospital structure. Most of our sample patients limit their contacts to telephone calls and visits from family members during the weekend.

Despite these interesting findings, there are some limitations in our study. It could be criticized that our data are based on patients with chronic disorder with a long course of illness and that the predicting effect could vary accordingly with the severity of the illness. Although there may be some characteristics specifically associated with the period of evolution in the illness, other authors[40,41] found similar results when samples were based on ambulatory (vs. hospitalized) patients with chronic schizophrenia.

Another limitation is related to the relationship between cognition and functional variables. In our case, a second evaluation was not performed on the patients at the 6-month follow-up period. Past literature has suggested the possible stability of cognitive symptoms for similar periods of follow-up.[45,46] Therefore, the relationship between cognition and functional outcome could be influenced by the stability of neurocognitive variables. It could also be suggested that the interaction among cognition and functional outcomes is partially based on common components of functioning shared by both abilities. Additionally, we should clarify that processing speed could act as a common underpinning mental ability, basic for most cognitive processes, and therefore could be easily related to other cognitive variables.

Our initial findings suggest that working memory, verbal memory, and (to a shorter extent) executive functioning all correlate significantly with measures of functional outcome. Deeper analyses through mediation clarify that only processing speed, and not the other 3 factors, predicts functional disability after 6 months in our sample. Whether this major finding is stressed by the common

underpinning component of processing speed on the rest of the cognitive variables remains unclear. This explanation could also be consistent with the common factor hypothesis suggested by previous literature.[47]

Finally, our study includes a short period of follow-up (6 months) for the assessment of functional outcome. Longer follow-up period data should clarify in the future if this predictive role is confirmed on changes over time with the course of illness. Moreover, considering the chronic profile and long period of time since first diagnosis, comparison with baseline at onset is not possible in our sample. Some previous literature[15] has suggested that patients' social functioning scores and their interactions with cognition remained stable over time, at least during a 2-year follow-up period. However, further analyses could contribute to clarify if the interactions are modified with aging or with significant clinical changes during longer follow-up periods.

Our data support recent suggestions in the literature of processing speed as a key measure in neuropsychological assessment in patients with schizophrenia.[17,20,39,41,48] The relevance of processing speed in the illness has more recently been hypothesized as a putative endophenotype for the disease.[20] We can infer from our data that processing speed is not simply a marker of schizophrenia related to cognitive and functional deficits. Processing speed is the strongest predictor of functional performance and furthermore indexes the degree of functional disability that results from the illness. The presence of this impairment in a premorbid and young high-risk group of patients would suggest that it may also serve as a predictor of illness. Our results also have implications for rehabilitation interventions, such as cognitive rehabilitation or new pharmacologic treatments targeting processing speed.

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