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Predicting real-world functioning in outpatients with schizophrenia: Role of inflammation and psychopathology

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ABSTRACT

Several studies indicate that negative and cognitive symptoms are determining factors of functioning in patients with schizophrenia. However, they do not usually include biological aspects, such as inflammatory markers. The current prospective study aims to identify clinical and biological factors predicting real-world functioning, at baseline and at one-year follow-up, of outpatients in an early stage of schizophrenia. Sample consist of 73 clinically stable patients with schizophrenia, of which 57 completed the one-year follow-up. Accurate psychopathology, functioning, and cognitive assessments were performed at baseline and follow-up (Positive and Negative Syndrome, Brief Negative Symptom, Calgary Depression, Personal and Social Performance Scales, and MATRICS Cognitive Consensus Battery). Biological biomarkers including anthropometric data and blood parameters were collected. Pearson correlation and multiple regression analyses including potential confounding factors were performed. Negative symptoms (especially asociality and avolition), along with the inflammatory biomarker interleukin-2, are the most important determining factors of poor real-world functioning in early-stage schizophrenia. The previous functioning, along with baseline cognitive performance in attention and vigilance, predicts functioning at one-year follow-up in these patients. Strategies aimed at improving negative and cognitive symptoms, as well as modifying certain inflammatory pathways, should be the targets to achieve functional recovery in the first years of schizophrenia.

1. Introduction

Schizophrenia is a serious, chronic, disabling disorder that causes deterioration in psychosocial functioning, including personal, social, and occupational areas. In fact, it represents the third leading cause of disability in young people under 45 years of age (WHO, 2011). Despite current treatments, 85% of patients still present some degree of impairment in their functionality (Wiersma et al., 2000), and it is known that clinical remission does not always lead to functional recovery (Bobes et al., 2009).

Disturbances in cognition are a core feature of the disorder (Green et al., 2019). Affected domains include the speed of processing, verbal learning and memory, visuospatial learning and memory, working memory, attention/vigilance, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004). Long-term memory and speed of processing are often marked as particularly deficient domains (Green et al., 2019).

Cognitive and negative symptoms have been described as the main clinical factors that determine the degree of functional impairment in these patients (Harvey, 2014a; Lahera et al., 2017; Strassnig et al., 2018). Cognitive deficits in schizophrenia, and particularly attention, working memory, executive function, and processing speed (Bowie et al., 2008), seem to have a greater impact on the residential and work functioning domains (Harvey, 2014b). Conversely, negative symptoms seem to have a greater impact on interpersonal and social functioning outcomes (Rocca et al., 2014). Also, Menendez-

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Miranda et al. (2015) found an association between negative dimensions and specific functional areas as relationships, self-care, and useful activities. However, among the negative symptoms, those related to motivation and pleasure, such as avolition, anhedonia, and asociality, seem to be the ones that have real negative consequences on functioning, while those related to expression, such as blunted affect, seem to have much less influence (Robertson et al., 2014; Rocca et al., 2014).

Depressive symptoms have also been suggested as factors related to worse real-world functioning in some studies (Strassnig et al., 2015), although others have reported a very weak relationship (Galderisi et al., 2014). On the other hand, positive symptoms may have an impact on specific areas such as self-care and aggressive behaviors (Menendez-Miranda et al., 2015), and recently the study by Rocca et al. (2018) concludes that conceptual disorganization is specifically the symptom with the greatest connection to real-world community-living activities.

Furthermore, a meta-analysis by Santesteban-Echarri et al. (2017) examined predictors of long-term functioning in patients with first-episode psychosis. These authors concluded that most cognitive variables, duration of untreated psychosis, and remission of positive and negative symptoms contribute to functional recovery, while other clinical, physical, and sociodemographic factors have little impact on functioning over time. However, these studies were carried out on patients with a wide spectrum of psychosis, including affective psychosis, and there is little data on predictors of long-term functionality in stable patients with an established diagnosis of schizophrenia.

Additionally, the presence of systemic inflammation has been related to worse levels of functioning in patients with first-episode psychosis and schizophrenia (García-Bueno et al., 2014; González-Blanco et al., 2018a). In a one-year follow-up study of patients with first-episode psychosis, improvements in the Global Assessment of Functioning scale (GAF) were associated with decreases in oxidative stress parameter levels (García-Bueno et al., 2014).

However, most studies examined only clinical and sociodemographic predictors of functioning, but did not examine biological variables, such as inflammatory markers, simultaneously.

1.1. Aims of the study

The aims of the current study were to explore determining factors of real-world functioning in stable outpatients during the first decade of schizophrenia, including both clinical and biological factors, and to determine predictors of functioning at one-year follow-up.

2. Methods

This is a naturalistic, prospective one-year follow-up study of outpatients with schizophrenia, consecutively recruited among those treated at community mental health facilities in Asturias, Spain. It consisted of a baseline assessment, including sociodemographic, clinical (psychopathology, cognition, level of functioning), and biological data, and a second evaluation at one-year follow-up (including psychopathology, cognition, and functioning). Written informed consent was obtained from all participants. The study was approved by the local Clinical Research Ethics Committee (Ref. 25/2014).

2.1. Sample

The sample consisted of 73 outpatients with a DSM-5 diagnosis of schizophrenia in their first 10 years of illness (18–45 years of age). They were clinically stable, defined as no changes in psychopharmacological treatment, relapses nor hospital admissions in the three months previous to the enrollment in the study. Exclusion criteria for all the participants were acute or chronic inflammatory comorbidities (fever, allergic or inflammatory processes, infections, autoimmunity disorders, or cancer), treatment with immunosuppressants or vaccines during the 6 months prior to enrollment, or treatment with anti-inflammatory drugs two days before blood collection. Also, a diagnosis of mental retardation or medical disorder that would affect cognitive functioning or the capacity to cooperate with assessment were exclusion criteria. Fifty-seven patients completed the one-year follow-up (78.1%), while 16 patients did not.

2.2. Assessment

All patients were assessed by semi-structured interview at inclusion in the study, and sociodemographic data, medical and psychiatric history, duration of illness, smoking history, and pharmacological treatment were collected.

2.2.1. Psychopathological and cognitive assessment

The psychopathological assessment, both at baseline and one-year follow-up, included the Spanish versions of the following scales: the Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994), the Calgary Depression Scale (CDS) (Sarro et al., 2004), and the Brief Negative Symptom Scale (BNSS) (Mane et al., 2014), which is organized into six subscales (anhedonia, distress, asociality, avolition, blunted affect, and alogia).

To explore cognitive performance, we employed the Spanish version of the MATRICS Consensus Cognitive Battery (MCCB), which evaluates seven cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Rodriguez-Jimenez et al., 2012). Cognitive evaluation at baseline was administered the same day or within the three days after the collection of blood sample. A second cognitive assessment was carried out at one-year follow-up, at the time of follow-up psychopathological assessment.

2.2.2. Functional assessment

We used the Personal and Social Performance Scale (PSP) to assess the level of global personal and social functioning, at baseline and one-year follow-up, specifically in the following four domains: (1) self-care, (2) useful activities including work and study, (3) personal and social relationships, and (4) disruptive and aggressive behaviors. Disability in each domain was scored using a six-point *Likert-type* scale (1 no disability to 6 very severe disability), and the overall score was obtained by applying an algorithm provided by the scale itself to the scores in the four domains, ranging from 1 (extremely poor functioning) to 100 (excellent functioning) (Garcia-Portilla et al., 2011).

2.2.3. Physical health and blood-based parameters

The biological assessment was performed at baseline, on the same day as the clinical evaluation, with collection of anthropometric data that allowed the body mass index (BMI; kg/m^2) and waist circumference (cm) to be obtained. Blood samples were collected in the morning by venipuncture after a confirmed overnight fast. Biochemistry tests including lipid profile, fasting glucose, uric, creatinine, insulin, prolactin, thyroid-stimulating hormone, C-reactive protein, and homocysteine were performed in the laboratory at *Hospital Universitario Central de Asturias*. Other blood samples were processed in the University of Oviedo laboratories of the Psychiatry and Cellular Response to Oxidative Stress Research Groups, to obtain oxidative stress biomarkers (percentage of hemolysis and lipid peroxidation subproducts) and an antioxidant biomarker (catalase activity in erythrocytes) using the techniques previously described in González-Blanco et al. (2018b). Additionally, cytokine concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-2, IL-1β, and IL-1 receptor antagonist were obtained (processing and measurement details in Gonzalez-Blanco et al. (2018a)).

2.3. Statistical analyses

The statistical analysis was performed using SPSS v.23.0. Bivariate

analyses, including *chi*-square tests and Student's *t*-tests for independent samples and Pearson correlations were first applied to explore the potential relationship between sociodemographic, clinical, and biological variables and functioning. Cytokines were log-transformed (ln), due to their irregular distribution, for the analyses. Student's *t*-test for repeated measures was used to test longitudinal changes. For multivariate analyses (stepwise linear multiple regression), as independent factors, we selected clinical and/or biological parameters statistically related to PSP scores, applying a Bonferroni correction for multiple comparisons (five tests; adjusted $p \leq 0.01$). Also, potential confounding factors selected from our analyses or based on the literature and expert criteria were entered as covariates. To analyze predictors of functioning, we repeated the same method using PSP scores assessed at one-year follow-up. Associations were considered statistically significant when $p \leq 0.01$ (Bonferroni correction for five tests).

3. Results

3.1. Sociodemographic, clinical, and biological characteristics

Participants, between 18 and 45 years of age, were mostly male (61.6%) and never married (80.9%). Most patients had been hospitalized at least once (74%) and about 20% had antecedents of suicidal behavior. Clinical characteristics, psychopharmacological treatment, and psychopathological, cognitive, and functional scores are detailed in Table 1. Mean concentrations of biological parameters that correlated with PSP scores are also presented in the table.

3.2. Baseline vs. one-year follow-up clinical differences

At one-year follow-up, patients showed improvements in PANSS total score [mean (SD); 59.3 (16.7) at baseline − 55.5 (16.0) at one-year follow-up], PANSS general psychopathology score [29.4 (8.7)–26.7 (8.0)], and BNSS blunted affect score [6.9 (6.9)–5.9 (6.9)], but there were no statistically significant differences in other psychopathological scores. Regarding cognitive performance, patient social cognition scores worsened, but processing speed scores improved (see Supplementary Material).

With respect to real-world functioning, a significant improvement was found only in the domain of self-care, with no statistical significance for other domains or total score (Table 2).

3.3. Determining factors of real-world functioning at baseline

Among sociodemographic factors, sex and education showed statistically significant associations with PSP scores. Women had higher mean PSP total scores (SD) than men [62.5 (17.1) vs. 53.0 (18.1); $t = -2.234$ ($p = 0.029$)]. Specifically, women performed better on useful activities [1.6 (1.3) vs. 2.6 (1.3); $t = -2.369$ ($p = 0.021$)], but no differences were found in other domains. Years of education also positively correlated with PSP [$r = 0.314$ ($p = 0.007$)].

Regarding psychopharmacological treatment, antipsychotic equivalent doses correlated with PSP total score [$r = -0.294$ ($p = 0.012$)], and scores on the self-care [$r = 0.249$ ($p = 0.034$)], useful activities [$r = 0.328$ ($p = 0.005$)], and relationships [$r = 0.279$ ($p = 0.017$)] domains. Diazepam equivalent doses correlated only with self-care functioning [$r = 0.310$ ($p = 0.008$)]. Furthermore, patients using antidepressants had lower PSP total scores [47.5 (12.7) vs. 59.2 (18.8); $t = -2.341$ ($p = 0.022$)] and showed worse functioning in self-care [2.0 (1.3) vs. 1.2 (1.1); $t = 2.458$ ($p = 0.016$)] and relationships [2.8 (0.8) vs. 1.9 (1.2); $t = 3.295$ ($p = 0.002$)].

Age, duration of illness, smoking, and BMI were not significantly associated with PSP scores; however, they were also used as covariates in regression analyses along with sex, years of education, chlorpromazine and diazepam equivalent doses, and use of antidepressants.

Simultaneously, we performed correlation analyses with Bonferroni corrections for multiple comparisons (five tests; adjusted $p \leq 0.01$) to select clinical and/or biological parameters related to PSP scores, and those were included as independent factors in multiple linear regression models (Table 3).

For PSP total score, we found statistically significant correlations with every psychopathological score and subscore (r from −0.717 to −0.378) and every cognitive domain of the MCCB (r from 0.420 to 0.347) except attention/vigilance and reasoning/problem solving. With respect to biological parameters, PSP negatively correlated with levels of IL-1beta ($r = -0.392$) and IL-2 ($r = -0.448$).

Regarding specific functional areas, self-care correlated with insulin ($r = 0.304$), LPO ($r = -0.324$) and IL-2 ($r = 0.389$); useful activities with triglycerides ($r = 0.297$) and IL-2 ($r = 0.393$); and relationships correlated with IL-1β levels ($r = 0.319$). On the other hand, at baseline, the aggressive behaviors domain did not significantly correlate with any of the peripheral biological parameters and only correlated with

Table 1
Demographic, clinical, and biological characteristics of patients at baseline ($N = 73$).

Mean age (SD)	31.7 (6.5)	PANSS [mean (SD)]	
Sex, males [n (%)]	45 (61.6%)	Positive	11.6 (4.8)
Marital status [n (%)]		Negative	17.6 (6.3)
Never married	59 (80.9%)	General	28.5 (8.3)
Married	9 (12.4%)	Total	57.7 (15.9)
Separated/divorced	5 (6.8%)	BNSS [mean (SD)]	
Education level [n (%)]		Anhedonia	6.9 (4.7)
Primary school	12 (16.4%)	Distress	1.2 (1.3)
Secondary school	25 (34.2%)	Asociality	4.2 (2.7)
Higher education	36 (49.3%)	Avolition	4.7 (2.7)
Years of education [mean (SD)]	15.3 (4.5)	Blunted affect	6.3 (6.9)
Work status [n (%)]		Alogia	3.0 (3.2)
Working	12 (16.4%)	Total	26.1 (15.1)
Not working	50 (68.5%)	CDS [mean (SD)]	2.7 (4.1)
Homemaker or student	11 (15.1%)	MCCB domains [mean (SD)]	
Tobacco users [n (%)]	36 (47.9%)	Processing speed	32.8 (11.8)
Cigarettes/day [mean (SD)]	18.3 (9.8)	Attention and vigilance	37.4 (12.6)
Length of illness, years [mean (SD)]	4.6 (3.4)	Working memory	41.8 (13)
Hospitalizations		Verbal learning	42.1 (10.8)
Yes [n (%)]	54 (74%)	Visual learning	39.6 (15.7)
Mean number (SD)	1.7 (2.0)	Reasoning and problem solving	35.9 (9.4)
Suicide attempts		Social cognition	50 (18.1)
Yes [n (%)]	14 (19.2%)	PSP [mean (SD)]	
		Self-care	1.4 (1.7)
BMI (kg/m^2) [mean (SD)]	28.2 (5.2)	Usual activities	2.1 (1.4)
Waist circumference (cm) [mean (SD)]	98.9 (18.5)	Relationships	2.1 (1.2)
Number of AP [n (%)]		Aggressive behaviors	0.2 (0.6)
0	5 (6.8%)	Total	56.6 (18.2)
1	51 (69.9%)	HDL (mg/dL) [mean (SD)]	48.2 (15.7)
>1	17 (23.3%)	Triglycerides (mg/dL) [mean (SD)]	123.1 (64.0)
Daily AP dose (mg) [mean (SD)]	475.1 (460)	Insulin (mg/dL) [mean (SD)]	15.8 (12.4)
BZ use [n (%)]	26 (35.6%)	Homocysteine (μmol/L) [mean (SD)]	12.1 (3.1)
Daily BZ dose (mg) [mean (SD)]	8.5 (18.4)	LPO (MDA nmol/g) [mean (SD)]	6075.4 (1350.4)
Antidepressant use [n (%)]	16 (21.9%)	IL-1β (pg/mL) [mean (SD)]	1.6 (2.9)
Mood stabilizer use [n (%)]	3 (4.1%)	IL-2 (pg/mL) [mean (SD)]	6.0 (6.9)

SD, standard deviation; BMI, body mass index; AP, antipsychotics; BZ, benzodiazepines; PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Syndrome Scale; CDS, Calgary Depression Scale; PSP, Personal and Social Performance Scale; MCCB, MATRICS Consensus Cognitive Battery; HDL, high-density lipoprotein; LPO, lipid peroxidation; IL, interleukin. Only biological parameters that correlated with PSP scores are included.

Table 2
Differences in real-world functioning over time.

	SZ baseline (n = 57) mean (SD)	SZ follow-up (n = 57) mean (SD)	Baseline vs. follow-up Paired Student's t (p)
PSP Total [1–100]	54.46 (18.43)	56.25 (18.85)	−1.397 *(0.168)*
Self-care [1–6]	**1.47 (1.24)**	**1.26 (1.19)**	2.695 *(0.009)*
Usual activities [1–6]	2.18 (1.39)	2.26 (1.33)	−0.778 *(0.440)*
Social relationships [1–6]	2.30 (1.18)	2.16 (1.21)	1.825 *(0.073)*
Aggressive behaviors [1–6]	0.18 (0.50)	0.12 (0.33)	0.772 *(0.443)*

PSP Total: better functioning represented by higher scores; domains: better functioning represented by lower scores.
SZ, schizophrenia; SD, standard deviation; PSP, Personal and Social Performance Scale.

Table 3
Linear regression models for predictors of real-world functioning at baseline (PSP total and domains).

	R^2	*dF*	*F*-value	*Beta*	*T*	Multicollinearity (VIF)
PSP Total						
Model	0.787	5	46.547**			
PANSS - General				−0.239	−3.110**	1.747
Asociality (BNSS)				−0.357	−4.863**	1.590
Avolition (BNSS)				−0.243	−2.100**	1.821
Blunted affect (BNSS)				−0.172	−2.579**	1.323
IL-2 (pg/mL)				−0.225	−3.610**	1.148
Self-care						
Model	0.592	3	29.004**			
PANSS - General				0.367	3.624**	1.505
Avolition (BNSS)				0.435	4.294**	1.512
Insulin (mg/dL)				0.262	3.169**	1.008
Useful activities						
Model	0.582	2	46.734**			
Avolition (BNSS)				0.684	8.291**	1.091
IL-2 (pg/mL)				0.192	2.330*	1.091
Relationships						
Model	0.731	3	58.736**			
PANSS - General				0.294	3.800**	1.448
Asociality (BNSS)				0.588	7.577**	1.452
Blunted affect (BNSS)				0.144	2.014*	1.236
Aggressive behaviors						
Model	0.352	2	18.990**			
PANSS - Positive				0.443	4.235**	1.183
Calgary Depression Scale				0.257	2.452*	1.183

Note: Statistical significance when $p \leq 0.01$.
* $p \leq 0.05$.
** $p \leq 0.01$. PSP, Personal and Social Performance Scale; PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Syndrome Scale; IL, interleukin; VIF, variance inflation factor.

PANSS-P (r = 0.544), PANSS-General (r = 0.474), and CDS (r = 0.431) scores. For detailed data, see Supplementary Material.

In the regression model, PSP total score was mainly associated with the BNSS asociality subscore, but also with its avolition and blunted affected subscores, the PANSS general psychopathology subscore, and IL-2 concentrations, accounting for 78.7% of variance. While asociality was the main symptom related to functioning in social and personal relationships, avolition was mainly associated with the self-care and useful activities domains. On the other hand, aggressive behaviors were predicted by the severity of PANSS positive symptoms. Among peripheral parameters, higher insulin concentrations were associated with worse self-care functionality. No covariate remained in the final model.

3.4. Predictive factors of real-world functioning at one-year follow-up

The second objective of this study was to determine clinical and/or biological factors at baseline that were predictors of functioning at one-year follow-up. We explored significant associations in bivariate analyses to select independent factors, and then we conducted multiple regression analyses, also including PSP total (or PSP domain) score at baseline as an independent variable along with the covariates previously used (age, sex, years of education, duration of illness, smoking, BMI, chlorpromazine and diazepam equivalent doses, and use of antidepressants).

For PSP total score at one-year, we found statistically significant correlations with every psychopathological baseline score (r = −0.364 to −0.694) except CDS score, and with every cognitive domain (r = 0.400 to 0.564) except reasoning and problem solving. With regard to baseline biological variables, a significant negative correlation was detected only with baseline IL-1 β level (r = −0.352).

On the other hand, at one-year follow-up, such specific PSP domains as self-care correlated with baseline homocysteine level (r = 0.357), useful activities with baseline HDL concentration (r = −0.360), and relationships with baseline IL-2 level (r = 0.352). Finally, the aggressive behaviors domain did not correlate with any of the baseline psychopathological variables and correlated only with baseline IL-2 level (r = 0.388). For detailed data, see Supplementary Material.

The regression model (Table 4) showed that baseline scores are the best predictors of real-world functioning at one-year follow-up, globally and for all functional domain scores except aggressive behavior. Furthermore, better baseline cognitive performance, specifically in the attention and vigilance domain, predicted better functioning in the domains of useful activities and relationships at one-year follow-up. Regarding sociodemographic factors, number of years of education predicted lower scores (better functioning) in useful activities including work and study. In addition, longer duration of illness predicted worse functioning in the relationships domain. Finally, the disruptive and aggressive behaviors domain was not predicted by any clinical or

Table 4
Linear regression models for predictors of real-world functioning at one-year follow-up (PSP total and domains).

	R^2	*dF*	*F*-value	*Beta*	*T*	Multicollinearity (VIF)
PSP Total						
Model	0.812	2	107.742**			
Baseline PSP Total				0.809	11.807**	1.246
Processing speed				0.176	2.565*	1.246
Self-care						
Model	0.826	3	106.578**			
Baseline Self-care				0.864	13.450**	1.065
Homocysteine (mg/dL)				0.140	2.179*	1.065
Useful activities						
Model	0.776	4	41.527**			
Baseline Useful activities				0.720	9.820**	1.152
Attention and vigilance				−0.396	−4.197**	1.975
Working memory				0.245	2.412*	2.202
Education (years)				−0.270	−3.672**	1.155
Relationships						
Model	0.857	4	71.959**			
Baseline Relationships				0.885	14.846**	1.192
Attention and vigilance				−0.296	−3.838**	1.998
Working memory				0.182	2.312*	2.092
Duration of illness (years)				0.164	2.952**	1.039
Aggressive behaviors						
Model	0.151	1	9.400**			
IL-2 (pg/mL)				0.388	3.066**	1.000

Note: Statistical significance when $p \leq 0.01$.
* $p \leq 0.05$.
** $p \leq 0.01$. PSP, Personal and Social Performance Scale; IL, interleukin; VIF, variance inflation factor.

sociodemographic factor, but only by the biomarker IL-2, accounting for 15% of variance.

4. Discussion

Our results show that negative symptoms, along with the inflammatory biomarker IL-2, are the main determining factors of poor real-world functioning in stable outpatients with established schizophrenia, even when cognition is considered. Furthermore, we found that previous functioning, already conditioned by negative symptoms, predicts functioning at one-year follow-up, along with baseline cognitive performance in attention and vigilance.

Negative symptoms related to motivation and pleasure, such as asociality and avolition, are key determinants of functional impairment in our sample, specifically in the domains of relationships, useful activities, and self-care, respectively. Several recent studies reported that reduced emotional experience (avolition and anhedonia) had the greatest impact on social functionality (Harvey et al., 2017a). In fact, avolition seems to be related to functional impairment in the interpersonal and work areas (Galderisi et al., 2018; Rocca et al., 2018), while symptoms such as disorganization and reduced emotional expression, as well as cognition mediated by functional capacity, seem to have greater impact on everyday life skills (Galderisi et al., 2018). Blunted affect is also a factor associated with global functioning in our sample, although with less impact. A meta-analysis by Najas-Garcia et al. (2018) concluded that neurocognition and mainly motivation strongly correlate with functional outcomes. Other studies considered neurocognition to be one of the most significant predictors of functionality (Bechi et al., 2017; Bosia et al., 2019). Bosia et al. (2019) reported that processing speed, which is considered the core deficit in schizophrenia, along with attention and working memory, have a major impact on functioning. Recent prospective studies concluded that negative and general symptoms mediated the effect of cognition on predicting functional outcomes (Ho et al., 2018; Simons et al., 2016). Furthermore, Strassnig et al. (2018) explained that cognitive deficits would have to be prominent to cause significant interference in global functioning, while the presence of minimal negative symptoms would already cause functional impairment (Harvey et al., 2018). Both hypotheses can explain our results.

While some authors found that subjective symptoms of depression in schizophrenia outpatients correlated with self-assessment of everyday functioning (Harvey et al., 2017b), others reported a very weak relationship between depression and functioning (Galderisi et al., 2014), in line with our findings. In our sample, only 12.3% exceeded the established cut-off point for clinical depression. We hypothesized that, unlike what occurs in other severe mental disorders such as bipolar disorder (Sole et al., 2018), subthreshold depressive symptoms do not seem to have as much influence on level of functioning in patients with schizophrenia or its effect is mediated by negative symptoms.

Regarding the predictors of real-world functioning at one-year follow-up, it is not surprising that baseline functioning is the major determinant, as negative symptoms were their main determinant. In addition, with respect to the cognitive aspect, what stands out is the impact of the attention and vigilance domain on social and occupational functioning. Another significant finding is that education level was related to functioning, at least in the domain of useful activities, as has been previously described (Bosia et al., 2019). Bucci et al. (2018) reported that worse academic and social premorbid adjustment were associated with real-life functional impairment and with cognitive impairment in schizophrenia. Furthermore, education, premorbid adjustment, and duration of active psychosis were significant predictors of functional recovery in patients with first-episode psychosis in a prospective study (Pelayo-Teran et al., 2018).

Still and all, studies analyzing the relationship between biological markers and functionality are scarce and inconclusive. Hope et al. (2013) reported poorer functioning related to IL-1 receptor antagonist and TNF receptor 1 levels. And recently, other authors have observed that social functioning is associated with increased cortisol response (Tas et al., 2018). We found that an inflammatory parameter, such as IL-2, seems to be a biomarker of poor real-world functioning. In this sense, we previously reported an association between this cytokine and greater severity of negative symptoms related to motivation and pleasure, as well as poorer functioning (González-Blanco et al., 2018a). Nevertheless, our current study shows that this association is independent of other clinical variables included in the regression analysis. In addition, our results indicate that increased insulin levels are

associated with worse functionality in self-care. This increase may reflect insulin resistance, associated in turn with metabolic syndrome. It seems obvious that poor functioning in health-related life habits is associated an increased risk of metabolic syndrome. Surprisingly, IL-2 at baseline may also constitute a biomarker that predicts aggressive behaviors at one-year follow-up, independently of previous functioning – a finding that merits further study.

Previous research about the determinants of functionality has not simultaneously addressed clinical and biological factors, including inflammatory markers. This consideration, together with the longitudinal design, are the key strengths of the current study. Nevertheless, one of the main limitations is the small sample size, especially with regard to the longitudinal phase. Also, the lack of measurement of biological markers at follow-up limits the ability to clarify the real implication of IL-2 in the pathophysiology of schizophrenia. In addition, as a naturalistic study, we did not control all factors during the one-year follow-up, such as changes in treatment or new physical comorbidities. Lastly, findings in the area of aggressive behaviors – a very different dimension from the others – warrant further research, since around 90% of sample had the minimum score in this domain, which could influence this result.

The present study suggests that negative symptoms, especially avolition and asociality, and the inflammatory parameter IL-2 are the main factors related to poor functioning, and that, at one-year follow-up, baseline functioning is the major determinant of this. As clinicians, intensive work is essential to achieve functional recovery in the first years of schizophrenia, especially knowing that poor functioning in self-care may contribute to an increased risk of metabolic syndrome and therefore increased morbimortality in these patients. That is why we must be cognizant that the path to functional recovery goes through improvement of negative symptoms and regulation of inflammatory pathways. Although there are no treatments that have shown proven efficacy in treating primary negative symptoms, there are interventions can be performed on those that may be secondary. Appropriate assessment is therefore essential in order to determine whether they are due to depressive or positive symptoms or related to adverse effects of treatments. Clinicians should also take into account the role that attention and vigilance plays in determining the level of functioning in the follow-up period. In conclusion, a correct approach to and treatment of the potential causes of secondary negative symptoms, along with limited use of sedative treatments to reduce attention deficit, should be the targets of intervention of these patients in clinical practice. More evidence is needed regarding the effect of interventions to address inflammatory pathways.

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Statement of interest

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CRediT authorship contribution statement

Leticia Gonzalez-Blanco: Data curation, Formal analysis, Writing - original draft, Supervision, Validation. **Maria Paz Garcia-Portilla:** Funding acquisition, Data curation, Formal analysis, Writing - review & editing, Supervision, Validation. **Francesco Dal Santo:** Data curation, Formal analysis, Writing - review & editing, Supervision, Validation. **Leticia Garcia-Alvarez:** Funding acquisition, Data curation, Formal analysis, Writing - review & editing, Supervision, Validation. **Lorena de la Fuente-Tomas:** Data curation, Writing - review & editing, Supervision, Validation. **Isabel Menendez-Miranda:** Writing - review & editing, Supervision, Validation. **Teresa Bobes-Bascaran:** Writing - review & editing, Supervision, Validation. **Pilar A. Saiz:** Funding acquisition, Data curation, Supervision, Validation. **Julio Bobes:** Funding acquisition, Writing - review & editing, Supervision, Validation.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112509.

References

Bechi, M., Bosia, M., Spangaro, M., Buonocore, M., Cavedoni, S., Agostoni, G., Bianchi, L., Cocchi, F., Guglielmino, C., Smeraldi, E., Cavallaro, R., 2017. Exploring functioning in schizophrenia: predictors of functional capacity and real-world behaviour. Psychiatry Res. 251, 118–124. https://doi.org/10.1016/j.psychres.2017.02.019.

Bobes, J., Ciudad, A., Alvarez, E., San, L., Polavieja, P., Gilaberte, I., 2009. Recovery from schizophrenia: results from a 1-year follow-up observational study of patients in symptomatic remission. Schizophr. Res. 115, 58–66. https://doi.org/10.1016/j.schres.2009.07.003.

Bosia, M., Bechi, M., Bosinelli, F., Politi, E., Buonocore, M., Spangaro, M., Bianchi, L., Cocchi, F., Guglielmino, C., Cavallaro, R., 2019. From cognitive and clinical substrates to functional profiles: disentangling heterogeneity in schizophrenia. Psychiatry Res. 271, 446–453. https://doi.org/10.1016/j.psychres.2018.12.026.

Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biol. Psychiatry 63, 505–511. https://doi.org/10.1016/j.biopsych.2007.05.022.

Bucci, P., Galderisi, S., Mucci, A., Rossi, A., Rocca, P., Bertolino, A., Aguglia, E., Amore, M., Andriola, I., Bellomo, A., Biondi, M., Cuomo, A., dell'Osso, L., Favaro, A., Gambi, F., Giordano, G.M., Girardi, P., Marchesi, C., Monteleone, P., Montemagni, C., Niolu, C., Oldani, L., Pacitti, F., Pinna, F., Roncone, R., Vita, A., Zeppegno, P., Maj, M., 2018. Premorbid academic and social functioning in patients with schizophrenia and its associations with negative symptoms and cognition. Acta Psychiatr. Scand. 138, 253–266. https://doi.org/10.1111/acps.12938.

Galderisi, S., Rossi, A., Rocca, P., Bertolino, A., Mucci, A., Bucci, P., Rucci, P., Gibertoni, D., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Brugnoli, R., Dell'Osso, L., De Ronchi, D., Di Emidio, G., Di Giannantonio, M., Fagiolini, A., Marchesi, C., Monteleone, P., Oldani, L., Pinna, F., Roncone, R., Sacchetti, E., Santonastaso, P., Siracusano, A., Vita, A., Zeppegno, P., Maj, M., 2014. The influence of illness-related

variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry 13, 275–287. https://doi.org/10.1002/wps.20167.

Galderisi, S., Rucci, P., Kirkpatrick, B., Mucci, A., Gibertoni, D., Rocca, P., Rossi, A., Bertolino, A., Strauss, G.P., Aguglia, E., Bellomo, A., Murri, M.B., Bucci, P., Carpiniello, B., Comparelli, A., Cuomo, A., De Berardis, D., Dell'Osso, L., Di Fabio, F., Gelao, B., Marchesi, C., Monteleone, P., Montemagni, C., Orsenigo, G., Pacitti, F., Roncone, R., Santonastaso, P., Siracusano, A., Vignapiano, A., Vita, A., Zeppegno, P., Maj, M., 2018. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: a network analysis. JAMA Psychiatry 75, 396–404. https://doi.org/10.1001/jamapsychiatry.2017.4607.

García-Bueno, B., Bioque, M., Mac-Dowell, K.S., Barcones, M.F., Martínez-Cengotitabengoa, M., Pina-Camacho, L., Rodríguez-Jiménez, R., Sáiz, P.A., Castro, C., Lafuente, A., Santabárbara, J., González-Pinto, A., Parellada, M., Rubio, G., García-Portilla, M.P., Micó, J.A., Bernardo, M., Leza, J.C., 2014. Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. Schizophr. Bull. 40, 376–387. https://doi.org/10.1093/schbul/sbt001.

Garcia-Portilla, M.P., Saiz, P.A., Bousono, M., Bascaran, M.T., Guzman-Quilo, C., Bobes, J., 2011. Validation of the Spanish personal and social performance scale (PSP) in outpatients with stable and unstable schizophrenia. Rev. Psiquiatr. Salud Ment. 4, 9–18. https://doi.org/10.1016/j.rpsm.2010.11.003.

González-Blanco, L., García-Portilla, M.P., García-Álvarez, L., de la Fuente-Tomás, L., Iglesias García, C., Sáiz, P.A., Rodríguez-González, S., Coto-Montes, A., Bobes, J., 2018a. Can interleukin-2 and interleukin-1β be specific biomarkers of negative symptoms in schizophrenia? Rev. Psiquiatr. Salud Ment. https://doi.org/10.1016/j.rpsm.2018.03.004.

González-Blanco, L., García-Portilla, M.P., García-Álvarez, L., de la Fuente-Tomás, L., Iglesias García, C., Sáiz, P.A., Rodríguez-González, S., Coto-Montes, A., Bobes, J., 2018b. Oxidative stress biomarkers and clinical dimensions in first 10 years of schizophrenia. Rev. Psiquiatr. Salud Ment. https://doi.org/10.1016/j.rpsm.2018.03.003.

Green, M.F., Horan, W.P., Lee, J., 2019. Nonsocial and social cognition in schizophrenia: current evidence and future directions. World Psychiatry 18, 146–161. https://doi.org/10.1002/wps.20624.

Harvey, P.D., 2014a. Assessing disability in schizophrenia: tools and contributors. J. Clin. Psychiatry 75, e27. https://doi.org/10.4088/JCP.13049tx5c.

Harvey, P.D., 2014b. Disability in schizophrenia: contributing factors and validated assessments. J. Clin. Psychiatry 75 (Suppl 1), 15–20. https://doi.org/10.4088/JCP.13049su1c.03.

Harvey, P.D., Deckler, E., Jarsksog, L.F., Penn, D.L., Pinkham, A.E., 2018. Predictors of social functioning in patients with higher and lower levels of reduced emotional experience : social cognition, social competence, and symptom severity. Schizophr. Res 6–11. https://doi.org/10.1016/j.schres.2018.11.005.

Harvey, P.D., Khan, A., Keefe, R.S.E., 2017a. Using the positive and negative syndrome scale (PANSS) to define different domains of negative symptoms: prediction of everyday functioning by impairments in emotional expression and emotional experience. Innov. Clin. Neurosci. 14, 18–22.

Harvey, P.D., Twamley, E.W., Pinkham, A.E., Depp, C.A., Patterson, T.L., 2017b. Depression in schizophrenia: associations with cognition, functional capacity, everyday functioning, and self-assessment. Schizophr Bull. 43, 575–582. https://doi.org/10.1093/schbul/sbw103.

Ho, E., Lee, M., Lai, C., Hui, M., Pui, K., Chan, K., Ying, P., Yeuk, E., Law, L., Shiu, C., Chong, Y., Chung, W., Kit, S., Chan, W., King, W., Wai, A., Lo, F., Pui, E., Pang, F., Fuk, E., Cheung, C., Gar, M., Yiu, C., Wai, D., Chung, S., Man, R., Ng, K., Song, W., Tak, W., Lo, L., Yu, E., Chen, H., 2018. The role of symptoms and insight in mediating cognition and functioning in first episode psychosis. Schizophr. Res. https://doi.org/10.1016/j.schres.2018.11.009.

Hope, S., Ueland, T., Eiel, N., Dieset, I., Lorentzen, S., Berg, A.O., Agartz, I., Aukrust, P., Andreassen, O.A., 2013. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr. Res. 145, 36–42. https://doi.org/10.1016/j.schres.2012.12.023.

Lahera, G., Ruiz, A., Branas, A., Vicens, M., Orozco, A., 2017. Reaction time, processing speed and sustained attention in schizophrenia: impact on social functioning. Rev. Psiquiatr. Salud Ment. 10, 197–205. https://doi.org/10.1016/j.rpsm.2017.04.001.

Mane, A., Garcia-Rizo, C., Garcia-Portilla, M.P., Berge, D., Sugranyes, G., Garcia-Alvarez, L., Bernardo, M., Bobes, J., Fernandez-Egea, E., 2014. Spanish adaptation and validation of the Brief Negative Symptoms Scale. Compr. Psychiatry 55, 1726–1729. https://doi.org/10.1016/j.comppsych.2014.05.024.

Menendez-Miranda, I., Garcia-Portilla, M.P., Garcia-Alvarez, L., Arrojo, M., Sanchez, P., Sarramea, F., Gomar, J., Bobes-Bascaran, M.T., Sierra, P., Saiz, P.A., Bobes, J., 2015. Predictive factors of functional capacity and real-world functioning in patients with schizophrenia. Eur. Psychiatry 30, 622–627. https://doi.org/10.1016/j.eurpsy.2014.12.011.

Najas-Garcia, A., Gomez-Benito, J., Huedo-Medina, T.B., 2018. The relationship of motivation and neurocognition with functionality in schizophrenia: a meta-analytic review. Community Ment. Health J. 54, 1019–1049. https://doi.org/10.1007/s10597-018-0266-4.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72, 29–39. https://doi.org/10.1016/j.schres.2004.09.007.

Pelayo-Teran, J.M., Gajardo-Galan, V., Gomez-Revuelta, M., Ortiz-Garcia de la Foz, V., Ayesa-Arriola, R., Tabares-Seisdedos, R., Crespo-Facorro, B., 2018. Duration of active psychosis and functional outcomes in first-episode non-affective psychosis. Eur. Psychiatry 52, 29–37. https://doi.org/10.1016/j.eurpsy.2018.03.003.

Peralta, V., Cuesta, M.J., 1994. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res. 53, 31–40.

Robertson, B.R., Prestia, D., Twamley, E.W., Patterson, T.L., Bowie, C.R., Harvey, P.D., 2014. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. Schizophr. Res. 160, 136–141. https://doi.org/10.1016/j.schres.2014.10.037.

Rocca, P., Galderisi, S., Rossi, A., Bertolino, A., Rucci, P., Gibertoni, D., Montemagni, C., Bellino, S., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Carpiniello, B., Cuomo, A., D'Ambrosio, E., dell'Osso, L., Girardi, P., Marchesi, C., Monteleone, P., Montemitro, C., Oldani, L., Pacitti, F., Roncone, R., Siracusano, A., Tenconi, E., Vita, A., Zeppegno, P., Steardo, L.J., Vignapiano, A., Maj, M., 2018. Disorganization and real-world functioning in schizophrenia: results from the multicenter study of the Italian Network for Research on Psychoses. Schizophr. Res. 201, 105–112. https://doi.org/10.1016/j.schres.2018.06.003.

Rocca, P., Montemagni, C., Zappia, S., Pitera, R., Sigaudo, M., Bogetto, F., 2014. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. Psychiatry Res. 218, 284–289. https://doi.org/10.1016/j.psychres.2014.04.018.

Rodriguez-Jimenez, R., Bagney, A., Garcia-Navarro, C., Aparicio, A.I., Lopez-Anton, R., Moreno-Ortega, M., Jimenez-Arriero, M.A., Santos, J.L., Lobo, A., Kern, R.S., Green, M.F., Nuechterlein, K.H., Palomo, T., 2012. The MATRICS consensus cognitive battery (MCCB): co-norming and standardization in Spain. Schizophr. Res. 134, 279–284. https://doi.org/10.1016/j.schres.2011.11.026.

Santesteban-Echarri, O., Paino, M., Rice, S., Gonzalez-Blanch, C., McGorry, P., Gleeson, J., Alvarez-Jimenez, M., 2017. Predictors of functional recovery in first-episode psychosis: a systematic review and meta-analysis of longitudinal studies. Clin. Psychol. Rev. 58, 59–75. https://doi.org/10.1016/j.cpr.2017.09.007.

Sarro, S., Duenas, R.M., Ramirez, N., Arranz, B., Martinez, R., Sanchez, J.M., Gonzalez, J.M., Salo, L., Miralles, L., San, L., 2004. Cross-cultural adaptation and validation of the Spanish version of the Calgary Depression Scale for schizophrenia. Schizophr. Res. 68, 349–356. https://doi.org/10.1016/S0920-9964(02)00490-5.

Simons, C.J.P., Bartels-velthuis, A.A., Pijnenborg, G.H.M., 2016. Cognitive performance and long-term social functioning in psychotic disorder: a three- year follow-up study. PLoS ONE 1–15. https://doi.org/10.1371/journal.pone.0151299.

Sole, B., Bonnin, C.M., Jimenez, E., Torrent, C., Torres, I., Varo, C., Valls, E., Montejo, L., Gomez-Ocana, C., Tomioka, Y., Vieta, E., Martinez-Aran, A., Reinares, M., 2018. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr. Scand. 137, 516–527. https://doi.org/10.1111/acps.12871.

Strassnig, M., Bowie, C., Pinkham, A.E., Penn, D., Twamley, E.W., Patterson, T.L., Harvey, P.D., 2018. Which levels of cognitive impairments and negative symptoms are related to functional de fi cits in schizophrenia? J. Psychiatr. Res. 104, 124–129. https://doi.org/10.1016/j.jpsychires.2018.06.018.

Strassnig, M.T., Raykov, T., O'Gorman, C., Bowie, C.R., Sabbag, S., Durand, D., Patterson, T.L., Pinkham, A., Penn, D.L., Harvey, P.D., 2015. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. Schizophr. Res. 165, 76–82. https://doi.org/10.1016/j.schres.2015.03.033.

Tas, C., Brown, E.C., Eskikurt, G., Irmak, S., Aydin, O., Esen-Danaci, A., Brune, M., 2018. Cortisol response to stress in schizophrenia: associations with oxytocin, social support and social functioning. Psychiatry Res. 270, 1047–1052. https://doi.org/10.1016/j.psychres.2018.05.011.

WHO, 2011. World report on disability.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., Nienhuis, F.J., Walsh, D., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. Psychol. Med. 30, 1155–1167.