Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2018: 1–15

DOI: 10.1111/acps.12949

Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis

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Amoretti S, Cabrera B, Torrent C, Mezquida G, Lobo A, González-Pinto A, Parellada M, Corripio I, Vieta E, de la Serna E, Butjosa A, Contreras F, Sarró S, Penadés R, Sánchez-Torres AM, Cuesta M, Bernardo M. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis.

Objective: Cognitive reserve (CR) refers to the brain's capacity to cope with pathology in order to minimize the symptoms. CR is associated with different outcomes in severe mental illness. This study aimed to analyze the impact of CR according to the diagnosis of first-episode affective or non-affective psychosis (FEP).
Method: A total of 247 FEP patients (211 non-affective and 36 affective) and 205 healthy controls were enrolled. To assess CR, common proxies have been integrated (premorbid IQ; education–occupation; leisure activities). The groups were divided into high and low CR.
Results: In non-affective patients, those with high CR were older, had higher socioeconomic status (SES), 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 SES, better functioning, and greater verbal memory performance.
Conclusion: CR plays a differential role in the outcome of psychoses according to the diagnosis. Specifically, in order to address the needs of non-affective patients with low CR, cognitive rehabilitation treatments will need to be 'enriched' by adding pro-cognitive pharmacological agents or using more sophisticated approaches. However, a functional remediation therapy may be of choice for those with an affective psychosis and low CR.

Significant outcomes

- A higher CR can result in a higher level of cognitive performance in patients with a first-episode of psychosis (FEP).
- In non-affective psychosis, CR level had an impact on cognitive outcomes at 2-year follow-up. Specifically, 11% of verbal memory score, 14% of attention, and 23% of working memory significantly increased from baseline to 2-year follow-up in the high CR group with minimal improvement in the low CR group.
- In affective psychosis, those with high CR presented a better functioning and better verbal memory performance.

Limitations

- The difference in the sample size between diagnoses (non-affective vs. affective). However, it was a naturalistic and longitudinal study, and the sample had been well characterized.
- There is no validated instrument for measuring CR. In the study the three proxies that are most often applied in the literature have been used.
- The diagnosis of first-episode psychosis is frequently modified during the course of the illness. However, to ensure diagnostic stability, this was determined at 2-year follow-up visit.

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Key words: cognition; first episode; cognitive remediation; neuropsychology; cognitive reserve

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Accepted for publication July 25, 2018

Introduction

The concept of cognitive reserve (CR) has been defined as the ability of a brain to cope with brain pathology in order to minimize symptoms (1). Therefore, CR refers to the capacity to make flexible and efficient use of cognitive networks and can become a skill set that allows some people to actively offset the effects of the disease (2).

At the beginning, the concept of CR was developed in the context of aging and dementia. In chronic neurodegenerative conditions such as Alzheimer's disease, human immunodeficiency virus (HIV) or multiple sclerosis, it has been widely studied (3–5). Some questionnaires were created to measure the cognitive reserve of patients with dementia and of the general population, including the 'cognitive reserve questionnaire' (6), 'CR Index questionnaire' (CRIq) (7) and 'Cognitive Reserve Scale' (8). In the field of mental disorder the concept of CR has not been accurately defined and has been characterized by different variables. In recent studies, a CR score is obtained based on the following variables: estimated premorbid IQ, educational level and occupational attainment and leisure activities (9–13). The existing literature demonstrates that the three components of CR are necessary. In dementia, it has been established that enriching environments promote neurogenesis in the dentate gyrus of the hippocampus (14). Thus, leisure activities provide a continuous mental exercise and stimulation that are fundamental to continue developing and maintaining the cognitive reserve. Another study found that CR behaved as a mediator of working memory; premorbid IQ, one of the components of CR, alone was not enough to mediate capacity (13). Therefore, as de la Serna et al. mentioned (12), while IQ, academic–occupational level and leisure activities are usually studied separately in terms of their relation to CR, taken together, they could reflect the compensation capacity of patients and have a strong influence on clinical and neuropsychological outcomes.

Genetic disposition and environmental exposure play important roles (15,16) in the development of several mental illnesses, but there is increasing evidence to show that the CR may be a resilience factor in at least some psychiatric disorders (17). The evidence suggests that higher CR is associated with a later onset of psychosis and a greater illness insight, which would lead to improved treatment adherence and translate into a better recovery (18,19). Studies carried out to date have shown that CR is a positive moderator of the impact of psychosis on clinical, functional and cognitive outcomes (9–13, 17–20). However, there are few studies about CR and mental disorder. In the field of schizophrenia, the CR was able to predict clinical, functional, and neurocognitive performance (12,13). In the case of bipolar disorder, CR has been associated with a better psychosocial and cognitive functioning (9, 10, 20).

The differences in premorbid adjustment, clinical, functional, and cognitive course between affective and non-affective psychosisare well known. In general, subjects with an affective disorder have a better premorbid IQ than the schizophrenia-spectrum disorders (21). Both disorders seem to suffer a deficit in cognitive function but the magnitude of the impairment is greater in schizophrenia than in bipolar disorder (22). It has been shown that cognition can be considered a predictor of patients' outcome (23) and that a poor premorbid functioning is associated with worse clinical and psychosocial functioning in

patients with a FEP (24). Thus, it is expected that there are differences between affective and non-affective psychotic disorders in terms of cognitive reserve.

Nevertheless, there are no studies analyzing whether there are differences in cognitive reserve between these disorders (non-affective vs. affective psychosis) and their impact on the outcomes (clinical, functional, and cognitive). If we could have this information, it would be possible to propose specific interventions increasing cognitive reserve and, therefore, improving patient recovery.

Aims of the study

The aim of this study was to analyze the role of CR according to diagnosis (non-affective psychosis vs. affective psychosis) in a FEP sample and to investigate the impact of the CR levels on the outcomes (clinical, functional, and neurocognitive measures). This research can allow us to obtain a better understanding of the heterogeneous profile of psychotic disorders and to define personalized interventions.

Material and methods

Sample

The sample of this study came from a multicenter, naturalistic, and longitudinal project 'Phenotype-genotype interaction. Application of a predictive model in first psychotic episodes' (PEPs Project) (24). A total of 247 first-episode psychosis (FEP) and 205 healthy controls (HC) were recruited from 16 centers located throughout the Spanish territory. For this study we included only the subjects who had all the information needed to calculate the cognitive reserve (see Assessments – Cognitive Reserve Assessment).

The inclusion criteria for patients were as follows: (i) aged between 18 and 35 years old at the time of first evaluation; (ii) the presence of psychotic symptoms of less than twelve month duration; (iii) speak Spanish correctly and (iv) signed informed consent. Exclusion criteria were as follows: (i) mental retardation according to DSM-IV criteria; (ii) history of head trauma with loss of consciousness and 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, major depression, or other serious psychiatric illnesses (e.g., bipolar disorder) 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 Ethics and Research Board.

All participants provided written informed consent prior to their inclusion in the study.

Assessments

Clinical and sociodemographic assessment. Clinical and sociodemographic data were systematically obtained for all participants and included the following: age, gender, education, and parental socioeconomic status (SES) determined using Hollingshead's Two-Factor Index of Social Position (26). The pharmacological treatment was measured by chlorpromazine equivalents (CPZE) following the international consensus (27) and the duration of untreated psychosis (DUP) was calculated as the number of days elapsed between the first manifestations of psychotic symptoms and the initiation of adequate treatment for psychosis. The drug misuse habits were also collected using an adapted version of the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence scale (28).

Diagnoses were determined with the Structured Clinical Interview for DSM (SCID-I-II) (29,30) according to DSM-IV criteria. To ensure diagnostic stability, the diagnoses of the patients who completed the study were 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 four scales: the Positive and Negative Syndrome Scale (PANSS) (31,32), the Young Mania Rating Scale (YMRS) (33,34), the Montgomery–Asberg Depression Rating Scale (MADRS) (35,36), and the Clinical Global Impression Scale (CGI) (37). On each scale, the items were summed to obtain a total score. Higher scores indicate greater severity.

Functional assessment. The overall functional outcome was assessed by means of the Functioning Assessment Short Test (FAST) (38) and The Global Assessment of Functioning (GAF) (39). The FAST is a scale used to evaluate six functional domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). Higher scores indicate worse functioning. 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) (40) was applied to assess premorbid adjustment retrospectively. Only childhood and early adolescence life periods have been taken into account as they are the two periods answered by all the participants. Higher scores on the test indicate worse premorbid adjustment.

Neuropsychological assessment. The neuropsychological assessment was made in the second month of evaluation to ensure the psychopathologic stability of patients and was repeated in the 2-year follow-up visit.

The premorbid IQ was estimated using the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III) for adults (41). Sustained attention was tested with the Continuous Performance Test–II (CPT-II) (42), version 5, corrected by age and educational level. Working memory was assessed by the Digit Span Subtest and the Letter-Number Sequencing Subtest of the WAIS-III. The executive functions were evaluated using the Wisconsin Card Sorting Test (43), corrected by age and educational level. To assess verbal memory, Verbal Learning Test Spain Complutense for adults (TAVEC) (44) was used. Inter-rater reliability of neuropsychological tests was undergone in the tests liable to present inter-rater variability ("Vocabulary of the WAIS-III" and "WCST").

A global cognition score was derived from the mean of the aforementioned cognitive domains. Higher scores correspond to better performance in all cognitive domains except for attention.

Cognitive reserve assessment. To assess cognitive reserve we have used the three most commonly proposed proxy indicators of CR which include the following: the premorbid IQ that was calculated with the vocabulary subtest of the WAIS-III; 'education-occupation' which was assessed taking into account the number of years of obligatory education that subjects had completed as well as parents' educational level; and the lifetime school performance and lifetime participation in leisure, social, and physical activities. The last proxy was assessed by PAS scale (scholastic performance) and by asking about involvement in social activities, ability to perform physical activities and enjoyment of hobbies. Higher scores correspond to better performance.

To summarize the information of the three main proxies of CR, a principal components analysis (PCA) was performed to create a "composite CR score" for each subject.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 18. Descriptive analyses were conducted using chi-square for categorical variables and Student's *t*-test for continuous variables. Group differences were examined using unpaired *t*-tests for normally distributed variables, or using Mann–Whitney *U*-tests for non-normal data. When comparing groups on clinical, sociodemographic and neuropsychological variables, analysis of variance (ANOVAS) and analysis of covariance (ANCOVAS) were used to show overall differences between groups.

Inter-rater reliability of neuropsychological tests was undergone in "Vocabulary of the WAIS-III" and "WCST". Ten cases of each test were sent to researchers for their correction. A comparison with the gold standard score, derived from the consensus of three expert evaluators in the administration and correction of these tests has been made. Interclass correlation coefficients (ICCs) were calculated for each test. Evaluators who did not exceed the established cut-off point (ICC > 0.80) had to repeat the process.

A PCA was performed to avoid redundant information of separate test cognitive variables and reduce measures to a few principal domains (see Table S1). The neurocognitive assessment was represented by four factor scores (verbal memory, executive function, attention and working memory) and an overall neurocognitive composite score was calculated as an average of the four domains. A composite score for CR was estimated from the aforementioned variables (see Assessments – Cognitive Reserve Assessment).

The groups were divided into high and low CR by calculating the total group median CR. Subjects with a value above the median were considered to have high CR, and those with a CR below median were assumed to have low CR (20, 45).

A linear regression analysis was carried out to assess the predictive value of CR on clinical, functional, and cognitive variables at 2-year follow-up. The dependent variables included in the model were the total scores of functional (GAF, FAST) and clinical scales (PANSS, YMRS, MADRS, CGI), global composite cognitive score (GCCS), and four neuropsychological domains. In a second step, the analysis was carried out controlling for possible confounders (CPZE, DUP, CGI, SES, tobacco and cannabis in patients and only tobacco and cannabis in the healthy control group).

A repeated-measure analysis of variance (ANOVA) was performed with time (baseline and

2-year follow-up) and group (low and high CR) as the between-group factor.

Results

Sociodemographic characteristics of the sample

A total of 247 FEP patients and 205 HC were enrolled in the PEPs Project. At 2-year follow-up, 162 patients and 156 controls were re-evaluated. The remainder of the sample discontinued or dropped out of the study, mostly due to a loss of follow-up or refusing re-evaluation.

Diagnoses of schizophrenia, schizophreniform, schizoaffective disorders and psychoses that are not otherwise specified were categorized into "non-affective psychoses", whereas bipolar disorder I and II and manic and depressive episodes with psychotic symptoms were grouped as "affective psychoses".

Regarding inter-rater reliability of neuropsychological tests, there was agreement among 90% of the neuropsychologists, surpassing the two phases of reliability in all the tests. Thus, the inter-judge reliability study guarantees that the neuropsychologists carried out a correct application and correction of the tests.

A summary of the baseline sociodemographic and clinical characteristics of patients and HCs is shown in Table 1. There were no differences between patients and healthy controls in terms of age and gender. Significant differences in SES, tobacco and cannabis use, functional outcomes (GAF and FAST), and CR proxies were found. The mean dose of antipsychotic medication was equivalent to 619.55 ± 468 mg/day of CPZE, and the mean of DUP was determined as 103.37 ± 122 days.

At baseline, there were significant differences in sociodemographic, clinical, functional and CR variables among the patient groups (non-affective psychoses vs. affective psychoses). The affective group showed lower negative symptoms and more manic symptoms. In addition, a higher premorbid IQ and composite CR was determined (see Table 2).

In patients with a non-affective psychosis, those who were assessed at follow-up ($n = 139$) were indistinguishable from those who were not ($n = 72$) in terms of age ($t = 0.51$, $P = 0.61$), gender ($\chi^2 = 1.04$, $P = 0.19$), age at first presentation ($U = 2879$, $P = 0.69$), SES ($\chi^2 = 6.54$, $P = 0.26$), DUP ($t = 1.05$, $P = 0.29$), positive PANSS (PANSS-P) ($t = 0.79$, $P = 0.43$), negative PANSS (PANSS-N) ($t = 1.55$, $P = 0.12$), general PANSS score ($t = 0.86$, $P = 0.39$), total PANSS score ($t = 1.23$, $P = 0.22$), total MADRS score ($t = 1.30$, $P = 0.20$), YMRS ($U = 4561$, $P = 0.08$), GAF ($t = 1.05$, $P = 0.30$), FAST score ($t = 0.50$, $P = 0.62$), tobacco ($\chi^2 = 0.02$, $P = 0.51$), and cannabis use ($\chi^2 = 0.43$, $P = 0.31$) at first presentation. They also failed to show differences in the cognitive domains (verbal memory, $t = -1.54$, $P = 0.13$; executive function, $t = 0.97$, $P = 0.34$; attention, $t = 0.47$, $P = 0.64$; working memory, $t = -0.42$, $P = 0.68$). However, these two groups differed in terms of CR ($t = -2.42$, Cohen's $d = 1.10$, $P = 0.016$), showing a lower CR in patients assessed at baseline and follow-up than those who were assessed only at baseline.

In patients with an affective psychotic disorder, those who were assessed at follow-up ($n = 23$) were indistinguishable from those who were not ($n = 13$) in terms of age ($t = 0.33$, $P = 0.75$), gender ($\chi^2 = 2.21$, $P = 0.13$), age at first presentation ($t = 1.14$, $P = 0.27$), SES ($t = 3.19$, $P = 0.67$), DUP ($t = 0.67$, $P = 0.51$), total MADRS score ($t = 0.90$, $P = 0.38$), GAF ($U = 471$, $P = 0.18$), FAST score

Table 1. Baseline sociodemographic, clinical, diagnosis, and CR proxies for patients with FEP and healthy controls

	Patients ($n = 247$)	Healthy controls ($n = 205$)	Statistic	*P*-value
Gender: Male *N* (%)	165 (67)	132 (64)	$\chi^2 = 0.29$	0.62
Age ($\bar{X} \pm$ SD)	25.25 ± 5	25.69 ± 6	$t = -0.87$	0.38
SES (%)			$\chi^2 = 19.16$	**0.002**
High	44 (18)	46 (22)		
Medium–High	24 (10)	40 (20)		
Medium	65 (26)	57 (28)		
Medium–Low	81 (33)	51 (25)		
Low	30 (12)	9 (4)		
Missing value	3 (1)	2 (1)		
Tobacco use: Yes *N* (%)	170 (69)	85 (41)	$\chi^2 = 34.11$	**<0.001**
Cannabis use: Yes *N* (%)	110 (45)	38 (19)	$\chi^2 = 34.38$	**<0.001**
GAF score	53.51 ± 18	93.02 ± 5	$U = 858.50$	**<0.001**
FAST	28.34 ± 16	2.90 ± 7	$U = 2669.00$	**<0.001**
Clinical variables ($\bar{X} \pm$ SD)				
PANSS positive	17.90 ± 8	NA		
PANSS negative	18.72 ± 8	NA		
PANSS general	37.24 ± 12	NA		
PANSS total	73.86 ± 23	NA		
YMRS score	8.29 ± 10	NA		
MADRS score	12.62 ± 9	NA		
CR proxies ($\bar{X} \pm$ SD)				
Education/ Occupation	4.69 ± 2	6.07 ± 2	$U = 15332.00$	**<0.001**
Leisure	1.21 ± 1	1.71 ± 0.2	$U = 15411.50$	**<0.001**
Premorbid IQ	92.29 ± 15	107.22 ± 13	$t = -11.09$	**<0.001**
Composite CR	75.22 ± 12	88.04 ± 11	$t = -11.81$	**<0.001**

SES, socioeconomic status; GAF, Global Assessment of Functioning; FAST, Functioning Assessment Short Test; PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; CR, cognitive reserve; IQ, Intelligence Quotient; NA, not applicable. Significant differences ($P < 0.05$) marked in bold.

Table 2. Baseline sociodemographic, clinical, functional, and CR proxies for patients (affective vs. non-affective)

	Patients (n = 247)			
	Non-affective (n = 211)	Affective (n = 36)	Statistic	P-value
Gender: Male N (%)	140 (66)	25 (69)	$\chi^2 = 0.13$	0.44
Age ($\bar{X} \pm$ SD)	25.33 ± 5	24.75 ± 6	$t = 0.62$	0.54
SES (%)			$\chi^2 = 10.93$	0.05
High	41 (19)	3 (8)		
Medium–High	19 (9)	5 (14)		
Medium	49 (23)	16 (44)		
Medium–Low	73 (35)	8 (22)		
Low	27 (13)	3 (8)		
Missing value	2 (1)	1 (3)		
DUP	108.73 ± 124	72.06 ± 101	$t = 1.58$	0.12
Age of onset	24.63 ± 6	25.57 ± 6	$t = -0.74$	0.46
CPZE	624.33 ± 441	589.79 ± 616	$t = 1.58$	0.70
Tobacco use: Yes N (%)	143 (68)	27 (75)	$\chi^2 = 0.75$	0.26
Cannabis use: Yes N (%)	97 (46)	13 (36)	$\chi^2 = 1.21$	0.18
GAF score	52.89 ± 18	57.14 ± 20	$t = -1.29$	0.20
FAST	28.64 ± 16	26.61 ± 15	$t = 0.71$	0.48
Clinical variables ($\bar{X} \pm$ SD)				
PANSS positive	17.96 ± 8	17.56 ± 7	$t = 0.29$	0.77
PANSS negative	19.33 ± 8	15.14 ± 7	$t = 3.03$	**0.003**
PANSS general	37.37 ± 12	36.44 ± 12	$t = 0.44$	0.66
PANSS total	74.66 ± 23	69.14 ± 22	$t = 1.33$	0.18
YMRS score	7.69 ± 9	11.81 ± 12	$t = -2.34$	**0.020**
MADRS score	12.42 ± 9	13.78 ± 10	$t = -0.80$	0.42
CGI score	4.12 ± 1	3.66 ± 2	$U = 3170.00$	0.27
CR proxies ($\bar{X} \pm$ SD)				
Education/ Occupation	4.68 ± 2	4.73 ± 2	$t = -0.17$	0.87
Leisure	1.19 ± 1	1.33 ± 1	$U = 3498.50$	0.39
Premorbid IQ	91.33 ± 14	97.92 ± 18	$U = 2915.50$	**0.025**
Composite CR	74.46 ± 11	79.66 ± 15	$t = 0.15$	**0.025**

SES, socioeconomic status; DUP, duration of untreated psychosis; CPZE, chlorpromazine equivalents; GAF, Global Assessment of Functioning; FAST, Functioning Assessment Short Test; PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impression Scale; CR, cognitive reserve; IQ, Intelligence Quotient; NA, not applicable. Significant differences ($P < 0.05$) marked in bold.

($t = 1.07$, $P = 0.29$), tobacco ($\chi^2 = 0.36$, $P = 0.41$), and cannabis use ($\chi^2 = 0.05$, $P = 0.52$) at first presentation. They also failed to show differences in CR ($t = -1.73$, $P = 0.09$) and in different cognitive domains (verbal memory, $t = -1.36$, $P = 0.19$), executive function, $t = 0.15$, $P = 0.88$; attention, $t = -0.36$, $P = 0.72$; working memory, $t = -0.10$, $P = 0.92$). However, these two groups differed in terms of PANSS-P ($t = 4.02$, Cohen's $d = 1.51$, $P < 0.001$), PANSS-N ($t = 2.07$, Cohen's $d = 1.05$, $P = 0.05$), general PANSS score ($t = 3.61$, Cohen's $d = 1.39$, $P = 0.001$), total PANSS score ($t = 2.89$, Cohen's $d = 1.50$, $P = 0.007$) and YMRS ($t = 2.46$, Cohen's $d = 0.62$, $P = 0.019$), showing a worse clinical outcomes in patients assessed at baseline and follow-up than those who were assessed only at baseline.

Comparison of cognitive reserve

Significant differences between patients and control groups in all CR proxies and in composite CR have been found. The patient group obtained lower scores on cognitive reserve compared to the control group (Cohen's $d = 1.01$). After performing a logistic regression to assess the predictive power of CR for each group (patients/controls), the model explained between 23.5% (Cox & Snell R Square) and 31.5% (Nagelkerke R Square) of the variance and correctly classified 70.6% of the cases ($B = 0.097$; $P < 0.001$; Exp(B) = 1.102). Between diagnostic groups, affective patients displayed higher scores than non-affective patients in terms of their composite CR score (Cohen's $d = 1.22$).

Predictive value of CR according to diagnoses

In the control group, the CR was not able to predict any measure except working memory at 2-year follow-up ($R^2 = 0.026$; $P = 0.021$). After adjusting for tobacco and cannabis (variables related to cognitive performance and functioning), the prediction did not remain significant ($P = 0.19$). The predictive capacity of premorbid IQ and GCCS was also evaluated. Neither was able to predict the functionality or neurocognitive performance in healthy controls (see Table S2).

A summary of the predictive capacity of patients' CR is shown in Table 3. The capacity of CR to predict outcome was better than premorbid IQ and neurocognition by itself (GCCS) in both diagnostic groups (non-affective and affective).

In the non-affective psychosis group, the CR was able to predict clinical, functional, and cognitive outcomes. The CR explained 5.5% of the variance on FAST, 3.4% on negative PANSS, 8.4% on verbal memory, 18.6% on attention, 19.4% on working memory, and 7.6% on GCCS. All predictions remained significant even after adjusting for potential confounding variables (CPZE, DUP, CGI, SES, tobacco, and cannabis).

In the affective psychotic disorder group, the CR explained 11.7% of the variance on FAST, 26.5% verbal memory and 32.1% on GCCS. In the next step, the potential confounders were incorporated in the analysis. Although this prediction in verbal memory and GCCS persists after controlling for possible confounders (CPZE, DUP, CGI, SES, tobacco and cannabis), the prediction did not remain significant on FAST ($P = 0.33$).

Table 3. Linear regression with cognitive reserve at 2-year follow-up

	Non-affective patients (n = 139)					Affective patients (n = 23)				
	R^2	B	SE	Beta	P	R^2	B	SE	Beta	P
Functional variables										
GAF	0.019	0.16	0.11	0.14	0.13	0.057	0.19	0.13	0.24	0.16
FAST	0.055	−0.30	0.11	−0.24	**0.008**	0.117	−0.23	0.11	−0.34	**0.042**
Clinical variables										
PANSS positive	0.008	−0.03	0.03	−0.09	0.33	0.047	−0.05	0.05	−0.22	0.36
PANSS negative	0.034	−0.10	0.05	−0.19	**0.037**	0.079	−0.11	0.09	−0.28	0.23
PANSS general	0.007	−0.06	0.07	−0.08	0.37	0.010	−0.05	0.11	−0.10	0.67
PANSS total	0.017	−0.19	0.13	−0.13	0.14	0.045	−0.21	0.23	−0.21	0.37
YMRS	0.002	0.01	0.02	0.02	0.87	0.040	−0.09	0.10	−0.20	0.40
MADRS	0.016	−0.07	0.05	−0.13	0.16	<0.001	−0.01	0.08	−0.02	0.95
Cognitive measures										
Verbal memory	0.084	1.24	0.41	0.29	**0.003**	0.265	1.41	0.63	0.52	**0.041**
Executive function	0.003	0.21	0.39	0.05	0.60	0.029	0.47	0.72	0.17	0.53
Attention	0.185	−0.43	0.09	−0.43	**<0.001**	0.227	−0.34	0.17	−0.48	0.06
Working memory	0.194	0.64	0.13	0.44	**<0.001**	0.074	0.37	0.35	0.27	0.31
GCCS	0.076	1.26	0.43	0.28	**0.005**	0.321	1.38	0.54	0.57	**0.022**

B, the unstandardized beta; SE, the standard error for the unstandardized beta; GAF, Global Assessment of Functioning; FAST, Functioning Assessment Short Test; PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; GCCS, Global Composite Cognitive Score. Significant differences ($P < 0.05$) marked in bold.

The impact of CR levels (high vs. low) and diagnosis on the outcome

Patients were grouped by diagnosis (affective vs. non-affective) and by cognitive reserve scores (low reserve vs. high reserve). Significant differences were found in functionality and cognitive performance among subjects with high and low cognitive reserve (see Table 4), independently of diagnosis.

An additional analysis was performed to test whether the accumulation of CR could be affected by premorbid adjustment in a FEP sample. Significant differences in PAS scores between groups were observed: The FEP group with high CR obtained lower scores than those with low CR ($P = 0.001$).

Non-affective psychotic patients. In the non-affective psychosis group, those with high CR were older and had a better socioeconomic status, as well as a shorter DUP and a later age of onset than those with low CR (see Table 4). At baseline, a significantly better performance was determined in non-affective patients with high CR in different cognitive measures (verbal memory, attention, working memory, and GCCS, $P < 0.001$). After the 2-year follow-up, the non-affective group showed significant differences in all the cognitive domains evaluated, except for executive functions In the non-affective psychosis group, those with high CR were older and had a better socioeconomic status, as well as a shorter DUP and a later age of onset than those with low CR (see Table 4).

Results from the repeated measures ANOVA revealed no significant time × CR level interactions for symptomatology (PANSS-P, $F = 1.36$, $P = 0.25$; PANSS-N, $F = 0.18$, $P = 0.68$; general PANSS, $F = 0.50$, $P = 0.48$; PANSS total, F = 0.47, $P = 0.49$; YMRS, F = 0.57, $P = 0.46$; MADRS, $F = 0.72$, $P = 0.40$), executive functions ($F = 0.91$, $P = 0.34$), FAST, $F = 2.27$, $P = 0.13$ and GAF although a trend was observed ($F = 3.43$, $P = 0.07$). However, there were significant time effects on all variables, indicating an improvement for both the low and high CR groups from baseline to the 2-year follow-up.

Results revealed a significant time × CR level interaction effect for the total score on verbal memory ($F = 13.86$, partial eta squared (ηp^2) = 0.11, $P < 0.001$), attention ($F = 15.57$, $\eta p^2 = 0.14$, $P < 0.001$), and working memory ($F = 34.96$, $\eta p^2 = 0.23$, $P < 0.001$), indicating that the total score of these cognitive domains significantly increased from baseline to 2-year follow-up in the high CR group with minimal improvement in the low CR group.

Affective psychotic patients. In the affective psychosis group, comparing those with high and low CR, there were no significant differences in terms of gender, age, DUP, or age of onset, although significant differences were found in socioeconomic level and education (see Table 4). At baseline, the patients with low CR performed worse in verbal memory compared to affective patients with high CR. At 2-year follow-up in the affective group, differences were observed in functionality. In terms of cognitive measures, there were differences in verbal

Table 4. Sociodemographic, clinical, functional, and cognitive performance among subjects with high and low cognitive reserve at 2-year follow-up

	Non-affective (n = 211)—At follow-up (n = 139)			Affective (n = 36)—At follow-up (n = 23)		
	Low (n = 108) -At follow-up (n = 68)	High (n = 103)—At follow-up (n = 71)	P	Low (n = 13)—At follow-up (n = 7)	High (n = 23)—At follow-up (n = 16)	P
Sociodemographic variables						
Gender: Male N (%)	65 (61)	75 (71)	0.08	8 (62)	17 (74)	0.34
Age ($\bar{X}$ ± SD)	23.31 ± 5	25.97 ± 6	**0.002**	23.08 ± 6	25.70 ± 5	0.18
SES (%)			**<0.001**			**0.049**
High	10 (9)	31 (30)		0 (0)	3 (13)	
Medium-High	7 (7)	12 (11)		1 (8)	4 (17)	
Medium	24 (23)	25 (24)		5 (38)	11 (48)	
Medium-Low	43 (41)	30 (29)		6 (46)	2 (9)	
Low	21 (20)	6 (6)		0 (0)	3 (13)	
Missing value	1 (1)	1 (1)		1 (8)	0 (0)	
Education/occupation	4.05 ± 1	5.32 ± 2	**<0.001**	3.78 ± 1	5.27 ± 2	**0.005**
DUP	127.00 ± 147	90.26 ± 93	**0.043**	110.10 ± 133	54.77 ± 80	0.15
Age of onset	23.31 ± 5	25.97 ± 6	**0.002**	26.57 ± 7	25.13 ± 6	0.63
Functional variables						
GAF baseline	51.23 ± 19	54.57 ± 17	0.18	51.858 ± 19	60.13 ± 20	0.24
GAF follow-up	71.16 ± 15	74.36 ± 13	0.19	68.86 ± 22	83.25 ± 7	**0.026**
FAST baseline	29.90 ± 15	27.36 ± 17	0.26	26.31 ± 16	26.78 ± 14	0.93
FAST follow-up	21.47 ± 16	17.40 ± 14	0.12	23.57 ± 13	9.29 ± 10	**0.012**
Clinical variables						
PANSS positive baseline	18.43 ± 8	17.49 ± 8	0.38	19.15 ± 5	16.65 ± 8	0.32
PANSS positive follow-up	11.10 ± 5	9.85 ± 4	0.11	10.33 ± 5	7.87 ± 2	0.08
PANSS negative baseline	20.25 ± 8	18.40 ± 8	0.09	16.85 ± 8	14.17 ± 6	0.27
PANSS negative follow-up	14.87 ± 7	14.04 ± 6	0.45	13.67 ± 6	10.60 ± 4	0.22
PANSS general baseline	38.25 ± 12	36.50 ± 12	0.28	41.08 ± 13	33.83 ± 11	0.09
PANSS general follow-up	26.59 ± 9	25.22 ± 8	0.37	25.67 ± 7	21.60 ± 6	0.20
PANSS total baseline	76.92 ± 23	72.38 ± 23	0.15	77.08 ± 22	64.65 ± 22	0.11
PANSS total follow-up	52.56 ± 19	49.11 ± 16	0.27	49.67 ± 18	40.07 ± 11	0.14
YMRS baseline	8.37 ± 9	7.01 ± 9	0.29	14.92 ± 12	10.04 ± 12	0.25
YMRS follow-up	2.38 ± 5	1.41 ± 3	0.16	5.57 ± 10	1.27 ± 3	0.12
MADRS baseline	13.49 ± 9	11.33 ± 9	0.09	16.54 ± 10	12.22 ± 11	0.24
MADRS follow-up	6.80 ± 7	5.37 ± 6	0.21	5.00 ± 7	3.53 ± 4	0.54
CGI baseline	3.98 ± 2	4.26 ± 1	0.16	2.92 ± 3	4.09 ± 1	0.09
CGI follow-up	1.70 ± 2	1.80 ± 2	0.51	1.62 ± 2	1.65 ± 2	0.95
Cognitive measures						
Verbal memory baseline	122.00 ± 49	148.21 ± 44	**<0.001**	115.93 ± 49	151.38 ± 47	**0.047**
Verbal memory follow-up	143.44 ± 48	169.39 ± 42	**0.002**	144.98 ± 64	189.75 ± 34	**0.039**
Executive function baseline	124.35 ± 47	126.54 ± 41	0.73	137.78 ± 53	129.05 ± 30	0.57
Executive function follow-up	146.34 ± 46	149.77 ± 40	0.67	142.66 ± 38	163.80 ± 32	0.20
Attention baseline	91.79 ± 8	87.22 ± 9	**<0.001**	88.11 ± 9	86.50 ± 10	0.68
Attention follow-up	90.86 ± 12	83.75 ± 8	**<0.001**	90.14 ± 8	85.62 ± 10	0.43
Working memory baseline	71.87 ± 14	84.97 ± 14	**<0.001**	76.36 ± 20	82.99 ± 15	0.26
Working memory follow-up	75.68 ± 14	87.63 ± 14	**<0.001**	77.38 ± 20	86.66 ± 18	0.29
GCCS baseline	281.62 ± 50	309.49 ± 46	**<0.001**	283.73 ± 42	307.61 ± 47	0.22
GCCS follow-up	313.01 ± 50	339.37 ± 45	**0.005**	318.91 ± 26	360.65 ± 30	**0.026**

SES, socioeconomic status; DUP, duration of untreated psychosis; PAS, Premorbid Adjustment Scale; GAF, Global Assessment of Functioning; FAST, Functioning Assessment Short Test; PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impression Scale; GCCS, Global Composite Cognitive Score. Significant differences ($P < 0.05$) marked in bold.

memory and in the global composite cognitive score.

Results from the repeated measures ANOVA revealed no significant time × CR level interactions for symptomatology (PANSS-P, $F = 2.063$, $P = 0.167$; PANS-N, $F = 0.22$, $P = 0.64$; PANSS general, $F = 1.35$, $P = 0.26$; PANSS total, $F = 1.33$, $P = 0.26$; YMRS, F = 2.20, $P = 0.15$; MADRS, F = 3.804, $P = 0.06$), functionality (FAST, $F = 3.97$, $P = 0.06$; GAF, $F = 2.63$, $P = 0.12$), and all cognitive domains (verbal memory, $F = 4.23$ $P = 0.06$; executive functions, $F = 2.13$, $P = 0.16$; attention, $F = 1.04$, $P = 0.32$; working memory, $F = 1.23$, $P = 0.28$). However, there were significant time effects on all variables, indicating an improvement for both the low and high CR groups from baseline to 2-year follow-up. A trend was observed in FAST ($F = 3.97$, $P = 0.06$) and verbal memory ($F = 4.23$ $P = 0.06$), indicating that the total score of functionality and verbal memory

increased from baseline to 2-year follow-up in the high CR group with minimal improvement in the low CR group.

Discussion

The most important finding of the study is that the patients with a FEP who have a high CR show a better neurocognitive performance. However, the implications of CR depend on whether the diagnosis is affective or non-affective. The CR possesses a predictive capability which persists even after potential confounding factors are controlled for (antipsychotic medication, duration of untreated psychosis, illness status, socioeconomic status, tobacco, and cannabis). This suggests that CR can be used as a reliable indicator for the evolution of patients with a FEP, especially for neurocognitive performance and functioning.

As expected, control subjects show a higher cognitive reserve level than the patients. This result is in accordance with previous studies in which the CR of both patients and control subjects was compared (10, 12, 13). They also match the neurological development deficit model, which considers that the accumulated CR can be affected by the age of illness onset (17). In addition, our results showed that the FEP group with high CR showed a better premorbid functioning compared to those with low CR, which could also indicate this inference in the accumulation of CR. In this regard, the literature suggests that neurodevelopmental impairment is present before illness onset (21) and that early insults to the brain are manifested through deviant neurodevelopmental trajectories before the onset of psychotic symptoms (46). However, other factors that could explain these results are the significant differences in years of schooling and socioeconomic level (47).

The group with an affective FEP shows a higher CR compared to those with a non-affective FEP. To our knowledge, there is no published research comparing CR levels according to diagnoses; however, some studies have already demonstrated that premorbid IQ (an essential component of the CR concept) is higher in affective patients (20, 48).

Regarding the CR's predictive quality, we have observed that in control subjects it cannot predict cognitive performance nor functionality level. One possible explanation of these results could be the CR concept itself, which refers to the brain's capacity to face a pathology using alternative, or more efficient, cerebral networks in order to minimize symptoms (1). In healthy control subjects, there is no pathology, and thus, CR does not possess any predictive quality in the various assessed outcomes. Another explanation could be that healthy controls acquire skills during the 2 year follow-up such as finishing school or starting a job. As mentioned previously, academic–occupational level, lifetime exposures and engaging in stimulating and physical activity increase the CR (2).

When it comes to patients, results suggest that the predictive quality of CR depends on diagnosis. In non-affective psychosis, CR predicts functioning, clinical and cognitive performance. These results are in line with previous studies (12,13) and confirm that a poor premorbid functioning is associated with a worse functioning in patients with a FEP (24) and to the symptoms severity, especially the negative ones (13, 49–51). However, it is important to note that this explains a low variance percentage both in functionality and in symptomatology. These findings indicate that, while this is an important factor in different outcomes, there are other variables that need attention: individual characteristics (including environmental risk factors, family support, treatments received, and aspects of symptomatology, cognition and personality) and antipsychotics dose (52), among others. Considering cognitive performance, CR predicts verbal memory, attention span, working memory, and global cognition in non-affective psychotic patients.

These findings show that CR can have a relevant role in cognitive performance. More precisely, working memory control is the domain most associated with CR in patients with first-episode psychoses and first-episode schizophrenia (12,13), in our case predicting 19.4% of variance.

In the case of patients with an affective psychotic disorder, the predictive quality is higher. CR predicts cognition (neither functionality nor clinical outcomes). In line with our results, previous publications have reported a large correlation between CR and cognitive performance within verbal memory in patients with bipolar disorder (9). In our case, this cognitive variable predicted a 26.5% of variance. A trend was observed in functionality (FAST scale) using a regression and ANOVA analysis, indicating that the total functionality score increased from baseline to 2-year follow-up in the high CR group with minimal improvement in the low CR group. Cognition and functionality are two associated concepts (53,54), and the obtained results confirm this association. Therefore, taking these results into account, it can be confirmed that patients with an affective FEP and with a high CR are able to function better.

Therefore, in our study as in the de la Serna and Amoretti studies (12,13), both including FEP samples, in non-affective psychosis CR mostly predicts

working memory and is less predictive of other cognitive domains. In affective psychosis, different studies (9, 10, 20) have shown that CR was significantly predictive of functioning and different cognitive domains. However, the results are more inconsistent, and CR largely fails to predict the same cognitive domain across the different studies. In euthymic bipolar patients, Forcada et al. (10) revealed that CR was significantly predictive of FAST score (54.4%), Executive Index (55%), and Visual Memory Index (39%), introducing CR, current age, age at illness onset, duration of illness, and period of clinical stabilization in the multiple linear regression models. On the other hand, Anaya et al. (9) have demonstrated that CR was significantly predictive of psychosocial functioning (23%), attention (10%), working memory (20%), verbal memory (20%), visual memory (14%), executive functioning (12%), and processing speed (18%) introducing CR, age, chronicity and bipolar type in the model. The differences between our results and the results of the aforementioned studies can be attributed to the fact that our sample was composed of affective FEP patients and the other studies were with euthymic bipolar patients. Other differences include the sample size (in our study 26 affective patients were assessed at follow-up) and the variables introduced in the multiple linear regression models.

Considering that these results show that the CR's prediction quality differs depending on diagnosis (non-affective or affective FEP), CR was divided into high and low to analyze its role more deeply. In non-affective patients, those subjects with a high CR show a higher socioeconomic level, a lower DUP and a later age of onset. This could indicate that those subjects with a higher CR are able to tolerate the pathology's effects for a longer time, as occurs with Alzheimer's disease (55). Regarding symptomatology, there are no significant differences between those non-affective patients with high and low CR. Thus, even if CR can predict symptomatology, its predictive capabilities are limited. CR alone is not enough to explain the heterogeneity of clinical repercussions that non-affective patients show after a FEP. In cognition, patients with a high CR show a better neuropsychological performance. Based on these results, an intervention oriented toward cognitive rehabilitation can be suggested (56) in patients with a low CR. As shown in previous studies, this intervention could improve performance in cognitive domains and therefore also improve functionality (57–59). Specifically, in order to address the needs of patients with low CR, cognitive rehabilitation treatments will need to be 'enriched' by adding some pro-cognitive pharmacological agents (60,61) or using more sophisticated approaches like the action-based cognitive remediation treatment (62).

In patients with affective psychosis, it has been observed that those with a low CR have a lower socioeconomic level and a worse performance in verbal memory compared to patients with a high CR. After 2 years of evolution, they present a lower functionality and they continue to show a lower global cognitive functioning and verbal memory. No significant differences were found in the other evaluated cognitive domains. In the same line, Grande et al. (20) showed that in euthymic bipolar patients, those with high and low CR differ in verbal memory performance. This result suggests that when facing a first psychotic episode with a low CR, interventions should be oriented toward improving verbal memory and functionality (63). Therefore, it is convenient to establish a functional remediation therapy in FEP affective patients with low CR as it is the intervention that has been shown to be most effective in improving psychosocial functioning and verbal memory, the only altered domain found in our study (64,65).

In summary, the results show that CR level can be a cognitive performance moderator during first psychotic episodes (affective or non-affective) and that a higher CR can lead to a better recovery and functioning in these patients. Despite the fact that these findings are in accordance with previous literature (20), to the best of our knowledge, none of the previous studies on CR focused on the impact of CR according to the diagnosis of first-episode affective or non-affective psychotic disorder.

These results lead us to consider that it can be very helpful to evaluate CR (2). Unlike a neurocognitive assessment, which should only be administered by a trained medical professional, the CR can be carried out by professionals from different areas (nurses, therapists and doctors, among others), which facilitates its application. The evaluation of CR may aid in the stratification of patients with FEP who could be more likely to present cognitive deterioration over the course of their illness. It can also serve as a resource to explore new therapeutic targets. There are already neuropsychological interventions aimed at improving cognitive functioning, but until now the impact of intervening on the different components of CR in FEP has not been explored.

Although there are important premorbid variables in the CR concept that are difficult to modify, such as premorbid IQ or education, the key role played by environmental factors, such as physical, social, or leisure activities, should also be taken into account. Some studies have shown that

physical and cognitive stimulation can increase CR and thus render individuals more capable of compensating for the development of the neuropathology (14, 66). In the case of dementia, this has been related to delayed onset (posterior to cognitive deficit) and to the appearance of clinically diagnosable dementia (67). Therefore, increasing CR can become a skill that will allow patients to cope better with the disease and minimize the decline in cognitive and psychosocial functioning (9, 13). We consider that the implementation of early interventions centered on CR stimulation and engaging lifestyle, conducted in the early stages of the illness, or even in people with a high risk of suffering psychosis, could be beneficial to preventing or reducing the impact of illness (68–70).

The present study backs the necessity of performing thorough assessment of cognitive reserve and diagnosis in patients before implementing personalized early intervention programs (71,72). It also emphasizes the need to explore the impact of specific interventions in areas such as social, mental, physical activities and hobbies on CR, as it could be useful to guide the development of personalized treatment programs.

This study has certain limitations which must be taken into account. First, a limitation is the difference between the group size of affective and non-affective psychotic groups, as well as the difference between patients who were assessed at follow-up and those who were not. In the affective group, the small sample size may have interfered with the results (low statistical power), and further larger studies are required to confirm these findings. However, it is important to note that this is a naturalistic, multicentric and longitudinal study. This fact makes the sample representative of FEP as it occurs in Spain. Furthermore, the sample is very well characterized because it includes different variables of interest and a longitudinal monitoring is performed. Second, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed (premorbid IQ, occupational/educational level, and free time activities). The final limitation would be the diagnostic instability of the first episodes of psychosis. However, the evidence suggests a high prospective consistency for schizophrenia and bipolar disorder (73,74). Depressive psychosis shows lower prospective consistency because a substantial percentage of cases develop bipolar affective disorder over time. Nevertheless, in this study, only two diagnostic categories were generated (affective/non-affective), thus in this case they would still belong to the same group. In addition, the diagnosis was established based on data collected in examinations after 2 years of monitoring. In spite of its limitations, the study shows innovative and significant results that can be implemented in daily clinical practice and, to the best of our knowledge, it is the first study to divide a FEP sample according to diagnosis with a view to analyzing the impact of CR in the long-term outcome of psychoses. In conclusion, the CR characterization can considerably improve our understanding of individual differences in the causes and consequences of neuropsychiatric disorders (17) and can be useful as a stratification tool in FEP patients, thus enabling the implementation of personalized interventions. Further research should be conducted on the possible differential effects of CR on different disorders and more longitudinal studies that determine an effective specific treatment for the improvement of CR are necessary to validate the results obtained.

Acknowledgements

We are extremely grateful to all participants. This study is part of a coordinated-multicentre Project, funded by the Ministerio de Economía y Competitividad (PI08/0208; PI11/00325; PI14/00612), Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional. Unión Europea. Un manera de hacer Europa, Centro de Investigación Biomédica en Red de salud Mental, CIBERSAM, by the CERCA Programme/Generalitat de Catalunya and Secretaria d'Universitats i Recerca del Departament d'Economia I Coneixement (2014SGR441). EV thanks the support of the Spanish Ministry of Economy and Competitiveness (PI15/00283) integrated into the Plan Nacional de I+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365). CT is funded by the Spanish Ministry of Economy and Competitiveness, Instituto Carlos III, through a 'Miguel Servet' postdoctoral contract (CPI14/00175) and a FIS (PI17/01066). Dr Torrent's project is also supported in part by a SLT006/17/352, integrated in the Strategic Plan of Research and Innovation in Health 2016-2020 (Health Department). CERCA Programme/Generalitat de Catalunya.

Declaration of interest

The authors report no biomedical financial interests or potential conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Principal Component Analysis (PCA) for cognitive variables.

Table S2. Linear regression with Cognitive Reserve (CR), Global Composite Cognitive Score (GCCS) and Premorbid IQ at 2-year follow-up after adjusting for tobacco and cannabis for healthy controls.

Appendix 1

We also would like to thank the authors of the PEPs group who participated in the development of this manuscript, namely, M Bioque (Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, University of Barcelona, Spain; Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain; August Pi I Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain), A Meseguer (Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, University of Barcelona, Spain; Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain; August Pi I Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain), S García (Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain; Araba University Hospital, Bioaraba Research Institute, Vitoria, Spain; University of the Basque Country (UPV-EHU), Vitoria, Spain), J Fernández (Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain; 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