Sex Differences in Cognitive Reserve in Patients with First Psychotic Episodes

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El presente Trabajo de Fin de Máster titulado ``Diferencias de Sexo en Reserva Cognitiva en Pacientes con Primeros Episodios Psicóticos´´ realizado y presentado por Rebeca Magdaleno Herrero como parte del cumplimiento de los requisitos para el Máster ``Iniciación a la Investigación en Salud Mental´´ de la Universidad de Cantabria, ha sido examinado y se recomienda su aceptación y aprobación para su presentación oral.

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Abbreviations

IQ: Intelligence Quotient

PremIQ: Premorbid IQ

CR: Cognitive Reserve

EQZ: Schizophrenia

FEP: First Psychotic Episode

DUI: Duration of illness without treatment

DUP: Duration of untreated psychosis

1. Abstract

Introduction: Cognitive reserve is a predictor of functionality and performance in patients with First Psychotic Episodes (FEP). Research shows that the higher the cognitive reserve (CR), the better the later functioning, both in terms of symptoms and performance in the cognitive domains. Few investigations have considered sex differences on CR.

Objective: To analyse the differences in CR according to sex in FEP patients and in which cognitive domains these differences are mainly observed.

Materials and methods: Retrospective work with 599 individuals (156 controls and 443 FEP patients) from the Programa de Atención a Fases Iniciales de Psicosis. An estimated CR was made by using the proxies: premorbid IQ, years of education and employment status. A neurocognitive battery was administered to evaluate the performance on the domains of verbal memory, visual memory, processing speed, working memory, executive functions, motor skills, attention and theory of mind. Analyses of variance was used to make comparisons between groups.

Results: FEP women had higher scores in estimating CR. In the attention domain, it was the FEP men with high CR who obtained the best scores. In the domains of verbal memory and processing speed FEP women with low CR obtained better scores than FEP men with low CR.

Discussion: These results confirm that FEP women have higher CR than FEP men, which could be related to the later onset of the disease allowing them to complete more years of education.

Keywords: CR, FEP, cognitive domain, sex, neurocognition.

Resumen

Introducción: La reserva cognitiva es un predictor de la funcionalidad y del rendimiento en pacientes con Primeros Episodios Psicóticos (PEP). Las investigaciones muestran que a mayor reserva cognitiva (CR) mejor funcionamiento posterior, tanto de la sintomatología como del rendimiento en los dominios cognitivos. Son pocas las investigaciones que han tenido en cuenta las diferencias de sexo sobre la CR.

Objetivo: Analizar las diferencias de la CR según el sexo en pacientes PEP y sobre qué dominios cognitivos se observan principalmente estas diferencias.

Materiales y métodos: Trabajo retrospectivo con 599 individuos (156 controles y 443 pacientes PEP) del Programa de Atención a Fases Iniciales de Psicosis. Se realizó una estimación de la CR mediante los proxies: IQ premórbido, años de educación y situación laboral. Se administró una batería neurocognitiva para medir los dominios memoria verbal, memoria visual, velocidad de procesamiento, memoria de trabajo, funciones ejecutivas, destreza motora, atención y teoría de la mente. Se utilizaron análisis de varianza para realizar las comparaciones entre grupos.

Resultados: Las mujeres PEP presentaban mayores puntuaciones en la estimación de la CR. En el dominio atención fueron los hombres PEP de alta CR los que obtenían mejores puntuaciones. En los dominios memoria verbal y velocidad de procesamiento las mujeres PEP de baja CR obtuvieron mejores puntuaciones que los hombres PEP de baja CR.

Discusión: Estos resultados confirman que las mujeres PEP presentan mayor CR que los hombres PEP, lo que podría relacionarse con el inicio más tardío de la enfermedad permitiéndoles completar más años de educación.

Palabras clave: CR, PEP, dominio cognitivo, sexo, neurocognición.

2. Introduction

The concept of cognitive reserve (CR) was introduced by Stern in 2002 as the ability of the brain to cope with deficits produced by pathologies (Stern, 2002). This function present in both cognitively impaired and healthy subjects refers to the use of alternative neural networks to increase performance in complex tasks (Stern, 2002). In the population with pathology, alternative networks are used in a flexible and efficient way to allow these subjects to increase their abilities and face their cognitive limitations through compensation (Stern, 2013).

At first, CR was studied in neurodegenerative conditions such as dementias, and conditions associated with diseases such as HIV or multiple sclerosis, with special interest in Alzheimer's disease, where subjects with a high previous educational level have advantages over the cognitive deficits of the disease (Carret et al., 2005) and previous elements such as functionality, intelligence and physical activity act as protective factors regarding the onset of the disease (Scarmeas y Stern, 2003). Subsequently, the study of CR is extended to other psychopathologies, discovering its influence on the evolution of the disorder, the expression of symptoms and the functionality of the subject, being a strong predictor of the evolution of the condition and allowing the establishment of more appropriate interventions. Thus, a subject with a lower level of CR will show greater vulnerability for the development of the disorder (Barnett et al., 2006).

In the field of schizophrenia, Aylward and colleagues (Aylward et al., 1984) showed that a low level of intelligence is a risk factor for the development of the disorder, explained by the research of Barnett and colleagues (Barnett et al., 2006) where cognitive processes mediate the way of perceiving strange experiences and therefore subjects with high cognitive capacity delay the onset of the disorder due to their ability to inhibit or reason such exposures. On the other hand, according to previous research, CR is important in the subsequent functioning

(Green et al., 2000) and use of social skills after the evolution of schizophrenia (Addington y Addington, 2000).

The practical implications of considering CR on cognitive performance during the evolution of first psychotic episodes (FEP) is an important aspect to consider when establishing interventions and treatments that prevent neurocognitive disorders. Furthermore, the evidence so far is contradictory and inconclusive (see **Table 5** in Annexes). Joyce and colleagues (Joyce et al., 2002) show that premorbid IQ was related to the domains of working memory, planning and executive tasks, but not with attention. They also indicate that subjects with FEP have worse impulse control (Joyce et al., 2002). Eberhard and colleagues showed a relationship between CR and the cognitive domains of reaction time and verbal memory (Eberhard et al., 2003).

The study of CR shows an evolution. In the first investigations, the score was obtained through questionnaires such as the *'Cognitive Reserve Questionnaire'* (González et al., 2011) Subsequently, the estimation of CR began to be carried out based on the sum of different factors called proxies such as the estimation of the premorbid intelligence quotient (IQ), educational level and work performance and leisure activities (Amoretti et al., 2016; de la Serna et al., 2013; Stern, 2005). This estimation of CR using different proxies is necessary since Amoretti and colleagues (Amoretti et al., 2016) found that premorbid IQ as the only measure was not sufficient to estimate CR. In accordance with this, de la Serna and colleagues (de la Serna et al., 2013) mentioned that IQ, leisure activities and academic-work level should be studied together in relation to CR, since they can reflect the ability to compensation for patients with clinical or neuropsychological limitations.

Subsequent longitudinal research indicates that subjects with FEP who have low levels of premorbid IQ show improvements over the years, while those with high premorbid IQ remain

stable (van Winkel et al., 2006). The IQ is a predictor of functionality and cognitive performance after the development of the disorder (van Winkel et al., 2007). Specifically, the cognitive domains associated with premorbid IQ were the executive function domain such as planning and working memory (Joyce et al., 2002). However, Leeson and collaborators (Leeson et al., 2009) mention that premorbid IQ will have a greater predictive potential on social functioning than on cognitive domains that are associated with verbal memory, verbal learning and planning (Leeson et al., 2009). Furthermore, these authors comment that the current IQ will be more important than the CR.

For their part, de la Serna and colleagues (de la Serna et al., 2013) report that CR has a predictive capacity on the working memory and attention domains but not on verbal memory and flexibility, while Amoretti and colleagues (S. Amoretti et al., 2016) mention that CR predicts negative symptoms, functionality and functioning in the cognitive domains of working memory and executive functions, subsequently adding verbal memory and attention (Amoretti et al., 2018, 2020; González-Ortega et al., 2019).

However, the literature is ambiguous and although the strong association between CR and the executive functions domain remains, the rest of the cognitive domains vary according to research. The association between CR and theory of mind (ToM) has also been studied, showing a direct relationship (Buonocore et al., 2018), even adding that social cognition is associated with processing speed and verbal memory, acting as a predictor of functionality. (González-Ortega et al., 2019).

When sex differences in CR and evolution of psychotic symptoms are compared, research is scarce and with non-significant results, as can be seen in **Table 1**. Men show higher performance in the domains of visual memory, reaction time and executive functions. compared to women who score better in verbal memory (Ayesa-Arriola et al., 2014).

Furthermore, a subgroup of women with a later onset (in perimenopause) show better performance in problem-solving tasks and visuospatial ability (Ayesa-Arriola et al., 2014). On the other hand, women show preserved IQ and a higher educational level (Leeson et al., 2011) while men have an early onset, lower educational and socioeconomic level along with a worse prognosis of the disease (Ayesa-Arriola et al., 2014). Therefore, subjects with low CR will present a global cognitive deterioration, especially in the processing speed and executive functions domains, with small gender differences where women show better baseline and longitudinal functioning than men (Ayesa-Arriola et al., 2018).

As mentioned, there is a lack of evidence on the diversity of cognitive task performance between women and men in FEP research. For this reason, the present work aims to find cognitive differences based on sex and the CR estimated through the proxies: premorbid IQ, years of education and work situation, in patients with FEP. Previous research found differences in brain structure and function with IQ according to sex in schizophrenic patients (Flaum et al., 1994). Therefore, we can observe that the differences according to sex during the course of the disease were determined by biological and behavioural interactions, a result of the age of onset and course of the disease (Mendrek y Mancini-Marïe, 2016).

As mentioned, no investigations have been found that directly relate CR and differences in cognitive domains according to sex in FEP patients. This work tries to find these differences by hypothesizing that FEP women have a higher CR than FEP men and a better performance in the verbal memory domain. While FEP men would have better performance in the domains of visual memory, reaction time and executive functions (Ayesa-Arriola et al., 2014). Finding these results would be important when establishing an adequate treatment that is as personalized and successful as possible for the patient, since we would know which, cognitive domains will a priori be more affected according to sex in FEP patients.

Table 1. Previous studies of sex differences in patients with FEP

Studies	Sample	Cognitive Reserve	Cognitive Reserve	Other Tests	Statistics	Results	Conclusions
Leeson, Sharma, Harrison, Ron,Barnes and Joyce (2011)	129 FEP	WTAR (WAIS-III)	FSIQ, RAVLT, CANTAB y WAIS-III: information, arithmetic, block design, and digit symbol.	PANSS, SFS, HDRS,YMRS, NOS, PSA and SAI-E.	ANOVA	Stable IQ after the start of psychosis. The IQ at the start of the disorder predicts the gravity of the psychosis. Women with FEP show a more stable IQ.	Low IQ after the start of the psychosis remains stable during the evolution of the disorder, while deteriorated or preserved IQ show improvement. Women with FEP show greater probability of having preserved IQ than men, influenced by more years of education and later debut.
Ayesa-Arriola, Rodriguez-Sanchez, Gomez-Ruiz, Roiz-Santiáñez, Reeves and Crespo-Facorro (2014)	160 FEP	Vocabulary (WAIS-III)	RAVLT, TMT, CPT, Grooved Pegboard, Zoo Map Test, ToL, RCF, FAS and Eye Task, WAIS-III: digits, letters and numbers.	DUP, SANS, SAPS, CDS, YMRS, BPRS, GAF and DAS.	MANCOVA	Women older at the start of the disorder (34,8 vs 27,92) and higher educational levels. Men precox debut, lower educational level and socioeconomic level, more disability, worse global functioning and disorder forecast. Women perform better in RAVLT and recall of list of words. Men better performance in RCF, blocks, ToL and CPT.	Some differences are found, although non significant. Men with FEP have better performance in visual memory, reaction time and executive functions. They present more functional limitations. Women with FEP perform better in verbal memory. Perimenopause women subgroup with later debut present good performance in verbal memory, problem solving and visual-spacial abilities.
Ayesa-Arriola, Setién-Suero, Neergaard, Balzunces, Contreras, Van Haren and Crespo-Facorro (2018)	397 FEP	Vocabulary (WAIS-III)	RAVL, RCF, WAIS III, TMT, Grooved, CPT,	SANS, SAPS, BPRS, CDSS, DAS.	ANOVA	Lower premIQ in men and youngsters, with fewer education years and lower socioeconomic level. General cognitive deterioration, especially in processing speed and executive functions.	The lower the CR, the greater the cognitive global deterioration, especially processing speed and executive functions. Women with FEP better basal functioning and after results than men. Furthermore, women improve over the years.

3. Objectives and hypotheses

General objective: to analyse whether CR presents differences according to sex in patients with FEP.

Specific objective: to study whether there are differences in the main cognitive domains according to sex and CR in patients with FEP.

Hypothesis 1: FEP women will have higher scores in the proxy estimation of CR than FEP men.

Hypothesis 2: FEP women will perform better in the verbal memory cognitive domain.

4. Material and method

4.1. Study design

This work studies the differences between CR in men and women with a first episode of psychosis. The data were obtained from the Program for Attention to Initial Phases of Psychosis (PAFIP), a current longitudinal and epidemiological program that is carried out at the Marqués de Valdecilla University Hospital in Cantabria, Spain (Pelayo-Terán et al., 2008).

Participation in PAFIP was voluntary. The participants were informed about the study and signed the informed consent. Participants were free to withdraw from the study at any time.

4.2. Participants

Five hundred and ninety-nine individuals participated in the present work: 156 controls (being 96 men and 60 women). 443 FEP patients (246 men and 197 women). Participants were part of the PAFIP and were recruited with the following inclusion criteria: 1) be between 15-55 years old, 2) be resident in Cantabria, 3) present a first episode of non-affective psychosis, 4) not have a plan of antipsychotic treatment or wearing less than 6 weeks, 5) follow the DSM-IV diagnostic criteria for schizophrenia spectrum disorders: schizophrenia,

schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and other unspecified psychotic disorders, excluding these types of psychotic disorders . The exclusion criteria were: 1) patients with a history of brain disease or injury or mental retardation, 2) DSM-IV addictive disorders (except nicotine dependence) (Pelayo-Terán et al., 2008).

4.3. Evaluation

4.3.1. Estimation of CR and definition of subgroups by CR

To estimate CR, proxies indicated by the literature were used (Amoretti et al., 2016; Ayesa-Arriola et al., 2018; de la Serna et al., 2013; Stern, 2005) that include: premorbid IQ, education and occupation. This joint estimate was made for the CR because it compensates for the clinical limitations of the FEP participants (de la Serna et al., 2013) and because the premorbid IQ is not sufficient to calculate the CR (Amoretti et al., 2016). Education was collected through the educational years of the participants. Occupation was obtained through information on the employment situation of the participants.

In this work, the premorbid IQ was obtained using the WAIS-III vocabulary subtest (Wechsler, 1997) in contrast to the reading tests administered in Anglo-Saxon research, based on research by Ayesa-Arriola and colleagues (Ayesa-Arriola et al., 2018). Vocabulary as a measure of crystallized intelligence is associated with the knowledge of the subjects including linguistic, phonological and semantic information of the mother tongue, generating an estimate of premorbid IQ in FEP patients and an estimate of IQ in controls.

The participants, both cases and controls, have been assigned to the groups according to the result of the estimation of the CR. The estimate of CR was obtained by adding the proxies of educational years, employment status and the result obtained in the vocabulary subtest of the WAIS-III (Wechsler, 1997). The summation was divided by 3. Considering the arithmetic

mean (score 7), two groups were formed: the low CR group with a score less than or equal to 7; the high CR group with a score greater than 7.

4.3.2. Premorbid and sociodemographic information

The sociodemographic variables considered were age, years of education, place of residence (urban or rural areas), employment status, marital status and parental status. This information was obtained through interviews with patients and relatives using Premorbid Adjustment Scales (PAS) (Cannon-Spoor et al., 1982), using a Likert scale between 0 (" very healthy ") to 6 (" unhealthy ").

4.3.3. Functional and clinical evaluation

For confirmation of diagnosis, the Structured Clinical Interview of the DSM-IV (SCID-I) was administered (First et al., 2001). Various clinical variables were collected. DUI as the time in months from when the first nonspecific symptoms appear until adequate antipsychotic treatment is started. DUP as the time in months since there are continuous positive symptoms until adequate psychotic treatment is started (Pelayo-Terán et al., 2018).

Positive psychotic symptoms were assessed with the Positive Symptom Rating Scale (SAPS) (Andreasen, 1984b), information on negative symptoms was also collected using the Negative Symptom Rating Scale (SANS) (Andreasen, 1984a). SANS and SAPS scores were used to generate symptom dimensions (positive, negative, and disorganized).

Depressive and manic symptoms were assessed with the Calgary Depression Scale (CDSS) (Addington et al., 1993) and Young Mania Rating Scale (YMRS) (Young et al., 1978) respectively. Participants' general psychopathology was also assessed with the Brief Psychiatric Rating Scale (BPRS) (Flemenbaum & Zimmermann, 1973) and functionality with the Global Assessment of Functioning (GAF) (Hall, 1995).

4.3.4. Neuropsychological evaluation

Neuropsychological evaluation was performed by trained neuropsychologists. The cognitive domains evaluated were the following: verbal memory, visual memory, processing speed, working memory, executive functions, motor skills, attention and theory of mind.

Verbal memory was assessed using Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964). This is a list of 15 unrelated words read out loud 5 times by the professional. After each reading, the participant is asked to repeat the words. Having an interference task with 15 other different words read and subsequently asked the participant only once. Immediately afterwards the participant must recall the first list to assess verbal memory. 30 minutes later, the participant can be asked if he remembers the list to evaluate deferred verbal memory, but this data has not been collected in this work.

Visual memory measured by the Rey Complex Figure Test (RFC) (Osterrieth, 1944), showing the participant a figure with abstract lines that must be copied as accurately as possible. Three minutes later the participant is asked to remember the drawing and do it again to assess visual memory. 30 minutes later the same task can be repeated to evaluate delayed visual memory, not required in this work.

Processing speed obtained using the key number subtest of the WAIS-III (Wechsler, 1997). The participant is provided with a table of numbers from 1 to 9 with a different symbol for each number. The participant in another table with numbers and empty boxes for symbols must write down the symbol corresponding to each number as quickly as possible in 120 seconds.

Working memory evaluated with the WAIS-III-digit subtest (Wechsler, 1997). It consists of showing the participant sequences of different digits that they must repeat in the same order that they have been told or the other way around.

Executive functions were obtained using the Trail Making Test (TMT) (Reitan & Wolfson, 1985). Part A requires the participant to connect circles with numbers ranging from 1 to 13. They must join the circles without lifting the pen and in the shortest time possible. In part B the circles contain a number from 1 to 13 or a letter from A to L, the participant must join the circles alternating letter and number in an ascending way, that is, 1-A, 2-B, 3-C ... in the shortest possible time. The completion time is collected to measure selective attention and cognitive flexibility, which are executive functions.

Motor dexterity through the administration of the Gooved Pegboard Test (Lezak, 1995). The participant is shown a table with twenty-five holes with randomly placed slot positions and pegs with keys on one side. The participant must place the pegs in the grooves in the correct position as quickly as possible using the dominant hand. The task is then repeated with the other hand. In this work, only the time required in the task of the dominant hand was collected.

Attention was measured with the Continuous Performance Test (CPT) computerized version (Cegalis, 1991). Letters are alternately presented to the participant on a black background on a computer screen. The participant must press the computer key each time the previously indicated target appears, for example 'the letter X'. For this work only the correct answer is studied.

Theory of Mind (ToM) obtained through the Reading the Mind in the Eyes (Eye Task) test. The participant is presented with 36 black and white photographs of the eye region on the computer screen. The participant is asked to choose between four adjectives (the correct one and three distractors) that describe what the person in the photograph may be feeling or thinking. In all cognitive tests the results were converted into Z scores based on previous research with PAFIP participants.

4.4. Statistical analysis

Statistical analyses are performed with the Statistical Package for Social Science version 22.0 (SPSS Inc, 2020). Comparisons were made between 4 groups: men low CR, men high CR, women low CR and women high CR, independently in FEP patients and in healthy controls. For the dichotomous sociodemographic qualitative variables, a chi-square test was performed.

The quantitative sociodemographic, clinical and functional variables, as well as the neurocognitive variables, were subjected to univariate analyses of variance (ANOVA) including the age of onset in the PAFIP program as a covariate.

Paired comparisons were subsequently made and corrected by Bonferroni. All statistics had two tails and significance was set at $p < 0.05$.

5. Results

In patients, 239 subjects (53%) have a low CR, being 148 (63%) men and 91 (38%) women; in the control group, 68 subjects (44%) had low CR, being 47 (69%) men and 21 (31%) women. On the other hand, in the subgroup with high CR there are 204 FEP patients (46%), of which 98 (48%) are men and 106 (52%) women; the 88 control subjects with high CR (56%), 49 (57%) were men and 39 (44%) were women.

5.1. CR subgroup comparisons

Table 2 shows the sociodemographic and clinical characteristics of the sample comparing the subgroups of low CR vs. high CR in FEP patients, as well as between sex.

Table 2. Sociodemographic and clinical comparisons in CR subgroups of FEP patients

	MALES				FEMALES						
	1: Low CR		2: High CR		3: Low CR		4: High CR				
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	Value	p	Post-Hoc
Age	*148*	25.85 (7.82)	*98*	29.76 (8.24)	*91*	32.60 (11.22)	*106*	35.00 (10.38)	*F* = 22.13	<0.001	1<2; 1<3; 1<4; 2<4*
Education years	*148*	7.97 (1.70)	*98*	12.43 (2.72)	*91*	8.46 (1.69)	*106*	13.73 (2.51)	*F* = 179.10	<0.001	1<2; 1<4; 3<2; 3<4; 2<4*
Urban area: N (%)	*148*	99 (66,9)	*98*	71 (72,4)	*91*	61 (67)	*106*	81 (76,4)	x^2 = 3.41	0.333	
Unemployed: N (%)	*148*	76 (51,4)	*98*	29 (29,6)	*91*	36 (39,6)	*106*	33 (31,1)	x^2 = 15.85	<0.001	1>2; 1>4
Single: N (%)	*148*	129 (87,2)	*98*	82 (83,7)	*91*	51 (56,0)	*106*	63 (59,4)	x^2 = 44.25	<0.001	1>3; 1>4; 2>3; 2>4*
No children: N (%)	*148*	141 (95,3)	*98*	92 (93,9)	*91*	76 (83,5)	*106*	88 (83)	x^2 = 15.59	<0.001	1>3; 1>4; 2>3; 2>4*
DUI	*143*	18.31 (25.19)	*93*	22.07 (28.47)	*89*	21.26 (41.71)	*100*	20.41 (38.55)	*F* = 0.37	0.774	
DUP	*147*	8.35 (13.67)	*97*	12.32 (24.14)	*89*	13.71 (35.78)	*106*	13.89 (28.80)	*F* = 0.14	0.935	
Positive subscale (SAPS)	*148*	13.82 (4.37)	*97*	13.45 (4.23)	*91*	14.27 (4.47)	*106*	13.74 (5.17)	*F* = 0.78	0.506	
Negative subscale (SANS)	*148*	7.49 (6.48)	*96*	6.17 (6.39)	*91*	5.85 (5.51)	*106*	6.31 (6.22)	*F* = 0.68	0.566	
Positive dimension	*148*	7.50 (2.33)	*97*	7.44 (2.53)	*91*	7.36 (2.32)	*106*	7.04 (2.52)	*F* = 0.25	0.865	
Negative dimension	*148*	5.58 (5.81)	*97*	4.90 (5.61)	*91*	3.44 (5.03)	*106*	4.39 (5.55)	*F* = 1.61	0.186	
Disorganized dimension	*148*	6.32 (3.35)	*97*	6.01 (3.39)	*91*	6.91 (3.76)	*106*	6.70 (3.82)	*F* = 1.45	0.229	
Depression (CDS)	*147*	2.46 (3.48)	*97*	1.88 (2.92)	*91*	2.20 (3.56)	*105*	2.25 (2.95)	*F* = 0.56	0.645	
Mania (YMRS)	*148*	13.22 (6.14)	*97*	12.24 (5.45)	*91*	13.25 (6.25)	*105*	12.82 (5.83)	*F* = 0.64	0.591	
General psychopathology (BPRS)	*148*	64.97 (13.82)	*97*	61.31 (13.62)	*91*	65.13 (14.28)	*106*	62.52 (15.20)	*F* = 1.64	0.180	
Global functioning (GAF)	*98*	47.89 (30.05)	*63*	47.06 (31.70)	*69*	59.86 (32.13)	*73*	55.41 (30.98)	*F* = 2.88	0.036	
Clinical impression (CGI)	*148*	6.36 (0.69)	*97*	6.28 (0.77)	*91*	6.38 (0.66)	*106*	6.17 (0.96)	*F* = 1.72	0.61	

* Group differences with Bonferroni post-hoc with significance p <0.05.

5.1.1. Sociodemographic and clinical findings

The group of FEP patients with low CR is made up of more men (N = 148, 62%) than women (N = 91, 38%), contrary to what occurs in the high CR group where women predominate (N = 106, 52%) versus men (N = 98, 48%).

Regarding the age of onset of psychosis, FEP men with low CR debut significantly earlier ($p < 0.001$), with a mean age of 25.85 years, compared to the rest of the subgroups. Furthermore, these men with low CR are more frequently unemployed (54%; $p < 0.001$) than the group with high CR, both men (27%) and women (31%). We also found a significant difference ($p < 0.001$) in the high CR subgroup where men debut younger (29.76 years) than women (35 years).

On the other hand, in the high CR group, both men and women have more years of education than the low CR group (men mean 7.97 years; SD = 1.70. Women mean 8.46 years; SD = 1.69; $p < 0.001$). While within this high CR group, men have fewer years of education (mean 12.43 years; SD = 2.72; $p < 0.001$) than women (mean 13.73 years; SD = 2.51).

Another significant difference ($p < 0.001$) is found in the single and childless variables. Men show a tendency to be more frequently single (87% low CR; 84% high CR) and not having children (95% low CR; 94% high CR) compared to women (single: 56% low CR; 59% high CR; no children: 84% low CR; 83% high CR).

Finally, no significant differences were found between the groups in clinical variables.

5.1.2. Neuropsychological results

Among FEP patients there are numerous significant differences in cognitive domains, as can be seen in **Table 3**.

Significant results ($p < 0.001$) are shown with the same direction in the cognitive domains of verbal memory and processing speed: the high CR group outperforms the low CR group. In both cognitive domains, men with low CR score significantly lower than men with high CR [low CR: verbal memory (mean -2.88; SD 1.23); processing speed (average -2.09; SD 0.86); high

CR: verbal memory (mean -2.05; SD 1.29); processing speed (mean -1.10; SD 1.04)]. Men with low CR also perform significantly lower than women in both CR groups [low CR: verbal memory (mean -2.45; SD 1.35); processing speed (mean -1.4; SD 0.93); high CR: verbal memory (mean -1.78; SD 1.44); processing speed (mean -0.67; SD 0.95)]. In turn, both high CR men and women significantly outperform low CR women in the domains of verbal memory and processing speed.

In the visual memory, working memory, executive functions and theory of mind domains, the high CR group shows significantly ($p < 0.001$) better performance compared to the low CR group. Low CR women present worse results than high CR women and men in these domains [low CR women: visual memory (mean -1.14; SD 0.82); working memory (mean -0.76; SD 1.11); executive functions (mean -2.23; SD 2.72); theory of mind (mean -0.89; SD 1.14). Women with high CR: visual memory (mean -0.53; SD 0.95); working memory (mean -0.40; SD 0.88); executive functions (mean -0.95; SD 2.05); theory of mind (mean -0.25; SD 0.97). Men with high CR: visual memory (mean -0.71; SD 1.01); working memory (mean -0.16; SD 0.75); executive functions (mean -0.42; SD 1.24); theory of mind (mean -0.38; SD 0.90)]. The high CR group also outperforms the low CR men in these domains [visual memory (mean -0.71; SD 1.01); working memory (mean -0.69; SD 0.70); executive functions (mean -1.68; SD 2.14); theory of mind (mean -1.04; SD 1.09)]. The same effect is observed in the motor skill domain, the high CR group has better performance than men with low CR [(motor dexterity: women high CR (mean -0.72; SD 2.12); men high CR (mean -0.76; SD 1.22); men low CR (mean -1.74; SD 2.93)].

The cognitive domain of attention shows significant differences ($p < 0.001$) between the men with high CR and the low CR group. Men with high CR perform better in care than men and women with low CR [men high CR (mean -0.72; SD 2.27); men low CR (mean -3.26; SD

4.93); women low CR (mean -3.77; SD 4.01)]. In turn, men with high CR obtained better results in the attention domain than women with high CR (mean -2.57; SD 4.65).

Table 3. Comparisons of cognitive domains in CR subgroups of FEP patients

	MALES				FEMALES						
	1: Low CR		2: High CR		3: Low CR		4: High CR				
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	F	p	Post-Hoc
Verbal memory	*148*	-2.88 (1.23)	*98*	-2.05 (1.29)	*91*	-2.45 (1.35)	*106*	-1.78 (1.44)	20.45	<0.001	1<2; 1<3*; 1<4; 3<2; 3<4
Visual memory	*145*	-0.71 (1.01)	*98*	-0.09 (0.93)	*91*	-1.14 (0.82)	*105*	-0.53 (0.95)	21.25	<0.001	1<2; 1<4; 3<2; 3<4
Processing speed	*148*	-2.09 (0.86)	*97*	-1.10 (1.04)	*91*	-1.41 (0.93)	*106*	-0.67 (0.95)	36.67	<0.001	1<2; 1<3*; 1<4; 3<2; 3<4
Working memory	*148*	-0.69 (0.70)	*98*	-0.16 (0.75)	*90*	-0.76 (1.11)	*106*	-0.40 (0.88)	11.90	<0.001	1<2; 1<4; 3<2; 3<4
Executive function	*143*	-1.68 (2.14)	*98*	-0.42 (1.24)	*80*	-2.23 (2.72)	*105*	-0.95 (2.05)	16.46	<0.001	1<2; 1<4; 3<2; 3<4
Motor dexterity	*143*	-1.74 (2.93)	*98*	-0.76 (1.22)	*90*	-1.33 (1.94)	*103*	-0.72 (2.12)	6.77	<0.001	1<2; 1<4
Attention	*136*	-3.26 (4.93)	*96*	-0.72 (2.27)	*85*	-3.77 (4.01)	*101*	-2.57 (4.65)	10.00	<0.001	1<2; 3<2; 4<2*
Theory of Mind	*96*	-1.04 (1.09)	*66*	-0.38 (0.90)	*73*	-0.89 (1.14)	*76*	-0.25 (0.97)	10.68	<0.001	1<2; 1<4; 3<2; 3<4

* Group differences with Bonferroni post-hoc with significance p <0.05.

5.2. Control group comparisons in neuropsychological test

Cognitive performance differences are found in the control group, although to a lesser extent than in patients, as seen in **Table 4**.

In the verbal memory domain, women with high CR have significantly higher performance than men with low CR (women with high CR (mean -0.76; SD 1.07); men low CR (mean -1.91; SD 1.27); $p < 0.001$). While in the motor dexterity domain, women with low CR are those with significantly higher scores than men with low CR (women with low CR (mean 0.48; SD 0.77); men with low CR (mean -0.43; SD 1.20); $p < 0.003$).

The cognitive domains visual memory and working memory have the same relationship. Men with high CR show better performance in visual memory ($p < 0.001$) and working memory ($p < 0.004$) than men and women with low CR [visual memory: men with high CR (mean 0.50; SD 0.90); men low CR (mean -0.14; SD 1.14); women low CR (mean -0.71; SD 1.07). Working memory: men high CR (mean 0.30; SD 0.91); men low CR (mean -0.34; SD 087); women low CR (mean -0.55; SD 0.98)].

Finally, the processing speed domain presents significantly lower scores in the low CR group ($p < 0.001$). Women with low CR (mean -0.23; SD 1.09) perform less on this domain than women with high CR (mean 0.47; SD 0.97). In turn, men with low CR have a lower performance in processing speed than the group with high CR [men low CR (mean -0.49; SD 0.95); men high CR (mean 0.07; SD 0.85); women with high CR (mean 0.47; SD 0.97)]. This same direction occurs in the executive function's domain, men with low CR perform significantly less ($p < 0.009$) than the group with high CR [men low CR (mean -0.48; SD 1.24); men high CR (mean 0.23; SD 0.64); women with high CR (mean 0.15; SD 1.02)].

Table 4. Comparisons of cognitive domains in control group

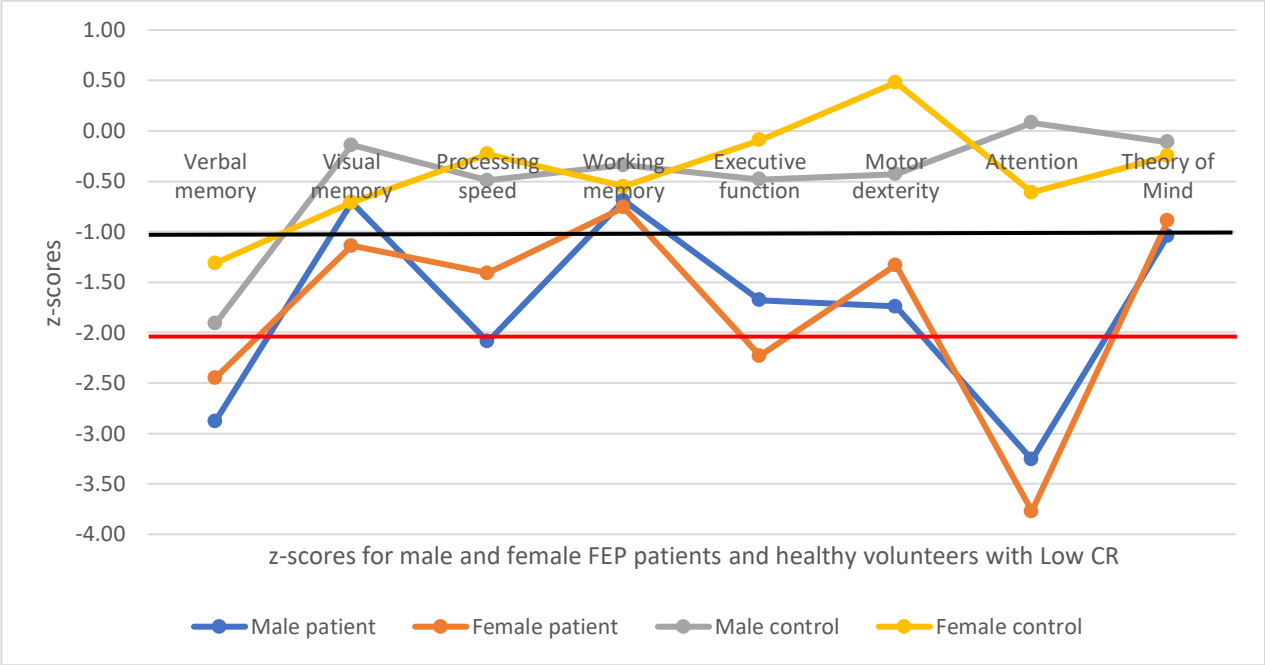
	MALES				FEMALES						
	5: Low CR		6: High CR		7: Low CR		8: High CR				
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	F	p	Post-Hoc
Verbal memory	*47*	1.91 (1.27)	*49*	1.21 (1.45)	*21*	1.31 (0.97)	*39*	0.76 (1.07)	6.46	<0.001	5<8
Visual memory	*47*	0.14 (1.14)	*48*	0.50 (0.60)	*21*	0.71 (1.07)	*39*	0.08 (0.97)	6.51	<0.001	5<6; 7<6
Processing speed	*47*	0.49 (0.95)	*49*	0.07 (0.85)	*21*	0.23 (1.09)	*39*	0.47 (0.97)	7.94	<0.001	5<6; 5<8; 7<8
Working memory	*47*	0.34 (0.87)	*49*	0.30 (0.91)	*20*	0.55 (0.98)	*39*	0.02 (0.93)	4.68	0.004	5<6; 7<6
Executive function	*47*	0.48 (1.24)	*49*	0.23 (0.64)	*21*	0.09 (1.10)	*39*	0.15 (1.02)	4.04	0.009	5<6; 5<8
Motor dexterity	*47*	0.43 (1.20)	*49*	0.04 (0.87)	*21*	0.48 (0.77)	*39*	0.16 (1.06)	4.88	0.003	5<7*
Attention	*43*	0.08 (0.93)	*46*	0.13 (0.90)	*20*	0.61 (1.30)	*36*	0.07 (0.95)	2.55	0.058	
Theory of Mind	*47*	0.11 (1.06)	*49*	0.10 (0.94)	*21*	0.25 (0.94)	*39*	0.12 (1.01)	0.91	0.440	

* Group differences with Bonferroni post-hoc with significance p <0.05.

5.3. Comparisons between groups and sexes in neuropsychological tests

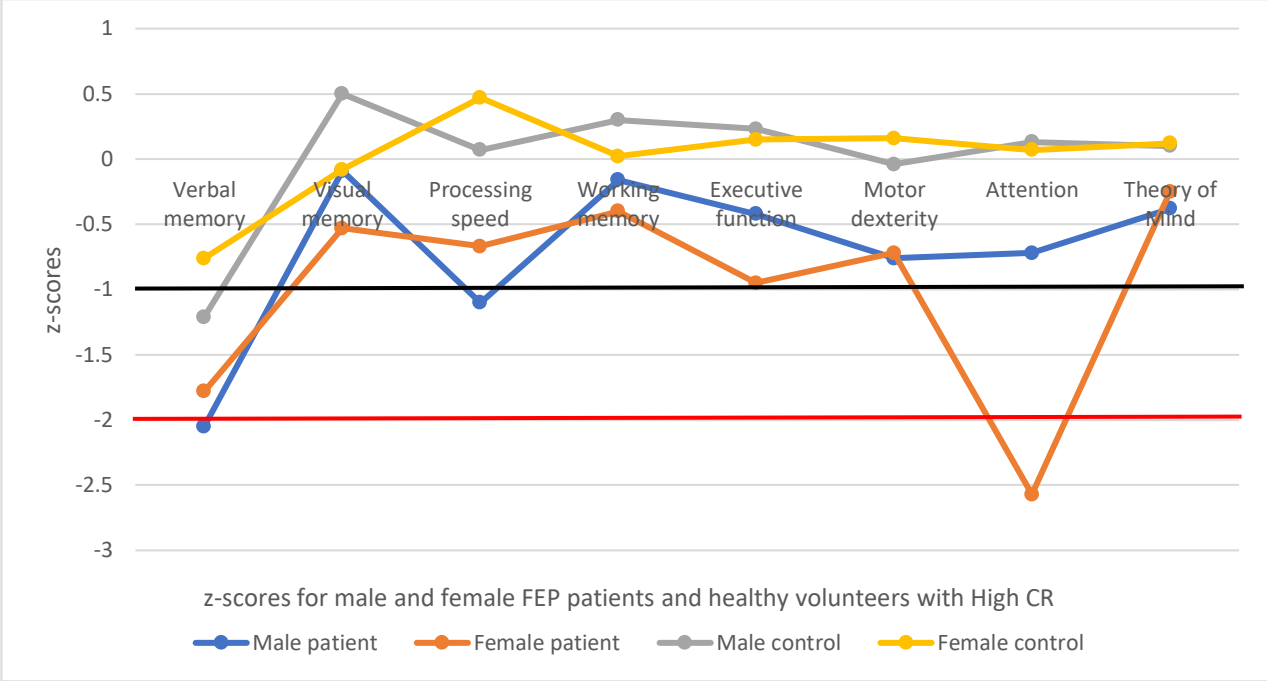
Making comparisons between sexes within the low CR group in both patients and controls, we can see variations in the cognitive domains as seen in **Figure 1**. Significant differences appear in the cognitive domains of verbal memory and processing speed with FEP women presenting higher performance than FEP men. While motor dexterity presents significant differences in the control group, women also have higher performance than men. As can be seen in **Figure 1**, in FEP patients we found serious alterations in the domains of attention and verbal memory, as well as executive functions in women and processing speed in men. It is striking to observe that the low CR controls present alterations in verbal memory.

Figure 1. Comparison of cognitive domains between men and women with FEP and control with low CR



On the other hand, comparisons between the high CR group only show significant differences between FEP patients, as shown in **Figure 2**. Men show better performance than women in the cognitive domain of attention, the severe alteration being very striking presented by FEP women with high CR in this domain. Also, in this group, the result obtained in the verbal memory domain is striking, being moderate-severe alteration in the FEP group and mild alteration in controls. It is very curious that the women with high CR controls did not obtain positive scores in the verbal memory domain.

Figure 2. Comparison of cognitive domains between men and women with FEP and control with high CR



6. Discussion

The objective of the present study was to explore whether CR presented differences between the sexes in patients with FEP, specifically if differences were shown in the performance of the verbal memory domain. The comparison between FEP men and FEP women showed that women had higher CR than men and better performance in verbal memory. This result is contrary to that observed in the controls, with men having more CR than women.

6.1. CR and age of onset of psychosis

Consistent with the literature, FEP men showed an earlier onset of the disorder (Barnett et al., 2006) and higher unemployment rates (Ayesa-Arriola et al., 2014, 2018), especially those

who had low CR (Amoretti et al., 2018; Ayesa-Arriola et al., 2018). This result could indicate that people with high CR better tolerate the effects of psychosis, as occurs with Alzheimer's disease (Leeson et al., 2011). In addition, the results coincide with the theory of Barnett and colleagues (Barnett et al., 2006) which reported that the onset of the disorder was delayed in a patient with high CR: the lower the CR, the greater the vulnerability to develop the disorder, responding to a greater capacity reasoning out strange perception (Stern, 2013). In this work we can say that the theory proposed by Barnett and colleagues (Barnett et al., 2006) was confirmed, given the circumstance that FEP women had higher CR, which in turn could influence that the later onset of the disease than in FEP men. Another way to explain this late onset in women would be that by having higher CR they have been able to count on alternative and therefore more flexible neural networks that have allowed them to enhance their abilities and compensate for limitations (Ayesa-Arriola et al., 2018; Heinrichs y Zakzanis, 1998). It was also observed that men were single and childless more frequently than women (Amoretti et al., 2018), variables that act as protective factors and good prognosis in mental disorder.

6.2. CR and years of education

Comparing the CR groups, it was shown that the high CR group had completed more years of education than the low CR group as shown in previous studies (Amoretti et al., 2018). Specifically, coinciding with previous research, the results of this study showed that women had a higher average number of years of education (de la Serna et al., 2013; Stern, 2002, 2005, 2006). This result was reflected when it came to seeing which sex had the highest CR, since years of education was a variable added as a proxy to the CR estimate (Amoretti et al., 2018). Therefore, the strong association between the participant's education, their CR and the age of onset of the disorder was appreciated. If the women in our study are the ones with the most educational years, it makes sense that they are the ones who later develop the disorder

because they have a greater capacity to use alternative neural networks to compensate for deficits (Stern, 2002) and because cognitive processes mediate the way of perceiving strange experiences causing subjects with high cognitive ability to delay the onset of the disorder (Barnett et al., 2006). It is possible that since years of education are one of the proxies used to estimate CR, presenting more educational years and therefore higher CR, it can be considered a protective factor for the development of psychosis.

6.3. CR and clinical variables

It is interesting that the present work did not show significant differences between the CR groups of FEP patients with respect to the severity of the symptoms. This follows the line of previous studies that did not show differences between premorbid IQ and clinical symptoms (Addington y Addington, 2000).

On the other hand, previous research found that patients with low CR had worse social skills (Green et al., 2000), worse economic status, deterioration of subsequent functioning and a longer DUP (Amoretti et al., 2018), this could indicate that participants with a lower CR are not able to tolerate the effects of the pathology for a long time, as occurs in Alzheimer's disease (Amoretti et al., 2018). This result occurred mainly in men and was explained by different coping styles (Joyce et al., 2002). It was found in previous research that FEP patients with low premorbid IQ improve their functionality and symptoms during the evolution of the disorder, while patients with high premorbid IQ present a tendency to remain stable (van Winkel et al., 2006), operating the Premorbid IQ as a predictor of functionality (van Winkel et al., 2007). This predictive value of premorbid IQ Leeson and colleagues (Leeson et al., 2009) specifically associated it with social functioning, adding that the current IQ of the patient was more important and not so much the premorbid one to the disorder. On the other hand, Amoretti and

colleagues showed that CR predicts initial and long-term cognitive performance, functioning, and negative symptoms. Thus, FEP patients with high CR showed better cognitive, functional and clinical results (Amoretti et al., 2016). This result is shown in line with previous research that confirms this association and indicates that individual differences prior to the onset of psychosis may influence these variables (Forcada et al., 2015).

6.4. CR and cognitive domains

The data showed that patients with high CR obtained better scores in all cognitive domains. This difference is not so clear in the results obtained in healthy subjects.

In the patient group, coinciding with previous works, the present study finds a relationship between CR and the verbal memory domain (Amoretti et al., 2018, 2020; Eberhard et al., 2003; González-Ortega et al., 2019; Leeson et al., 2009). However, these results disagree with studies that show no association with the verbal memory domain (de la Serna et al., 2013). The present study shows that in the domains of verbal memory and processing speed, the high CR group shows better scores than the low CR group. In addition, within the low CR group, we see that women perform better in these domains than men. On the one hand, these results coincide with the literature in that they show us that lower cognitive functioning indicates a greater deterioration in processing speed (Ayesa-Arriola et al., 2018). But on the other hand, previous research showed that FEP women with high cognitive functioning presented better performance in the verbal memory domain than men with both high and low cognitive functioning (Ayesa-Arriola et al., 2014) and not only with the men with low CR as indicated by the results of this work.

In healthy subjects, the results on these cognitive domains were different. The present study shows that women with higher CR performed better in the verbal memory domain only

compared to men with low CR. These results coincide with previous research showing that healthy women perform better than healthy men in the verbal memory domain (Ayesa-Arriola et al., 2014). Regarding the processing speed domain, men with high CR were better than men with low CR, but not than women with low CR. While women with high CR had better scores in the processing speed domain than men and women with low CR. This result coincides with previous studies that showed the highest performance of women, both FEP and controls, compared to men in the processing speed domain (Ayesa-Arriola et al., 2014).

Regarding performance in the visual memory, working memory, executive functions and theory of mind domains, our results in patients showed the same intergroup direction: the high CR group showed better performance than the low CR group. These results are consistent with the research by Ayesa-Arriola and colleagues which indicated that the lower the cognitive functioning, the greater the overall cognitive deterioration, especially in the executive functions domain (Ayesa-Arriola et al., 2018). This was consistent with previous research that showed that premorbid IQ was related to the working memory and executive functions domains, although they did not value the relationship with the other cognitive domains (Joyce et al., 2002). In turn, studies on CR were associated with the working memory domain (Amoretti et al., 2016, 2018, 2020; de la Serna et al., 2013; González-Ortega et al., 2019).

The executive functions domain shows discrepancies throughout the literature. Although the association between CR and the executive functions domain is strong both in this work and in previous research (Amoretti et al., 2016, 2018, 2020; González-Ortega et al., 2019), there are differences as to which executive function specifically, it is part of the association. On the one hand, a greater association with the planning domain (Joyce et al., 2002; Leeson et al., 2009) and on the other hand, no association with the flexibility domain (de la Serna et

al., 2013), therefore we suggest that this aspect should be further studied. Regarding the differences according to sex, as previously mentioned, both men and women with high CR have better performance than both sexes in the low CR group on the domains of visual memory, working memory, executive functions and ToM. But without significant differences in the same sex with different CR, while previous research showed that FEP men had higher performance than FEP women on the domains of visual memory, executive functions and reaction time (Ayesa-Arriola et al., 2014). We observed similar results in the motor dexterity domain, with patients (both men and women) with high CR being better only than men with low CR.

The present work includes results on the ToM domain defined as the ability to represent the experiential and intentional perspective of other people for successful socialization (Atenas et al., 2019). The results showed that the higher the CR, the higher the ToM in FEP patients, as shown in other studies (Joyce et al., 2002). For their part, González-Ortega and colleagues (González-Ortega et al., 2019) studied social cognition including social perception, ToM and empathy. Their results showed that it was social cognition and not CR that predicted the patient's functionality and that was associated with the processing speed and verbal memory domains, and it was not clear whether it is the premorbid functioning of social cognition that influences the evolution of the disease (González-Ortega et al., 2019) or if, on the contrary, it is CR that influences the social cognition and functioning of the patient as occurs in this work and previous studies (Joyce et al., 2002).

Healthy subjects differ from patient outcomes. In the visual and working memory domains, only men with high CR were better than the low CR group, a result that coincides with previous research (Ayesa-Arriola et al., 2014). While in the executive functions' domain the literature

reports that there are no differences in performance according to sex (Ayesa-Arriola et al., 2014). But in this research, it was found that both genders with high CR were significantly better than men with low CR.

In addition, the motor skill domain in healthy subjects showed differences within the low CR group, with women's scores being better than those of men, as in previous research (Ayesa-Arriola et al., 2014). Regarding the theory of mind domain, our results are shown in agreement with the literature, showing that there are no significant differences in healthy subjects according to sex (Ayesa-Arriola et al., 2014; Buonocore et al., 2018).

Regarding the cognitive domain of attention, only the FEP patient group presented significant differences. There is incongruity regarding the results of the literature regarding this domain since in certain studies of premorbid IQ they found no relationship with the attention domain (Amoretti et al., 2018, 2020; de la Serna et al., 2013; González-Ortega et al., 2019), but research on CR did find an association with the attention domain (Amoretti et al., 2018, 2020; de la Serna et al., 2013; González-Ortega et al., 2019). Perhaps in previous research the difference is since only the association with premorbid IQ or with CR is studied where more variables come into play for its estimation. Our results showed that in FEP patients, men with high CR performed better than both sexes with low CR. Even our data showed differences in FEP patients within the high CR group in the care domain, with men being better than women. As in previous research, no differences have been found in the care domain in healthy subjects according to sex (Ayesa-Arriola et al., 2014).

In conclusion, the first hypothesis of this work was fulfilled since the data showed that FEP women had more CR than FEP men. Regarding the second hypothesis, the results indicate that it is only fulfilled in the group with low CR, with FEP women having better performance

than FEP men in the verbal memory domain and also in processing speed. The significant difference that occurs in patients on the cognitive domain of attention stands out, where FEP men with high CR score better than women with both high and low CR and men with low CR.

7. Limitations and strengths

The main limitation was to estimate the CR and specifically calculate the premorbid IQ, which was measured using the WAIS-III vocabulary test, which, although it has been previously tested to measure crystallized intelligence (Ayesa-Arriola et al., 2018), intelligence could have been impaired in the premorbid period. Another limitation is not having considered other CR proxies proposed in other investigations (Amoretti et al., 2016; de la Serna et al., 2013; Stern, 2005) such as leisure activities, physical activity or the educational level of parents who can influence CR.

The main strength lies in the size and homogeneity of the samples that allowed making subgroups of FEP patients with different degrees of CR and making comparisons with a control group.

8. Conclusions

The objective of this work, to analyse the differences in CR and specifically differences in the cognitive domains in FEP patients according to sex, has been achieved. The results show:

- In the low CR group, FEP men predominated with an earlier onset of the disease (25.85 years), higher unemployment rates and fewer years of education.

- No significant differences were found in the comparisons between the CR groups regarding the clinical variables.

Conclusions regarding FEP patients:

- Women had higher scores in the estimation using CR proxies.
- Better performance of the high CR group in the cognitive domain of visual memory, verbal memory, working memory, processing speed, executive functions and theory of mind.
- The cognitive motor skills domain shows that in both genders the high CR group perform better than the low CR men.
- Men with high CR obtained significantly higher scores in the attention domain than women with high CR.
- Low CR women had better performance scores in the verbal memory and processing speed domains than low CR men.

Conclusions regarding healthy subjects:

- There are fewer significant differences regarding the performance of the cognitive domains compared to FEP patients, but it was observed that the line is followed that the higher the CR, the better the scores.
- The only difference found between sexes with the same CR level was that women with low CR obtained better scores in the motor skill domain than men with low CR.

In the future, it would be interesting to carry out more comparisons between the sexes to know in detail the differences in the cognitive domains, since we have seen that the literature on the matter is scarce and shows discrepancies. It would be interesting to specify which

cognitive functions are associated to a greater extent with CR. The results of this work provide information on how to increase CR and thus design an intervention according to sex, enhancing those cognitive domains depending on whether the patient is male or female.

9. References

Addington, D., Addington, J., & Maticka-tyndale, E. (1993). Assessing Depression in Schizophrenia: The Calgary Depression Scale. *British Journal of Psychiatry*, *163*(S22). https://doi.org/10.1192/S0007125000292581

Addington, J., & Addington, D. (2000). Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophrenia Research*, *44*(1). https://doi.org/10.1016/S0920-9964(99)00160-7

Amoretti, S., Bernardo, M., Bonnin, C. M., Bioque, M., Cabrera, B., Mezquida, G., Solé, B., Vieta, E., & Torrent, C. (2016). The impact of cognitive reserve in the outcome of first-episode psychoses: 2-year follow-up study. *European Neuropsychopharmacology*, *26*(10), 1638–1648. https://doi.org/10.1016/j.euroneuro.2016.07.003

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, A. M., Cuesta, M., Bernardo, M., Bioque, M., Meseguer, A., … Balanzá-Martínez, V. (2018). Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. *Acta Psychiatrica Scandinavica*, *138*(5), 441–455. https://doi.org/10.1111/acps.12949

Amoretti, Silvia, Rosa, A. R., Mezquida, G., Cabrera, B., Ribeiro, M., Molina, M., Bioque, M., Lobo, A., González-Pinto, A., Fraguas, D., Corripio, I., Vieta, E., de La Serna, E., Morro, L., Garriga, M., Torrent, C., Cuesta, M. J., & Bernardo, M. (2020). The impact of cognitive reserve, cognition and clinical symptoms on psychosocial functioning in first-episode psychoses. *Psychological Medicine*. https://doi.org/10.1017/S0033291720002226

Andreasen, N. (1984a). *The scale for the Assessment of Negative Symptoms (SANS)*. The University of Iowa.

Andreasen, N. (1984b). *The scale for the assessment of positive symptoms (SAPS)*. The University of Iowa.

Atenas, T. L., Ciampi Diaz, E., Venegas Bustos, J., Uribe San Martín, R., & Cárcamo Rodríguez, C. (2019). Cognición Social: Conceptos y Bases Neurales. *Revista Chilena de Neuro-Psiquiatría*, *57*(4). https://doi.org/10.4067/S0717-92272019000400365

Ayesa-Arriola, R., Rodriguez-Sanchez, J. M., Gomez-Ruiz, E., Roiz-Santiáñez, R., Reeves, L. L., & Crespo-Facorro, B. (2014). No sex differences in neuropsychological performance in first episode psychosis patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *48*, 149–154. https://doi.org/10.1016/j.pnpbp.2013.09.009

Ayesa-Arriola, R., Setién-Suero, E., Neergaard, K. D., Belzunces, À. A., Contreras, F., van Haren, N. E. M., & Crespo-Facorro, B. (2018). Premorbid IQ subgroups in first episode non affective psychosis patients: Long-term sex differences in function and neurocognition. *Schizophrenia Research*, *197*, 370–377. https://doi.org/10.1016/j.schres.2017.12.006

Aylward, E., Walker, E., & Bettes, B. (1984). Intelligence in Schizophrenia: Meta-analysis of the Research. *Schizophrenia Bulletin*, *10*(3). https://doi.org/10.1093/schbul/10.3.430

Barnett, J. H., Salmond, C. H., Jones, P. B., & Sahakian, B. J. (2006). Cognitive reserve in neuropsychiatry. In *Psychological Medicine* (Vol. 36, Issue 8, pp. 1053–1064). https://doi.org/10.1017/S0033291706007501

Buonocore, M., Bechi, M., Uberti, P., Spangaro, M., Cocchi, F., Guglielmino, C., Bianchi, L., Mastromatteo, A. R., Bosia, M., & Cavallaro, R. (2018). Cognitive reserve profiles in chronic schizophrenia: Effects on theory of mind performance and improvement after training. *Journal of the International Neuropsychological Society*, *24*(6), 563–571. https://doi.org/10.1017/S1355617718000012

Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of Premorbid Adjustment in Chronic Schizophrenia. *Schizophrenia Bulletin*, *8*(3). https://doi.org/10.1093/schbul/8.3.470

Carret, N. le, Auriacombe, S., Letenneur, L., Bergua, V., Dartigues, J.-F., & Fabrigoule, C. (2005). Influence of education on the pattern of cognitive deterioration in AD patients: The cognitive reserve hypothesis. *Brain and Cognition*, *57*(2). https://doi.org/10.1016/j.bandc.2004.08.031

Cegalis, J. (1991). *Vigil: software for the assessment of attention* . Forthought.

de la Serna, E., Andrés-Perpiñá, S., Puig, O., Baeza, I., Bombin, I., Bartrés-Faz, D., Arango, C., Gonzalez-Pinto, A., Parellada, M., Mayoral, M., Graell, M., Otero, S., Guardia, J., & Castro-Fornieles, J. (2013). Cognitive reserve as a predictor of two year neuropsychological performance in early onset first-episode schizophrenia. *Schizophrenia Research*, *143*(1), 125–131. https://doi.org/10.1016/j.schres.2012.10.026

Eberhard, J., Riley, F., & Levander, S. (2003). Premorbid IQ and schizophrenia: Increasing cognitive reduction by episodes. *European Archives of Psychiatry and Clinical Neuroscience*, *253*(2), 84–88. https://doi.org/10.1007/s00406-003-0412-y

First, M., Spitzer, R., Gibbon, M., & Williams, J. (2001). *User's guide for the Structured clinical interview for DSM-IV axis I disorders SCID-I: clinical version*. New York State Psychiatric Institute Biometrics Department.

Flaum, M., Andreasen, N. C., Swayze, V. W., O'Leary, D. S., & Alliger, R. J. (1994). IQ and brain size in schizophrenia. *Psychiatry Research*, *53*(3). https://doi.org/10.1016/0165-1781(94)90053-1

Flemenbaum, A., & Zimmermann, R. L. (1973). Inter- and Intra-Rater Reliability of the Brief Psychiatric Rating Scale. *Psychological Reports*, *33*(3). https://doi.org/10.2466/pr0.1973.33.3.783

Forcada, I., Mur, M., Mora, E., Vieta, E., Bartrés-Faz, D., & Portella, M. J. (2015). The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. *European Neuropsychopharmacology*, *25*(2). https://doi.org/10.1016/j.euroneuro.2014.07.018

González-Ortega, I., González-Pinto, A., Alberich, S., Echeburuá, E., Bernardo, M., Cabrera, B., Amoretti, S., Lobo, A., Arango, C., Corripio, I., Vieta, E., de La Serna, E., Rodriguez-Jimenez, R., Segarra, R., López-Ilundain, J. M., Sánchez-Torres, A. M., Cuesta, M. J., Zorrilla, I., López, P., … Selva, G. (2019). Influence of social cognition as a mediator between cognitive reserve and psychosocial functioning in patients with first episode psychosis. *Psychological Medicine*. https://doi.org/10.1017/S0033291719002794

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive Deficits and Functional Outcome in Schizophrenia: Are We Measuring the "Right Stuff"? *Schizophrenia Bulletin*, *26*(1). https://doi.org/10.1093/oxfordjournals.schbul.a033430

Hall, R. C. W. (1995). Global Assessment of Functioning. *Psychosomatics*, *36*(3). https://doi.org/10.1016/S0033-3182(95)71666-8

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*, *12*(3). https://doi.org/10.1037/0894-4105.12.3.426

Joyce, E., Hutton, S., Mutsatsa, S., Gibbins, H., Webb, E., Paul, S., Robbins, T., & Barnes, T. (2002). Executive dysfunction in first-episode schizophrenia and relationship to duration of untreated psychosis: The West London Study. *British Journal of Psychiatry*, *181*(S43). https://doi.org/10.1192/bjp.181.43.s38

Leeson, V. C., Barnes, T. R. E., Hutton, S. B., Ron, M. A., & Joyce, E. M. (2009). IQ as a predictor of functional outcome in schizophrenia: A longitudinal, four-year study of first-episode psychosis. *Schizophrenia Research*, *107*(1), 55–60. https://doi.org/10.1016/j.schres.2008.08.014

Leeson, V. C., Sharma, P., Harrison, M., Ron, M. A., Barnes, T. R. E., & Joyce, E. M. (2011). IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: A 3-year longitudinal study. *Schizophrenia Bulletin*, *37*(4), 768–777. https://doi.org/10.1093/schbul/sbp143

Lezak, M. (1995). *Neuropsychological Assessment.* Oxford University Press.

Mendrek, A., & Mancini-Marïe, A. (2016). Sex/gender differences in the brain and cognition in schizophrenia. *Neuroscience & Biobehavioral Reviews*, *67*. https://doi.org/10.1016/j.neubiorev.2015.10.013

Osterrieth, PA. (1944). Le test de copie d'une figure complexe. . *Archives de Psychologie* , *30*, 206–256.

Pelayo-Terán, José M., Pérez-Iglesias, R., Ramírez-Bonilla, M., González-Blanch, C., Martínez-García, O., Pardo-García, G., Rodríguez-Sánchez, J. M., Roiz-Santiáñez, R., Tordesillas-Gutiérrez, D., Mata, I., Vázquez-Barquero, J. L., & Crespo-Facorro, B. (2008). Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the Clinical Programme on Early Phases of Psychosis. *Early Intervention in Psychiatry*, *2*(3). https://doi.org/10.1111/j.1751-7893.2008.00074.x

Pelayo-Terán, José María, Gajardo-Galán, V., Gómez-Revuelta, M., Ortiz-García de la Foz, V., Ayesa-Arriola, R., Tabarés-Seisdedos, R., & Crespo-Facorro, B. (2018). Duration of active psychosis and functional outcomes in first-episode non-affective psychosis. *European Psychiatry*, *52*. https://doi.org/10.1016/j.eurpsy.2018.03.003

Rami González, L., Valls Pedret, C., Bartrés Faz, D., Caprile Elola-Olaso, C., Solé Padullés, C., Castellví Sampol, M., Olives Cladera, J., Bosch Capdevila, B., & Molinuevo Guix, J. L. (2011). Cuestionario de reserva cognitiva. Valores obtenidos en población anciana sana y con enfermedad de Alzheimer. *Revista de Neurología*, *52*(04). https://doi.org/10.33588/rn.5204.2010478

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation* (Vol. 4). Reitan Neuropsychology.

Rey, A. (1964). L'examen clinique en psychologie. *Presses Universitareies de France*.

Scarmeas, N., & Stern, Y. (2003). Cognitive Reserve and Lifestyle. *Journal of Clinical and Experimental Neuropsychology*, *25*(5). https://doi.org/10.1076/jcen.25.5.625.14576

SPSS Inc. (2020). *IBM SPSS Statistic 22.0 [Internet]*. https://www.ibm.com/support/pages/spss-statistics-220-available

Stern, Y. (2005). Brain Networks Associated with Cognitive Reserve in Healthy Young and Old Adults. *Cerebral Cortex*, *15*(4). https://doi.org/10.1093/cercor/bhh142

Stern, Yaakov. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc.*, *8*(3), 448–460. https://pubmed.ncbi.nlm.nih.gov/11939702/

Stern, Yaakov. (2006). Cognitive Reserve and Alzheimer Disease. *Alzheimer Disease & Associated Disorders*, *20*(Supplement 2). https://doi.org/10.1097/00002093-200607001-00010

Stern, Yaakov. (2013). Cognitive Reserve: Implications for Assessment and Intervention. *Folia Phoniatrica et Logopaedica*, *65*(2). https://doi.org/10.1159/000353443

van Winkel, R., Myin-Germeys, I., de Hert, M., Delespaul, P., Peuskens, J., & van Os, J. (2007). The association between cognition and functional outcome in first-episode patients with schizophrenia: Mystery resolved? *Acta Psychiatrica Scandinavica*, *116*(2), 119–124. https://doi.org/10.1111/j.1600-0447.2007.01014.x

van Winkel, Ruud, Myin-Germeys, I., Delespaul, P., Peuskens, J., de Hert, M., & van Os, J. (2006). Premorbid IQ as a predictor for the course of IQ in first onset patients with

schizophrenia: A 10-year follow-up study. *Schizophrenia Research*, *88*(1–3), 47–54. https://doi.org/10.1016/j.schres.2006.06.033

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-III*. The Psychological Corporation.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A Rating Scale for Mania: Reliability, Validity and Sensitivity. *British Journal of Psychiatry*, *133*(5). https://doi.org/10.1192/bjp.133.5.429

10. Annexes

Table 5. Previous studies with FEP

Study	Sample	Cognitive Reserve	Cognitive Tests	Other Tests	Statistics	Results	Conclusions
Joyce, Hutton,Mutsatsa, Gibbins, Webb, Paul, Robbin and Barnes (2002)	136 FEP	NART (reading)	CANTAB	SAPS, SANS, DUP	ANOVA, ANCOVA	NART correlates with special span, special pattern, recognition spatial memory, spatial working memory and planification. FEP respond faster in planification than other controls but take the same time while solving a task.	PremIQ correlates with working memory, planification and executive functions. FEP worst impulse control.
Eberhard, Riley and Lavender (2003)	35 EQZ	Educación (educational degree)	APT: PLA, ltm task, span task, digits, FTT, K-tests, labrynth task, reaction time and word recognition task.	PANSS and GAF	ANOVA. ANCOVA. Regression analysis.	Verbal skills related to years of education remain stable. The more PremIQ, the bigger the deficit but better results in simple reaction time and short terms verbal memory.	CR correlates with **reaction time** and **short-term verbal memory**. Vocabulary remains intact. PremIQ is a protective factor for deterioration, so it takes longer to deteriorate but it shows the most significant drop.
van Winkel, Myin-Germeys, de Hert, Delespaul, Peuskens,van OS (2006)	100 FEP	VIS (reading) y HAEL (education)	WAIS: tota IQ, verbal IQ, IQ performance	PANSS	Multilevel regression analysis.	There is no difference between premIQ and lowIQ subgroup at the age of 10, but there is with subgroup of highIQ. More deterioration in the moment of admission.	FEP with low premIQ improves over the years. FEP with high premIQ remains stable over the years. No deterioration in any subgroup as premIQ modules current IQ. High IQ subgroup has more neuroplasticity.
van Winkel, Myin-Germeys, de Hert, Delespaul, Peuskens,van OS (2007)	Initation: 100 FEP 10 years: 53 FEP	VIS (reading)	WAIS	WHO life chart	Linear regression analysis.	Relation between PremIQ and functionality 10 years.	PremIQ is a better predictor of functionality and cognitive domains. No relation between PremIQ and functionality at the time of admission.
Leeson, Barnes, Hutton, Ron and Joyce (2009)	54 FEP	NART (reading)	WAIS-R, CANTAB: PRM, SWM, SSP, SOC, ASS.	SAPS, SFS	Repeated measures regression analysis.	Low premIQ is a risk factor to develop chronic schizophrenia. PremIQ predictor of social functioning.	PremIQ is a predictor of better social functioning than cognitive domains. Beginning of illness IQ is irrelevant.
Leeson, Sharma, Harrison, Ron, Barnes and Joyce (2009)	Initiation: 129 FEP. 1year: 78 FEP. 3yeas: 60 FEP.	WTAR (reading)	RAVLT, CAMDEX, SWM, ToL, WAIS-III: information, arithmetic's, blocks and digits.	PANSS, SFS, HDRS, YMRS, PSA	Linear mixed models: Pearson	Correlation premIQ: immediate verbal memory, verbal learning and planification. Subgroup with deteriorated IQ has the lowest premIQ.	Current IQ more important than CR. High premIQ high global deterioration in FEP but better resistance to brain impact. CR correlates with verbal memory, verbal learning, and planning.

de la Serna, Andrés-Perpiñá, Puig, Baeza, Bombín, Bartés-Faz, Arango, González-Pinto, Parellada, Mayoral, Graell, Otero, Guardia and Castro-Fornieles (2013)	35 FEP	Vocabulary (WAIS-III), education-occupation and leisure-social	TMT, TAVEC, WSCT, STROPP, CPT, WAIS-III: digits, letters and numbers.	K-SADS-PL, PANSS	Logistic regression analysis and linear regression analysis.	CR predicts working memory and attention but shows not correlation with verbal memory and flexibility. PremIQ predicts results in working memory.	Proxys to estimate CR are premIQ, academic-work level and leisure. Study proxies to the set as they compensate for clinical limitations. CR correlates with **working memory** and **attention**. The onset of the disease hinders the accumulation of CR.
Amoretti, Bernardo, Bonnin,Bioque, Cabrera, Mezquida, Solé, Vieta and Torrent (2016)	52 FEP	Vocabulary (WAIS-III), PAS (education) and FAST (leisure time, physical activity and social)	CPT-II, TMT, WCST, CVLT, WAIS-III: digits, letters and numbers.	PANSS, YMRS, MADRS, DUP	Linear-logistic regression analysis and ANOVA, ANCOVA	Low premIQ related with lower educational level. Mediation between CR and working memory and executive functions. Partial mediation between CR, attention and verbal memory. Significant improvement in verbal memory and attention subgroups.	Proxys to estimate CR are premIQ, academic-work level and leisure. PremIQ not enough to estimate CR. CR predicts global cognition. CR predictor or negative symptoms, functioning and cognitive domains, especially **working memory** and **executive functions**.
Buonocore, Bosinelli, Bechi, Spangaro, Piantanida, Cocchi, Bianchi, Guglielmino, Mastromatteo, Cavallaro and Bosia (2018)	79 EQZ	PAS (social and academic)	BACS, WAIS-R: information, digits, arithmetic's, comprehension, similarities, incomplete figures, image display, cubes, number key and montage.	PANSS, QLS	Linear regression analysis.	Significant correlation between PAS and working memory.	Only correlation between poor social relationships and adjustment in school with working memory.
Amoretti, Cabrera, Torrent, Mezquida, Lobo, González-Pinto, Parellada, Corripio, Vieta, de la Serna, Butjosa, Contreras, Sarró, Penadés, Sánchez-Torres, Cuesta, Bernardo and FEP's group (2018)	247 FEP	Vocabulary (WAIS-III), PAS (education) and FAST (leisure time, physical activity and social)	CPT-II, WCST, TAVEC, WAIS-III: digits, letters and numbers.	PANSS, YMRS, GAF, MADRS, GCI	Linear regression analysis and ANOVA	Higher CR in older patients, better socioeconomic level and shorter DUP, with better performance in verbal memory, working memory and attention.	CR predictor or FEP evolution, functionality and cognitive performance, especially working memory, verbal memory and attention. Better prediction over working memory. Higher CR protector of the effects of the pathology for a longer period.
Buonocore, Bechi, Uberti, Spangaro, Cocchi, Guglielmino, Bianchi, Mastromatteo, Bosia and Cavallaro (2018)	60 EQZ	PAS	WAIS-R: verbal, performance and total IQ. BACS: word recall, digit sequence, orders, symbol code, fluency and ToL.	PANSS, PST	ANOVA and ANCOVA	Correlation Theory of Mind and executive functions. High CR better Theory of Mind.	CR is a protector of dysfunctionality and social cognitive deterioration. Correlation CR with **Theory of Mind.**
González-Ortega, González-Pinto, Alberich, Echeburúa, Bernardo, Cabrera, Amoretti, Lobo, Arango, Corripio, Vieta, de la Serna, Rodriguez-Jiménez, Segarra, López-Ilundain, Sánchez-Torres, Cuesta and FEP's group (2019)	282 FEP	Vocabulary (WAIS-III), education and occupation (Hollingshead-Redlich Scale)	TMT, STROOP, CPT-II, TAVEC, FAS, WCST, WAIS-III: digits, letters and numbers.	Emotional Intelligent test, FAST	Linear regression analysis.	In 2 years, there is no significant improvement in executive functions and working memory. There is improvement in social cognition and functioning. Correlation between CR and global functioning. In baseline, association between social cognition with processing speed and verbal memory.	Social Cognition predicts functionality and is associated to **processing speed** and **verbal memory**. Social cognition is a better predictor of performance than neurocognition.
Amoretti, Rosa, Mezquida, Cabrera, Ribeiro, Molina, Bioque, Lobo, González-Pinto, Fraguas, Corripio, Vieta, de la Serna, Morro, Garriga, Torrent, Cuesta, Bernardo and FEP's group (2020)	Initiation: 211 FEP 2 years: 139 FEP	Vocabulary (WAIS-III), PAS (education) and FAST (leisure time, physical activity and social)	CPT-II, TAVEC, WCST, WAIS-III: digits, letters and numbers.	PANSS, YMRS, MADRS, DUP	ANOVA and mediation analysis.	Medium CR in 2 follow-up years in verbal memory and working memory while in baseline with attention and verbal memory.	Little influence of CR with cognitive domains at the start of the illness. Influence of CR in symptoms, performance, and cognitive domains, especially **working memory**, **executive functions**, **verbal memory** and **attention**.