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Cognitive clusters in first-episode psychosis

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ABSTRACT

Impairments in a broad range of cognitive domains have been consistently reported in some individuals with first-episode psychosis (FEP). Cognitive deficits can be observed during the prodromal stage. However, the course of cognitive deficits is still unclear. The aim of this study was to identify cognitive subgroups over time and to compare their sociodemographic, clinical and functional profiles. A total of 114 patients with Schizophrenia Spectrum Disorders were included in the present study. We assessed subjects through psychiatric scales and eight neuropsychological tests at baseline and at two-year follow-up visit. We performed the Partition Around Medoids algorithm with all cognitive variables. Furthermore, we performed a logistic regression to identify the predictors related to the different cognitive clusters at follow-up. Two distinct subgroups were found: the first cluster characterized by cognitive impairment and a second cluster had relatively intact cognition in comparison with norms. Up to 54.7% of patients with cognitive deficits at baseline tended to improve during the first two years of treatment. Patients with intact cognition at follow-up had a higher socioeconomic status, later age of onset, lower negative symptoms and a higher cognitive reserve (CR) at baseline. CR and age of onset were the baseline variables that predicted cognitive impairment. This research allows us to obtain a better understanding of the heterogeneous profile of psychotic disorders. Identifying the characteristics of patients who will

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present a cognitive impairment could improve early detection and intervention. These results suggest that enhancing CR could contribute to improving the course of the illness.

1. Introduction

Impairment in a broad range of cognitive domains has been consistently reported in individuals with first-episode psychosis (FEP), including attention, verbal memory, processing speed, working memory and executive functioning (Carrión et al., 2018). Cognitive deficits are observed during the prodromal stage. The literature suggests that cognition may be considered a predictor of patients' outcome (Green, 1996), and that cognitive dysfunction is associated with prominent functional impairment, which involves social, occupational and independent living activities (van Winkel et al., 2007; Hall et al., 2019). Furthermore, a normal cognitive function is strongly associated with clinical improvement in FEP. A systematic review of associations between psychotic psychopathology and measures of cognitive impairment in subjects with a lifetime history of non-affective psychosis has reported that cognitive deficits are associated with negative and disorganized dimensions rather than positive and depressive dimensions (Dominguez et al., 2009). Other studies showed that patients who experienced higher cognitive performance also had a greater reduction in the severity of negative symptoms (Allott et al., 2011; Rodríguez-Sánchez et al., 2013). Besides, a relationship between neurocognitive performance and cognitive reserve (CR) was found (de la Serna et al., 2013; Anaya et al., 2016; Amoretti et al., 2016, 2018).

Several studies in patients with a FEP, schizophrenia or bipolar disorder suggest that higher CR is associated with a later onset of psychosis and better recovery, as well as it being considered a positive moderator of the impact of pathology on clinical course, functional outcome and cognitive performance (de la Serna et al., 2013; Anaya et al., 2016; Amoretti et al., 2016, 2018, 2019, 2020; Herrero et al., 2019). However, it has been shown that CR plays a differential role in the outcome of psychoses according to the diagnosis (Amoretti et al., 2018). In Schizophrenia Spectrum Disorders (SSD) patients, those with high CR were older, had higher socioeconomic status, shorter duration of untreated psychosis, and a later age of onset. They also showed greater performance in most cognitive domains. In affective patients, those with a greater CR showed a higher socioeconomic status, better functioning, and greater verbal memory performance (Amoretti et al., 2018). In fact, the current data support the idea that affective and SSD patients show some differences in clinical aspects, premorbid adjustment and cognitive function, particularly executive measures such as verbal fluency, which may influence global functioning at follow-up (Torrent et al., 2018).

Nonetheless, the course of cognitive deficits is still unclear. Different studies have shown that neuropsychological deficits after a FEP appeared to remain stable over time (Bozikas and Andreou, 2011; Sánchez-Torres et al., 2018), whereas others have shown that cognitive dysfunction deteriorates further (Kurtz, 2005) or improves over time (Jahshan et al., 2010). In any case, most of the affected functions seem to improve modestly after treatment (Hill et al., 2004). Cluster analysis provides an opportunity to group individuals using a data-driven approach and permits individuals to be classified based on their neurocognitive profiles. It may throw light on homogeneous phenotypic targets to understand the subtle neuropathologic differences among individuals with FEP, since individuals within the same cluster may share cognitive, genetic, and neurophysiologic features. This approach has been widely used to demonstrate specific brain phenotypes, genetic alterations, and cognitive deficits among bipolar disorder and schizophrenia patients (Green et al., 2020). Different data collected through cluster studies of patients with schizophrenia and bipolar disorder have shown that there are distinct cognitive subgroups of patients; one with intact cognition or "neuropsychologically normal", another one with severe and broad impairment and other groups with an intermediate performance of mixed neurocognitive deficits (Heinrichs and Awad, 1993; Goldstein et al., 1998; Lewandowski et al., 2014; Burdick et al., 2014; Van Rheenen et al., 2017). Some differences have been showed in cognitive subtypes across diagnoses. For example Lewandowski et al. reported that subjects with bipolar disorder with psychosis were overrepresented in "neuropsychologically normal" cluster (63%) compared with subjects with schizoaffective disorder (26%) and schizophrenia (11%) (Lewandowski et al., 2014). Cognitive clusters are also associated with distinct clinical characteristics. The intact cognition group are more likely to present predominantly positive symptoms, and better premorbid and functional profiles, whereas cognitively impaired cluster groups are more likely to present more prominent negative symptoms (Heinrichs and Awad, 1993; Goldstein et al., 1998; Lewandowski et al., 2018; Sánchez-Torres et al., 2018).

Although there was evidence of distinct cognitive subgroups of patients, the differences in clinical, functional and sociodemographic characteristics of each cognitive subgroup and their course in SSD subjects were not clear. Given their significant impact on psychosocial functioning and quality of life, identifying differences between people with and without cognitive impairment can provide extremely useful information for the definition of personalized interventions. The aims of this study were 1) to identify cognitive profiles in SSD using Cluster Analysis at baseline and follow-up; 2) to examine their stability or movement towards another group at follow-up; and 3) to identify the predictors related to cognitive clusters at follow-up.

2. Material and methods

2.1. Participants

The sample of this study came from a multicenter, naturalistic and longitudinal project called "Phenotype-genotype interaction: Application of a predictive model in first psychotic episodes" (PEPs Project) (Bernardo et al., 2013, 2019). A total of 335 patients with a FEP and 253 healthy controls (HC) were recruited from April 2009 to April 2011. To ensure more homogeneous sample diagnoses, for the current study we only included patients with SSD, as we considered affective first-episode patients a subgroup displaying several specific characteristics in terms of clinical course, functional outcome and antipsychotic treatments. We considered SSD diagnoses of schizophrenia, schizophreniform, schizoaffective disorders and psychoses that are not otherwise specified according to DSM-IV-TR. We included also all those with less than 6% missing data in neuropsychological tests at baseline and follow-up for the cluster analyses, all the information needed to calculate CR (see Subsection 2.2. Assessments - Cognitive Reserve Assessment) and, additionally, belonging to the SSD diagnostic category. The final sample for this study consisted of 114 SSD patients and 128 HC.

For this study, the inclusion criteria for patients were: 1) between 18 and 35 years of age at the time of first evaluation; 2) presence of psychotic symptoms of less than twelve months' duration; 3) ability to speak Spanish correctly; and 4) signed informed consent. Exclusion criteria were: 1) mental retardation according to DSM-IV-TR criteria; 2) history of head trauma with loss of consciousness; and 3) organic disease with mental repercussions. The patients matched with HC age (± 10%), gender and parental socioeconomic status (± 1 level). The exclusion criteria for controls were the same as for the patients, yet also included the presence of a current or past psychotic disorder or major depression and having a first degree relative with psychotic disorder history.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic of Barcelona Ethics and Research Board. All participants provided

written informed consent prior to their inclusion in the study.

2.2. Assessments

2.2.1. Clinical and sociodemographic assessment

We gathered all the relevant clinical and sociodemographic data for all participants. Parental socioeconomic status (SES) was determined using Hollingshead's Two-Factor Index of Social Position (Hollingshead and Redlich, 1958); pharmacological treatment was measured by chlorpromazine equivalents (CPZ) based on international consensus (Gardner et al., 2010); and the Duration of Untreated Psychosis (DUP) was calculated as the number of days between the first manifestations of psychotic symptoms until the initiation of adequate treatment for psychosis. Drug misuse habits were also collected. In order to represent the entire population of FEP, participants with current substance abuse/dependence comorbid diagnosis were not excluded.

Diagnoses were determined with the Structured Clinical Interview for DSM (SCID-I-II) (First et al., 1997a, 1997b) according to DSM-IV criteria. Taking into consideration potential changes across time and in order to ensure diagnostic stability, the diagnosis of the patients who completed the study was determined based on information gathered at 2-year follow-up visit.

A psychopathological assessment was carried out with the Spanish validated versions of the following scales: Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994), the Young Mania Rating Scale (YMRS) (Colom et al., 2002) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Lobo et al., 2002). Higher scores indicate greater severity.

Traumatic events were assessed by the Traumatic Experiences in Psychiatric Questionnaire (Davidson and Smith, 1990), which was coded as a dichotomous variable (yes/no).

2.2.2. Functional assessment

The overall functional outcome was assessed by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) and The Global Assessment of Functioning (GAF) (Endicott et al., 1976). The FAST scale comprises 24 items and higher scores indicate worse functioning. They are divided according to six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. The GAF is a scale designed to assess the severity of symptoms and the level of functioning. Higher scores correspond to better functioning.

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was applied retrospectively to assess premorbid adjustment. Only childhood and early adolescence life periods have been taken into account since they are the two periods answered by all the participants. Higher scores on the test indicate worse premorbid adjustment.

2.2.3. Neuropsychological assessment

The neuropsychological assessments were performed in the second month of evaluation in order to ensure the clinical stability of patients and were repeated in the two-year follow-up visit. The neuropsychological battery measured the following cognitive domains: 1) Processing speed was tested with the Trail Making Test, form A (TMT-A) (Reitan and Wolfson, 1993); 2) Verbal learning and memory, assessed with the Verbal Learning Test Spain Complutense for adults (TAVEC) (Benedet, 1998); 3) Working memory was assessed with the Digit Span Subtest and the Letter-Number (LN) Sequencing Subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997); 4) The executive functions were evaluated using the Stroop Test, word-color interference effect (Golden and Freshwater, 1978); Controlled Oral Word Association Test composed by phonemic verbal fluency: FAS, and semantic fluency: animal naming) (Peña-Casanova, 1990; Loonstra et al., 2001). Higher T-scores correspond to better performance in all the cognitive domains.

To evaluate the differences between raters, an interrater reliability study was also conducted among different neuropsychologists at each center. A table of the ratings of WAIS Vocabulary subtest (0 to 2 for each item) was constructed and, for each pair, we consider agreement as a dichotomous variable: "1" for agreement or "0" for disagreement. Those who failed the first evaluation, this mean that intraclass correlation coefficient (ICC) was below 0.80, were reassessed (Bernardo et al., 2013). A good to excellent inter-rater reliability among psychologists was indicated by ICC $>$ 0.80 in the WAIS Vocabulary subtest (Cuesta et al., 2015). Thus, the inter-judge reliability study guarantees that the neuropsychologists carried out a correct application and correction of the test.

2.2.4. Cognitive reserve assessment

We have used the three most commonly proposed proxy indicators of CR to assess it (de la Serna et al., 2013; Anaya et al., 2016; Amoretti et al., 2016, 2018, 2020), which include premorbid intellectual functioning (IQ), education and lifetime participation in leisure, social and physical activities. The premorbid IQ was calculated with the vocabulary subtest of the WAIS-III as a measure reflecting premorbid crystallized intelligence. 'Education', the second proxy, was assessed taking into account the number of years of obligatory education that subjects completed as well as parents' educational level, and lifetime school performance (assessed by PAS scale - scholastic performance). Finally, lifetime participation in leisure, social and physical activities was assessed by FAST scale. Higher scores correspond to better performance.

2.3. Analysis

2.3.1. Pre-processing

All cognitive variables were converted into T-score based on normative data of the general population, which comes from the normative table of the validation studies of each cognitive test. We performed all the steps of this section in R (Version 3.5.3) and Rstudio (Version 1.1.44) (https://www.Rproject.org/). We used Multivariate Imputation by Chained Equations algorithm (Van Buuren and Groothuis-Oudshoorn, 2011) to impute missing data, setting the number of iterations equal to 50 and used the Predictive Mean Matching Imputation (PMM) method for all cognitive variables. All cognitive variables contained less than 6% and 2% missing data at baseline and 2-years follow-up, respectively (Supplementary Fig. S1). We needed to impute data because the clustering algorithm does not permit missing values (Supplementary Fig. S2).

2.3.2. Machine learning technique

After, we performed the Partition Around Medoids (PAM) algorithm (Schubert and Rousseeuw, 2019) to identify cognitive clusters of subjects with FEP at baseline and 2-years follow-up using all neuropsychological tests (TMT-A, TAVEC, LN, Stroop, FAS, and Animal), that is, we performed cluster analysis in only patient group. We decided to use PAM algorithm rather than k-means, a classical clustering algorithm, because PAM is more robust to noise and outliers, minimizing the sum of dissimilarities between data points in place of a sum of squared Euclidean distances. We used Gower's distance (Gower, 2012) to calculate the dissimilarities between pairs of subjects.

The optimal number of clusters was determined by the average silhouette width. The silhouette indicates how well objects are clustered, ranging from −1 (poorly) to 1 (well clustered). Hence, the algorithm suggests the number optimal of clusters based on the number of subgroups with the highest value for the average silhouette width. Dunn index means the ratio between compactness within cluster and separation between clusters (Hassani and Seidl, 2017; Tomasini et al., 2017). We performed Dunn index to verify the internal quality of clustering at baseline and follow-up. The packages used were "mice", "cluster", "factorextra", "NbClust", and "fpc".

2.3.3. Statistical analysis

We used Statistical Package for the Social Sciences (SPSS) (Version

19) to perform statistical analysis. Descriptive analyses were conducted using chi-square for categorical variables and Student's test for continuous variables. Demographic, clinical and neuropsychological differences between the groups were examined and effect sizes were reported. Cohen's d was used to indicate the standardized difference between two means, Odds ratio (OR) was used for 2 × 2 contingency table analyses and Cramer's V accounts for multi-categorical variables. A Principal Components Analysis (PCA) was performed to create a "Cognitive reserve score" for each subject with the three main proxies.

Backward stepwise logistic regression analyses were performed in this study to identify the factors related to cognitive clusters at follow-up. The threshold for statistical significance was $p < 0.05$.

3. Results

3.1. Sociodemographic characteristics of the sample

A total of 114 patients with SSD and 128 HC were included in the present study and were re-evaluated at 2-year follow-up. Sixty-seven percent of patients were male with a mean age of 25.22 years (age at onset of psychosis was 25 years). The mean dose of antipsychotic medication was equivalent to 596.40 ± 408.96 mg/day of CPZ and the mean of DUP was determined as 109.40 ± 126.19 days. See Supplementary Table 1 for details of cognitive characteristics of patients and HC, and the differences between groups.

3.2. Cognitive clusters in SSD patients and their stability

In relation to clustering performance, PAM algorithm achieved an average Silhouette width equals to 0.71, and Dunn index equal to 0.75 at baseline. At 2-years follow-up, the measures were 0.77, and 0.80, respectively (Supplementary Fig. S3). The average Silhouette width is used to determine the optimal number of clusters and the Dunn index is used for internal validation.

At baseline, two distinct clusters were found: the first cluster with mild to moderate cognitive impairments in processing speed, verbal learning, working memory and verbal fluency (executive function task) ($n = 64$, 56.1%) and the second one with relatively intact cognition (results within the typical limits in all scores on standardized tests) ($n = 50$, 43.9%). Table 1 contains a summary of the baseline characteristics of patients and the differences between clusters. The relatively cognitively intact group performed worse than HC on LN ($p = 0.032$), verbal memory ($p < 0.001$) and verbal fluency (Animals, $p = 0.001$ and FAS, $p < 0.001$). No significant differences were found on Digits ($p = 0.087$), TMT-A ($p = 0.566$) and Stroop ($p = 0.120$).

At 2-year follow-up, the same two clusters were maintained: one with cognitive impairment ($n = 36$, 31.6%) and another one with relatively intact cognitive function ($n = 78$, 68.4%). As shown in Fig. 1, 63% of patients ($n = 72$) were unchanged, showing a certain degree of cognitive stability over time. Thirty-five patients (30.7% of the whole sample and 54.7% of those with cognitive impairment at baseline) improved their cognitive performance, crossing from cognitive impairment to the relatively cognitively intact group after two years, while seven patients (6.1% of the whole sample and 14% of those with intact cognition) crossed from the relatively cognitively intact group to the cognitive impairment cluster at follow-up. See Supplementary Table 2 for details of sociodemographic, clinical, functional and cognitive characteristics of patients and the differences between groups. The

Table 1
Baseline sociodemographic, clinical, functional and cognitive reserve for non-affective patients and among clusters.

	Cognitive impairment (n = 64)	Relatively cognitively intact (n = 50)	*P*	Cohen's *d*/Odds Ratio/Cramer's V
Sociodemographic variables				
Gender: Male *N* (%)	40 (63)	36 (72)	0.286	OR = 1.54
Age ($\bar{x}$±SD)	24.44 ± 5.16	26.22 ± 5.06	0.068	0.35
SES (%)			**0.002**	Cramer's V = 0.39
High	12 (19)	14 (28)		
Medium-High	1 (2)	11 (22)		
Medium	15 (23)	8 (16)		
Medium-Low	26 (41)	15 (30)		
Low	10 (16)	2 (4)		
DUP	128.41 ± 144.72	86.42 ± 95.85	0.088	0.34
Age of onset	24.11 ± 5.26	26.11 ± 5.67	0.135	0.37
CPZ	641.98 ± 449.45	531.75 ± 338.06	0.177	0.28
Tobacco: Yes *N* (%)	44 (68)	31 (62)	0.289	OR = 0.74
Can-bis: Yes *N* (%)	32 (50)	18 (36)	0.096	OR = 0.56
Trauma: Yes *N* (%)	37 (58)	29(58)	0.961	OR = 1.02
Clinical variables				
PANSS positive	19.13 ± 8.58	16.64 ± 7.05	0.100	0.32
PANSS negative	20.98 ± 7.65	17.04 ± 6.55	**0.004**	**0.55**
PANSS general	38.34 ± 12.40	36.28 ± 12.28	0.378	0.17
PANSS total	78.45 ± 25.32	69.96 ± 22.73	0.066	0.35
YMRS	8.02 ± 9.88	5.90 ± 8.11	0.223	0.23
MADRS	11.33 ± 10.10	11.78 ± 8.46	0.800	0.05
FAST	31.17 ± 16.96	24.62 ± 14.61	**0.032**	**0.41**
GAF	52.84 ± 19.12	56.68 ± 17.50	0.272	0.21
Neuropsychological performance				
Cognitive reserve	70.55 ± 10.12	81.42 ± 9.85	**<0.001**	**1.01**
LN	39.17 ± 9.04	48.94 ± 10.32	**<0.001**	**1.01**
Digits	41.03 ± 7.24	48.92 ± 8.51	**<0.001**	**1.00**
TAVEC	30.78 ± 11.45	46.40 ± 9.64	**<0.001**	**1.48**
TMT-A	33.94 ± 12.92	47.74 ± 11.33	**<0.001**	**1.18**
Stroop interference	50.11 ± 6.64	52.98 ± 10.90	0.105	0.32
FAS	34.27 ± 5.91	44.64 ± 7.82	**<0.001**	**1.50**
Animal	37.83 ± 9.12	48.56 ± 9.58	**<0.001**	**1.15**

Abbreviations: SES=Socioeconomic status, DUP = Duration of Untreated Psychosis, CPZ = Chlorpromazine equivalents, PANSS = Positive and Negative Symptom Scale, YMRS = Young Mania Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, FAST = Functioning Assessment Short Test, GAF = Global Assessment of Functioning, LN = Letter-Number, TAVEC = Verbal Learning Test Spain Complutense for adults, TMT-A = Trail Making Test, form A, FAS = Phonemic Verbal Fluency. Significant differences ($p < 0.05$) marked in bold.

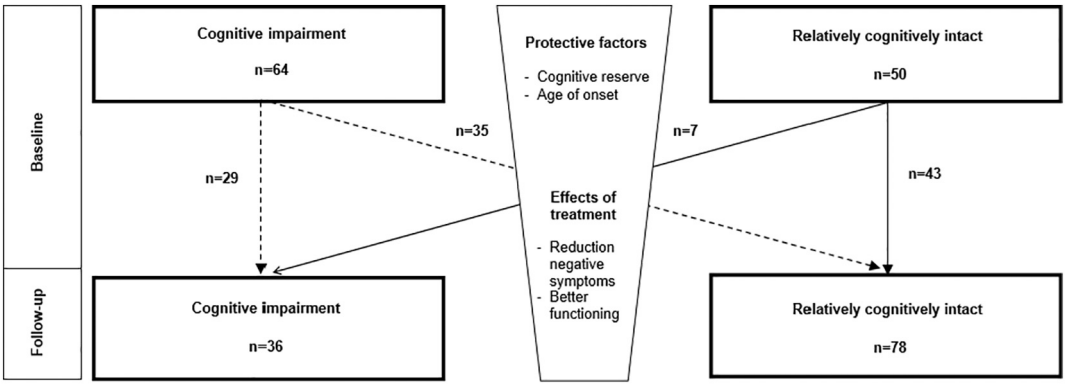

Fig. 1. Longitudinal change pattern of clusters.

relatively cognitively intact group performed worse than HC on all cognitive domains evaluated.

3.3. Cluster characteristics and follow-up predictors

When comparing the clinical and sociodemographic profiles we found significant differences in SES, baseline negative symptoms, functional outcomes (autonomy of FAST scale, $p = 0.020$, and total FAST scale, $p = 0.032$) and CR between both clusters classified at baseline. They also showed significant differences in the entire cognitive subtest evaluated, except for Interference Stroop (executive task), demonstrating a good split among groups (see Fig. 2). There were no differences between clusters at baseline in terms of age, gender, DUP, age of onset, CPZ, tobacco or cannabis use and history of traumatic events/experiences (see Table 1). For clusters classified after two years of follow-up, subjects with relatively intact cognition had higher SES, later age of onset, lower baseline negative symptoms, lower scores of PANSS follow-up in all subscales and a higher CR at baseline (see Table 2). They showed differences in all areas of functioning (autonomy ($p < 0.001$), cognitive functioning ($p = 0.001$), financial issues ($p = 0.022$),

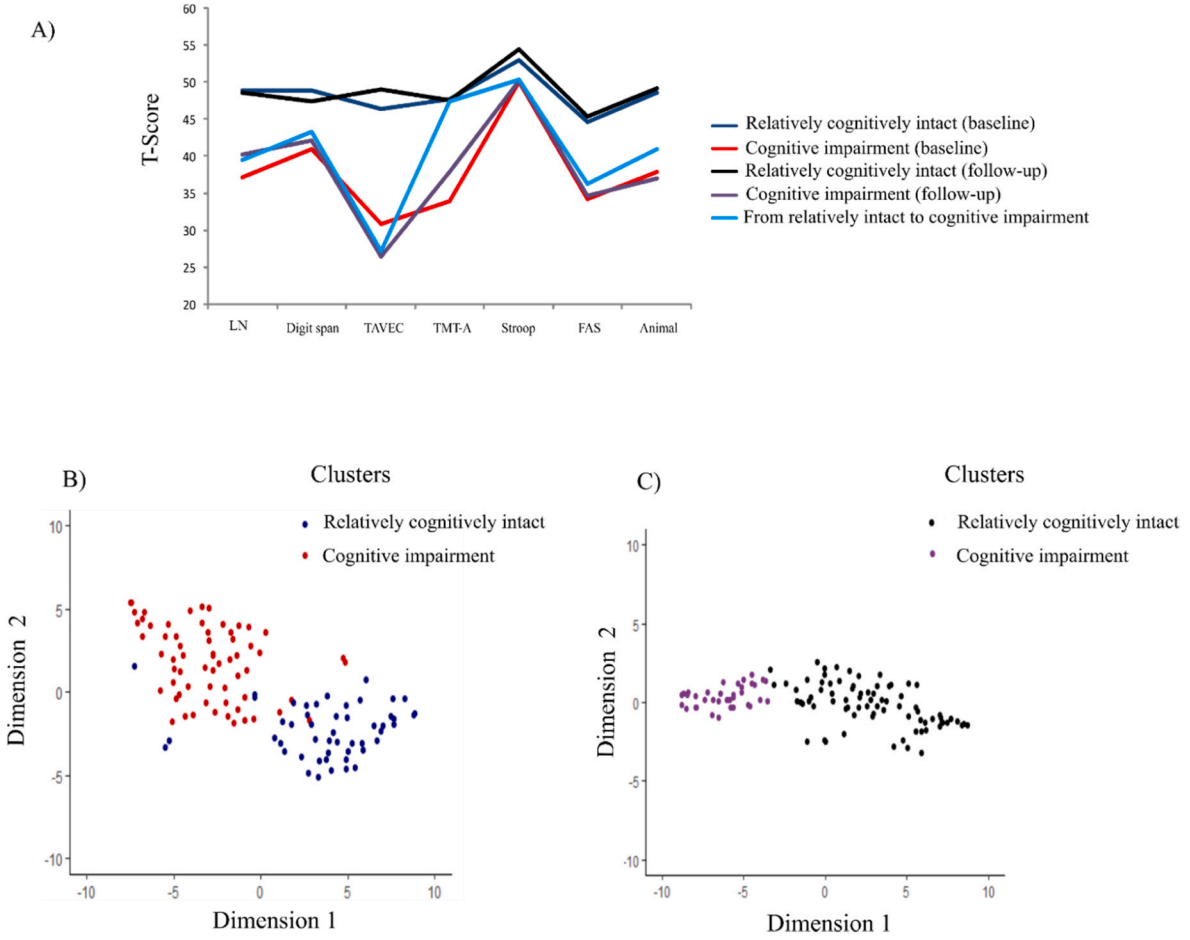

Fig. 2. Cluster distribution at baseline and 2-year follow-up visit.
a) Cognitive performance among cognitive clusters during baseline and follow-up. Each line represents the mean of cluster. b) Cluster distribution at baseline. c) Cluster distribution at 2-year follow-up. The graph "b" and "c" are 2D visualizations of the unsupervised reduced dimension representation through t-Distributed Stochastic Neighbor Embedding (t-SNE) (van der Maaten and Hinton, 2008). Each axis means a non-linear reduction of cognitive tests and each point is a subject.

Table 2
Sociodemographic, clinical, functional and cognitive performance among clusters at 2-year follow-up.

	Cognitive impairment (n = 36)	Relatively cognitively intact (n = 78)	*p*	Cohen's *d*/Odds Ratio/Cramer's V	Healthy controls	*p*
Sociodemographic variables						
Gender: Male *N* (%)	25 (69)	51 (63)	0.419	OR = 1.71	84 (66)	0.448
Age ($\bar{x}$±SD)	24.78 ± 4.99	25.42 ± 5.27	0.531	0.14	25.77 ± 5.83	0.244
SES (%)			**0.002**	Cramer's V = 0.381		0.119
High	5 (8)	21 (42)			33 (26)	–
Medium-High	0 (0)	12 (24)			29 (23)	–
Medium	5 (8)	18 (36)			29 (23)	–
Medium-Low	19 (30)	22 (44)			30 (23)	–
Low	7 (11)	5 (10)			7 (5)	–
DUP	133.11 ± 118.96	97.70 ± 128.80	0.175	0.29	–	–
Age of onset	22.77 ± 5.15	26.02 ± 6.20	**0.022**	0.57	–	–
CPZ	677.91 ± 425.63	561.67 ± 399.10	0.216	0.28	–	–
CPZ follow-up	494.48 ± 276.76	391.31 ± 220.40	0.152	0.41	–	–
Tobacco: Yes *N* (%)	24 (67)	51 (65)	0.534	OR = 0.94	52 (41)	**<0.001**
Tobacco follow-up	23 (64)	47 (60)	0.149	OR = 0.82	44 (34)	**0.001**
Can-bis: Yes *N* (%)	17 (47)	33 (42)	0.386	OR = 1.29	25 (20)	**<0.001**
Can-bis follow-up	6 (17)	9 (12)	0.093	OR = 0.65	25 (20)	0.141
Trauma: Yes *N* (%)	18 (50)	48 (63)	0.132	OR = 1.71	68 (53)	0.268
Clinical variables						
PANSS positive	18.94 ± 7.81	17.62 ± 8.11	0.412	0.17	–	–
PANSS positive follow-up	11.90 ± 5.34	9.74 ± 3.54	**0.016**	0.48	–	–
PANSS negative	21.53 ± 7.91	18.21 ± 6.99	**0.026**	0.45	–	–
PANSS negative follow-up	17.23 ± 6.26	12.93 ± 5.70	**0.001**	0.82	–	–
PANSS general	39.28 ± 11.41	36.59 ± 12.72	0.281	0.23	–	–
PANSS general follow-up	27.61 ± 9.99	24.41 ± 7.73	**0.077**	0.36	–	–
PANSS total	79.75 ± 24.05	72.41 ± 24.49	0.137	0.30	–	–
PANSS total follow-up	56.74 ± 19.50	47.08 ± 15.38	**0.008**	0.55	–	–
YMRS	6.72 ± 8.32	7.26 ± 9.59	0.774	0.06	–	–
YMRS follow-up	2.39 ± 4.23	1.26 ± 2.56	0.095	0.32	–	–
MADRS	11.19 ± 9.08	11.68 ± 9.57	0.799	0.05	–	–
MADRS follow-up	7.61 ± 7.37	5.03 ± 5.98	0.062	0.38	–	–
FAST	30.61 ± 16.27	27.23 ± 16.21	0.303	0.21	2.19 ± 5.16	**<0.001**
FAST follow-up	25.39 ± 15.09	15.64 ± 13.71	**0.002**	0.67	2.29 ± 6.63	**<0.001**
GAF	55.72 ± 16.69	53.97 ± 19.27	0.640	0.10	93.48 ± 5.00	**<0.001**
GAF follow-up	68.52 ± 11.61	75.14 ± 12.76	**0.017**	0.54	92.57 ± 4.14	**<0.001**
Neuropsychological performance						
Cognitive Reserve	69.36 ± 10.73	78.08 ± 10.47	**<0.001**	0.82	89.99 ± 10.01	**<0.001**
LN	37.39 ± 9.27	46.25 ± 10.25	**<0.001**	0.91	52.53 ± 9.49	**<0.001**
LN follow-up	40.28 ± 8.89	48.53 ± 10.14	**<0.001**	0.87	52.77 ± 10.76	**<0.001**
Digits	41.22 ± 7.89	46 ± 8.72	**0.006**	0.57	53.63 ± 9.44	**<0.001**
Digits follow-up	42.14 ± 8.49	47.40 ± 8.49	**0.003**	0.61	52.62 ± 9.18	**<0.001**
TAVEC	30.56 ± 13.72	40.90 ± 11.64	**<0.001**	0.81	53.31 ± 9.35	**<0.001**
TAVEC follow-up	26.39 ± 6.39	48.97 ± 8.31	**<0.001**	3.05	56.59 ± 9.31	**<0.001**
TMT-A	34.83 ± 13.24	42.37 ± 13.78	**0.007**	0.56	49.00 ± 13.88	**<0.001**
TMT-A follow-up	37.83 ± 12.44	47.52 ± 10.81	**<0.001**	0.83	54.19 ± 8.65	**<0.001**
Stroop Interference	48.06 ± 8.04	52.90 ± 8.82	**0.006**	0.57	55.51 ± 9.50	**0.004**
Stroop Interference follow-up	50.25 ± 9.14	54.45 ± 7.56	**0.011**	0.50	57.11 ± 8.00	**0.001**
FAS	35.50 ± 7.38	40.34 ± 8.62	**0.004**	0.60	49.13 ± 8.97	**<0.001**
FAS follow-up	34.64 ± 7.46	45.40 ± 9.44	**<0.001**	1.27	51.47 ± 9.49	**<0.001**
Animal	37.53 ± 10.60	44.85 ± 10.01	**0.001**	0.71	57.81 ± 12.06	**<0.001**
Animal follow-up	36.97 ± 8.38	49.10 ± 10.35	**<0.001**	1.29	59.41 ± 12.07	**<0.001**

Abbreviations: SES=Socioeconomic status, DUP = Duration of Untreated Psychosis, CPZ = Chlorpromazine equivalents, PANSS = Positive and Negative Symptom Scale, YMRS = Young Mania Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, FAST = Functioning Assessment Short Test, GAF = Global Assessment of Functioning, LN = Letter-Number, TAVEC = Verbal Learning Test Spain Complutense for adults, TMT-A = Trail Making Test, form A, FAS = Phonemic Verbal Fluency. Significant differences ($p < 0.05$) marked in bold.

interpersonal relationships ($p = 0.008$), and leisure time ($p = 0.004$)) except occupational functioning ($p = 0.381$). They also differed in terms of neurocognitive performance, showing a lower cognitive functioning in all subtests evaluated at baseline and follow-up in patients with cognitive impairment than those with intact cognitive functioning.

To identify the predictors related to cognitive clusters at follow-up a backward stepwise logistic regression analysis was performed. The cluster group was the outcome variable and the predictors included in the model were those that showed statistically significant differences between the groups at baseline in the univariate analysis: SES, age of onset, negative symptoms and CR. Only CR (OR = 1.073, 95%CI [1.020–1.130], $p = 0.007$) was significantly associated with cluster membership at follow-up. The results showed that the adjusted logistic regression had a good model fit ($x^2 = 14.192$, $p < 0.001$, Nagelkerke $R^2 = 0.221$) and allowed for a correct classification of 75.9% of the cases. However, it is possible that changes in cognitive performance may be related to changes in the severity of symptoms or functionality. For that reason, we included in the subsequent model these clinical and functional changes as a predictors. CR (OR = 1.071, 95%CI [1.005–1.141], $p = 0.035$), FAST at baseline (OR = 0.948, 95%CI [0.900–0.999], $p = 0.046$), age of onset (OR = 1.133, 95%CI [1.012–1.268], $p = 0.031$), changes in FAST (OR = 0.931, 95%CI [0.883–0.983], $p = 0.009$) and changes in negative symptoms (OR = 1.161, 95%CI [1.035–1.303], $p = 0.011$) were significantly associated with cluster cognition at follow-up.

The results showed that the adjusted logistic regression had also a good model fit ($x^2 = 26.369$, $p < 0.001$, Nagelkerke $R^2 = 0.446$) and allowed for a correct classification of 83.6% of the cases.

4. Discussion

Four main findings emerged from the present study: 1) There are two well defined cognitive clusters at baseline in patients with SSD (cognitive impairment and relatively intact cognition); 2) At follow-up, the same clusters were found showing a certain degree of cognitive stability among FEP. However, 35/64 (54.7%) of them improved their performance (changed from the cognitively impaired cluster to the cognitively intact group) and only 7/50 (14%) patients crossed from the intact group to that with cognitive impairment; 3) The cognitively impaired group at two-year follow-up was more likely to present lower SES, early age of onset, more prominent negative symptoms (baseline), greater total PANSS score (follow-up) and lower CR; 4) Finally, CR was the only variable that predicted cognitive impairment after adjusted analysis. However, when clinical and functional changes were included in the model, CR, FAST at baseline, age of onset, changes in FAST and changes in negative symptoms were significantly associated with cluster cognition at follow-up.

Previous publications have reported evidence of a cognitively intact cluster in patients with psychosis that did not differ from normative means (Uren et al., 2017; Lewandowski et al., 2018). In a FEP sample, Uren et al. (2017) described three clusters (widespread cognitive impairments, moderately impaired cognitive functioning, and pattern of cognitively intact performance across all domains). Furthermore, Lewandowski et al. (2018) have recently demonstrated 4 cognitive clusters in patients with psychosis (a neuropsychologically normal cluster, a globally impaired cluster, and two clusters of mixed profiles). The strengths of our study were that the FEP sample was very well characterized and the period of follow-up was longer than the previously mentioned studies (24 months vs. 6 months or without follow-up). Our results showed that relatively cognitively intact group showed a worse cognitive profile than HC, thus, it cannot be considered as an intact cluster as that group performs in the normal range but there is no confirmation of them not having declined from premorbid levels. At 2-year follow-up, the same two groups were maintained. Findings in our sample showed that up to 54.7% of patients with cognitive deficits at baseline tended to improve during the first two years of treatment and at follow-up just 31.6% of patients presented cognitive impairment. Thus, these results suggest that cognitive impairment is relatively stable after a FEP, but when patients do show changes they are more likely to improve than to decline. In fact, longitudinal studies in first episode patients have shown that most of the functions affected seem to improve modestly after the start of treatment (Hill et al., 2004; Haring et al., 2017). Our study suggests that in SSD patients, those subjects with a lower SES, early age of onset, higher negative symptoms, lower CR and worse cognitive performance have an increased risk of cognitive impairment at follow-up, which is in accordance with previous publications in which a large correlation between CR, SES, negative symptoms and cognition have also been reported (Puig et al., 2017; Amoretti et al., 2018). Therefore, identifying differences between people with and without cognitive impairment can provide extremely useful information in order to define personalized interventions in FEP (Sánchez-Torres et al., 2018). Thus, the improvement could be attributed to protective factors (CR and age of onset) and the effects of treatment (greater reduction in the severity of negative symptoms and better functioning), which are in line with the findings of longitudinal studies performed in adults with FEP (Davidson et al., 2009).

Despite the fact that several variables have been associated with cognition, CR was the only variable at baseline that predicted cognitive impairment at follow-up and allowed for a correct classification of 75.9% of the cases. These patients with relatively intact cognition profiles exhibited greater CR, which is in accordance with previous studies in which the CR and cognitive performance has been analyzed in a FEP sample (de la Serna et al., 2013; Amoretti et al., 2016, 2018, 2020). Together with previous studies, our results lead us to consider that it can be very helpful to evaluate CR as it may aid in the stratification of patients with FEP. Based on these results, if conducted in the early stages of the illness or even on people with a high risk of suffering psychosis, the implementation of early interventions centered on CR stimulation and engaging lifestyle could be beneficial in preventing or reducing the impact of illness. However, future and longer follow-up studies are needed to further explore the implementation of these interventions. Also, as suggested in earlier papers (Amoretti et al., 2018, 2019), patients with a FEP and low CR could benefit from a cognitive rehabilitation program. Since cognitive deficits predicted long-term functioning, they serve as natural targets. Nevertheless, this study emphasizes those with low CR who will present a cognitive impairment.

Because previous studies have shown that patients who demonstrate a better cognitive performance also display a greater reduction in the severity of negative symptoms (Milev et al., 2005; Rodríguez-Sánchez et al., 2013) and improvements in cognitive domains seem to be significantly correlated with better functioning in SSD patients (Rodríguez-Sánchez et al., 2013), we introduced changes in the severity of symptoms and functionality to the predictive model. The results showed that the cognitive functioning of our patients at follow-up could be attributed to CR, age of onset and improvement in the severity of negative symptoms and functioning. These results suggest two important findings that should be further explored: 1) The concept of CR has been defined as the ability of a brain to cope with brain pathology in order to minimize symptoms (Stern, 2002). Thus, probably patients with relatively intact cognition may also have experienced neuroprogressive effects, but starting from a higher baseline due to CR (Lewandowski et al., 2018). Besides, CR, cognition and functionality are associated concepts and the results obtained confirm this association; and 2) Improvement in the severity of negative symptoms and psychosocial functioning in early stages could predict better cognitive performance. Thus, we consider that early implementation of cognitive-behavioral therapy interventions could be beneficial to reducing the impact of illness (Granholm et al., 2018).

Some limitations of our work should be taken into consideration before translating these findings into clinical practice. Firstly, a limitation present in all CR studies undertaken on a psychiatric population is that at this time there was no validated instrument to measure CR so criteria established and replicated in previous studies were followed. In 2019, the Cognitive Reserve Assessment Scale in Health (CRASH) (Amoretti et al., 2019) has been validated. It is the first measure developed specifically for patients with severe mental illness with optimal psychometric properties, facilitating reliable and valid measurement of CR. A second limitation is the diagnostic time instability of the FEP. However, the evidence suggests a high prospective consistency for schizophrenia and bipolar disorder (Fusar-Poli et al., 2016). The diagnosis was established based on data collected at a two-year follow-up visit. In spite of its limitations, the study shows innovative and significant results that can be implemented in daily clinical practice.

In summary, our results showed that CR and age of onset were identified as the only baseline variables that predicted cognitive profile. This research allowed us to obtain a better understanding of the heterogeneous profile of FEP and also suggested that CR measure should be considered as a tool that is supplemental to the comprehensive assessment of this group of patients and may be useful for prognosis and treatment. Future research should be conducted to explore cognitive profiles using Cluster Analysis at baseline and follow-up according to diagnosis (SSD vs. affective FEP).

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CRediT authorship contribution statement

SA and FDR designed the study, managed the literature searches and analyses, undertook the statistical analysis, and wrote the first draft of the manuscript.

ARR, EV and MBe revised the first draft and added critical comments to guide the redaction of the final manuscript.

GM, AMS, DF, BC, AL, AG, LP, IC, CT, ES, DB, MBi, MG, MS and MJC revise the second draft of the article and provided critical comments to guide the redaction of the final manuscript.

All the authors within the PEPs Group recluted patients and healthy controls at their centers, provided the anonymous data and revise the final manuscript.

All authors approved the final manuscript.

Declaration of competing interest

MBi has received honoraria from talks and consultancy of Adamed, has received honoraria from consultancy of Ferrer, has received research support and honoraria from talks and consultancy of Janssen-Cilag, has received honoraria from talks and consultancy of Lundbeck, has received honoraria from talks and consultancy of Otsuka, and a research prize from Pfizer.

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The rest of authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

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