Journal of Affective Disorders

Is the effect of cognitive reserve in longitudinal outcomes in first-episode psychoses dependent on the use of cannabis?

--Manuscript Draft--

Manuscript Number:	JAFD-D-21-04057R1
Article Type:	Research Paper
Keywords:	first episode; functioning; Cognition; Cannabis; cognitive reserve
Corresponding Author:	Eduard Vieta Hospital Clinic of Barcelona, University of Barcelona. IDIBAPS. CIBERSAM Barcelona, Catalonia Spain
First Author:	Silvia Amoretti
Order of Authors:	Silvia Amoretti
	Norma Verdolini
	Cristina Varo
	Gisela Mezquida
	Ana M. Sánchez-Torres
	Eduard Vieta
	Clemente Garcia-Rizo
	Antonio Lobo
	Ana González-Pinto
	Renzo Abregú-Crespo
	Iluminada Corripio
	Maria Serra
	Elena de la Serna
	Anna Mané
	J Antoni Ramos-Quiroga
	Marta Ribases
	Manuel J Cuesta
	Miguel Bernardo
	PEPs Group
Abstract:	Background Cognitive reserve (CR) is a protective factor against cognitive and functional impairment in first-episode psychosis (FEP). The aim of this study was to evaluate the differences in clinical presentation according to the use of cannabis (cannabis users vs non-users) among patients presenting a FEP (non-affective vs affective psychosis), to investigate the impact of CR and cannabis use on several outcomes and to explore the potentially mediatory role played by CR in the relationship between cognitive domains or clinical status and functionality, depending on the use of cannabis. Methods Linear regression analysis models were carried out to assess the predictive value of CR on clinical, functional and cognitive variables at baseline and at two-year follow-up. The mediation analyses were performed according to the principles of Baron and Kenny.

	Results CR was associated with better cognitive performance, regardless of cannabis consumption or diagnosis. In both diagnoses, CR was associated with better clinical and functional outcomes in those patients who did not use cannabis. In terms of mediation procedure, CR mediates the relationship between some cognitive domains and functioning at follow-up only in patients without cannabis use. Limitations The small sample size of the affective group. Conclusions CR plays a differential role in the outcome of psychoses according to whether patients are cannabis users or not. Both in affective and non-affective groups CR exerted a greater effect in patients without cannabis use. Our results suggest that the deleterious effect of cannabis use on functioning in FEP surpasses the protective effect of CR.
Suggested Reviewers:	Katherine Burdick kburdick1@bwh.harvard.edu
	Maria Portella MPortella@santpau.cat
	Rosa Ayesa rayesa@idival.org
	Kamilla Miskowiak kamilla.miskowiak@regionh.dk
Opposed Reviewers:	
Response to Reviewers:	We thank the referee for carefully reading our manuscript. Authors are grateful to the reviewer for his/her positive and encouraging comments.

UNIVERSITAT DE BARCELONA

January 12th, 2022

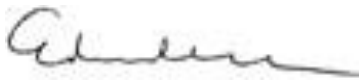
Prof. Eduard Vieta
Bipolar and Depressive Disorders Unit,
Institute of Neuroscience,
University of Barcelona,
IDIBAPS CIBERSAM
Hospital Clínic de Barcelona, 170 Villarroel st, 12-0,
08036 Barcelona, Catalonia (Spain)

Journal of Affective Disorders

Dear Professor Paolo Brambilla, Editor-in-Chief,

We thank the referee for carefully reading our manuscript entitled "**Is the effect of cognitive reserve in longitudinal outcomes in first-episode psychoses dependent on the use of cannabis?**" (NO: JAFD-D-21-04057) and for the comments. Since no specific comments were raised by the reviewer, the submitted files are identical in content with the last version.

Yours sincerely,



Eduard

Prof Eduard Vieta, M.D., Ph.D.

ANSWERS TO REVIEWERS

Reviewer #1: The article is interesting and well written and illustrates an innovative concept, relating cognitive reserve with the use of cannabis in patients with psychotic onset and in healthy controls. The statistical analyzes are convincing and the discussion is well argued. There are no further clarifications that seem necessary for publication.

We thank the referee for carefully reading our manuscript. Authors are grateful to the reviewer for his/her positive and encouraging comments.

Highlights

- CR was associated with better cognitive performance, regardless of cannabis consumption or diagnosis
- Both in affective and non-affective groups, CR was associated with better clinical and functional outcomes in those patients who did not use cannabis.
- CR seems to be a protective factor, especially in those FEP without cannabis use
- The deleterious effect of cannabis use on functioning in FEP surpasses the protective effect of CR.

Abstract

Background: Cognitive reserve (CR) is a protective factor against cognitive and functional impairment in first-episode psychosis (FEP). The aim of this study was to evaluate the differences in clinical presentation according to the use of cannabis (cannabis users vs non-users) among patients presenting a FEP (non-affective vs affective psychosis), to investigate the impact of CR and cannabis use on several outcomes and to explore the potentially mediatory role played by CR in the relationship between cognitive domains or clinical status and functionality, depending on the use of cannabis.

Methods: Linear regression analysis models were carried out to assess the predictive value of CR on clinical, functional and cognitive variables at baseline and at two-year follow-up. The mediation analyses were performed according to the principles of Baron and Kenny.

Results: CR was associated with better cognitive performance, regardless of cannabis consumption or diagnosis. In both diagnoses, CR was associated with better clinical and functional outcomes in those patients who did not use cannabis. In terms of mediation procedure, CR mediates the relationship between some cognitive domains and functioning at follow-up only in patients without cannabis use.

Limitations: The small sample size of the affective group.

Conclusions: CR plays a differential role in the outcome of psychoses according to whether patients are cannabis users or not. Both in affective and non-affective groups CR exerted a greater effect in patients without cannabis use. Our results suggest that the deleterious effect of cannabis use on functioning in FEP surpasses the protective effect of CR.

Key words: first episode, functioning, cognition, cannabis, cognitive reserve

Title Page

Is the effect of cognitive reserve in longitudinal outcomes in first-episode psychoses dependent on the use of cannabis?

Short running title: Cognitive reserve and cannabis use

Silvia Amoretti [1,2,3,4,a], Norma Verdolini [2,3,a], Cristina Varo [2,3], Gisela Mezquida [1,2], Ana M. Sánchez-Torres [5,6], Eduard Vieta [2,3,*], Clemente Garcia-Rizo [1,2,*], Antonio Lobo [2,7], Ana González-Pinto [2,8,9], Renzo Abregú-Crespo [2,10], Iluminada Corripio [2,11], Maria Serra [3], Elena de la Serna [2,12], Anna Mané [2,13], J Antoni Ramos-Quiroga [2,4,14,15], Marta Ribases [2,4,14], Manuel J Cuesta [5,6], Miguel Bernardo [1,2]; PEPs Group.

[1] Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, University of Barcelona, August Pi I Sunyer Biomedical Research Institute (IDIBAPS), Spain.
[2] Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain.
[3] Bipolar and Depressive Disorders Unit, Hospital Clinic of Barcelona, Institute of Neurosciences, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain.
[4] Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR); Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain
[5] Department of Psychiatry, Complejo Hospitalario de Navarra, Pamplona, Spain
[6] IdiSNA, Navarra Institute for Health Research, Pamplona, Spain
[7] Department of Medicine and Psychiatry. Zaragoza University. Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain.
[8] Araba University Hospital, Bioaraba Research Institute, Spain.
[9] University of the Basque Country (UPV-EHU), Spain.
[10] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, Madrid, Spain.
[11] Department of Psychiatry, Institut d'Investigació Biomèdica-Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.
[12] Department of Child and Adolescent Psychiatry and Psychology, SGR2017881, Institut Clinic de Neurociències, Hospital Clínic Universitari, CIBERSAM, IDIBAPS, Department of Medicine, University of Barcelona, Barcelona, Spain.
[13] Hospital del Mar Medical research Institute (IMIM), Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.
[14] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain.
[15] Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain.

[a] S Amoretti and N Verdolini should be considered joint first author

***Corresponding authors:**

Eduard Vieta

E-mail address: evieta@clinic.cat

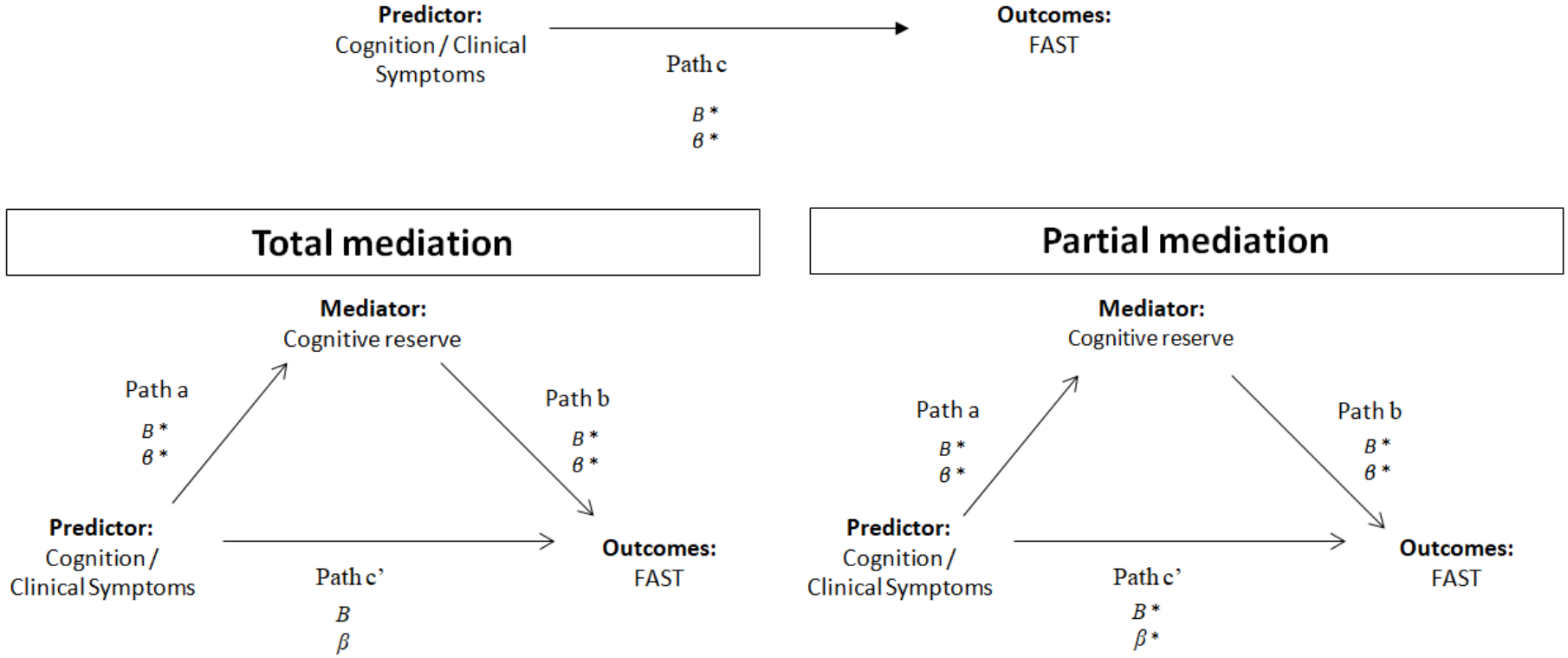
Clemente Garcia-Rizo

E-mail address: cgarcia3@clinic.cat

Department of Psychiatry and Psychology. Clinical Institute of Neuroscience. Hospital Clinic of Barcelona, Villarroel, 170. 08036 Barcelona, Spain.
Tel.: +34 93 227 54 00; fax: +34 93 227 92 28

Word count: 4702

Figure 1. Path analyses: effect of subject on cognitive domains or clinical symptoms mediated by cognitive reserve.



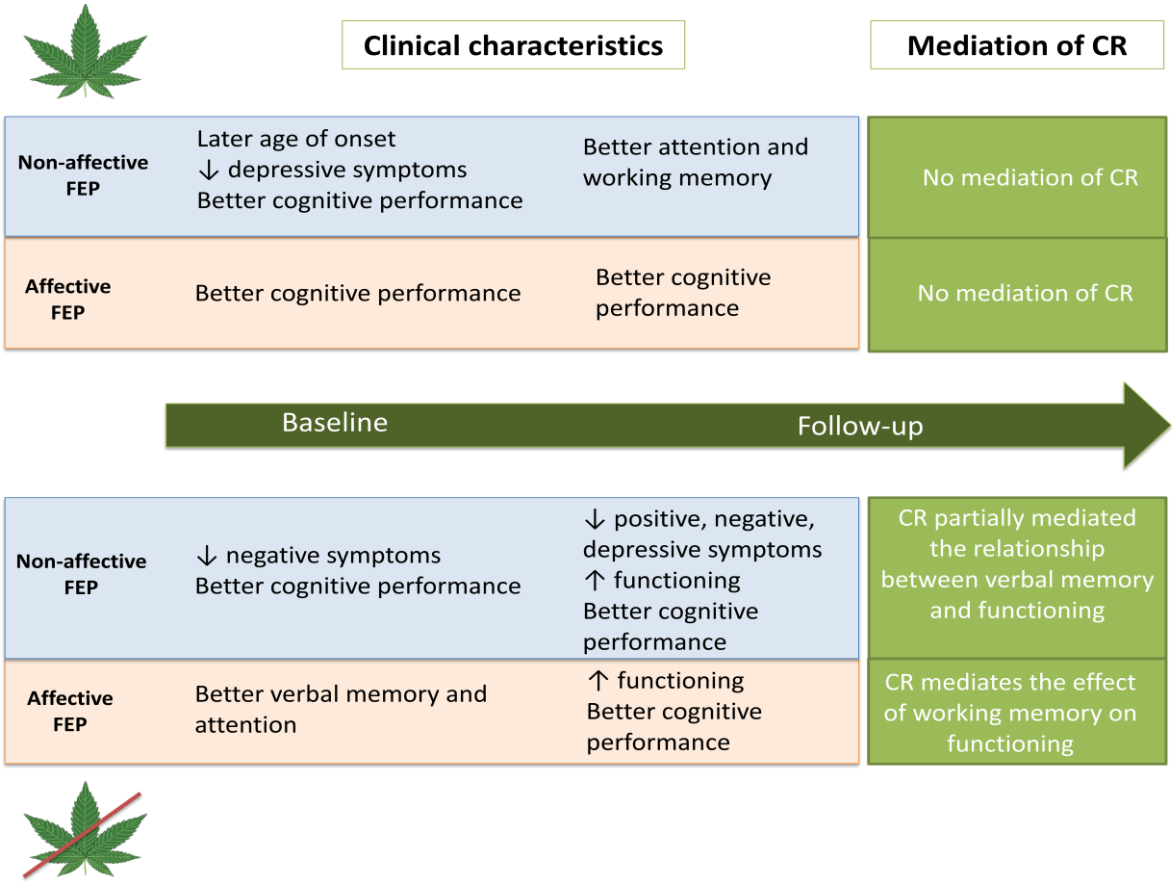
B=unstandardized values; *β*= standardized values. * p < 0.05.
Abbreviations: FAST=Functioning Assessment Short Test.

B=unstandardized values; *β*= standardized values. * p < 0.05.

Abbreviations: FAST=Functioning Assessment Short Test.

Mediation was identified if the following criteria were met: 1) The independent variable was significantly related to the dependent variable (path c); 2) The independent variable was significantly related to the proposed mediator (path a); 3) The proposed mediator was significantly related to the dependent variable when controlling for the effects of the independent variable (path b); 4) The independent variable was not significantly related to the dependent variable when controlling for the effects of the proposed mediator (path c').

Figure 2. Clinical characteristics and effect exerted by cognitive reserve across time in the patients groups (affective vs non-affective FEP) depending on cannabis use



Abbreviations: CR=Cognitive Reserve; FEP= First Episode of Psychosis.

Table 1. Baseline and follow-up sociodemographic, clinical, functional and cognitive reserve for patients and healthy controls

	Patients				Healthy controls			
	At baseline (n=259)	**At follow-up (n=158)**	***p***	**Partial eta squared**	**At baseline (n=205)**	**At follow-up (n=140)**	***p***	**Partial eta squared**
Sociodemographic variables								
Gender: Male *N* (%)	173 (67)	106 (67)	-		132 (64)	94 (67)	-	
Age (M±SD)	24.77±5.58	27.19±5.14			25.69±5.62	27.98±5.87		
SES (%)								
High	48 (19)	36 (23)			46 (22)	33 (24)		
Medium-High	25 (10)	17 (11)			40 (20)	31 (22)		
Medium	65 (25)	40 (25)			57 (28)	34 (24)		
Medium-Low	85 (33)	49 (31)			51 (25)	33 (24)		
Low	33 (13)	15 (10)			9 (4)	8 (6)		
Missing value	3 (0)	1 (1)			2 (1)	0 (0)		
Tobacco use: Yes *N* (%)	177 (69)	93 (59)			85 (41)	50 (36)		
Cannabis use: Yes *N* (%)	115 (44)	29 (18)			38 (19)	30 (21)		
Monthly cannabis use (M±SD)	87.54±96.79	35.81±50.62			13.30±21.40	24.13±32.57		
Age at first use (M±SD)	16.38±2.82				16.73±1.87			
Years of regular use (M±SD)	5.75±4.11				6.30±4.19			
Clinical and functional variables (M±SD)								
PANSS positive	17.97±7.80	10.09±4.32	**<0.001**	0.402	-	-	-	-
PANSS negative	18.54±7.75	13.73±6.15	**<0.001**	0.204	-	-	-	-
PANSS general	37.29±12.01	25.13±8.55	**<0.001**	0.397	-	-	-	-
PANSS total	73.80±23.15	48.95±17.22	**<0.001**	0.415	-	-	-	-
YMRS score	8.49±10.09	1.93±4.25	**<0.001**	0.236	-	-	-	-
MADRS score	12.72±9.78	5.52±6.27	**<0.001**	0.260	-	-	-	-
FAST	27.61±15.98	18.83±15.20	**<0.001**	0.135	2.90±7.069	2.82±8.60	0.314	0.007
Cognitive measures (M±SD)								
Attention	89.22±9.14	86.62±10.44	**0.001**	0.091	81.48±8.46	80.23±7.26	**0.028**	0.039
Verbal memory	135.30±49.10	160.31±48.25	**<0.001**	0.162	190.26±31.87	205.56±24.56	**<0.001**	0.137
Working memory	78.45±15.92	81.99±16.52	**0.003**	0.056	93.29±14.83	94.90±14.77	0.259	0.009
Executive function	126.51±145.23	150.15±40.97	**<0.001**	0.188	145.23±29.85	161.16±31.84	**<0.001**	0.178
GCI	295.62±50.21	330.60±48.00	**<0.001**	0.313	353.21±31.65	371.12±28.89	**<0.001**	0.227
Cognitive reserve and premorbid adjustment (M±SD)								
CR	75.19±12.28		-		88.04±10.77		-	
PAS	23.29±13.49		-		11.25±8.02		-	

Abbreviations: M=Mean, SES=Socioeconomic status, PANSS= Positive and Negative Symptom Scale, YMRS= Young Mania Rating Scale, MADRS= Montgomery-Asberg Depression Rating Scale, FAST=Functioning Assessment Short Test, GCI= Global Cognition Index, CR= Cognitive Reserve, PAS= Premorbid Adjustment Scale. Significant differences ($p<0.05$) marked in bold.

Table 2. Differences between patients who use cannabis and those who do not at baseline

	Non-affective FEP			Affective FEP		
	Cannabis users (n=97)	**Non cannabis users (n=114)**	***p***	**Cannabis users (n=18)**	**Non cannabis users (n=30)**	***p***
Sociodemographic variables						
Gender: Male *N* (%)	78 (80)	62 (54)	**<0.001**	13 (72)	20 (67)	0.472
Age (M±SD)	24.45±4.86	26.08±5.37	**0.023**	22.06±6.36	22.43±6.74	0.378
SES (%)			0.232			0.400
High	15 (16)	26 (23)		3 (17)	5 (17)	
Medium-High	7 (7)	12 (11)		1 (6)	5 (17)	
Medium	30 (31)	19 (17)		6 (33)	10 (33)	
Medium-Low	32 (33)	41 (36)		7 (39)	5 (17)	
Low	12 (12)	15 (13)		1 (6)	4 (13)	
Missing value	1 (1)	1 (1)		0 (0)	1 (3)	
DUP	108.61±130.39	108.84±118.99	0.990	123.41±145.99	76.48±121.88	0.265
Age of onset	24.00±5.75	25.21±5.40	0.175	25.00±7.15	23.15±6.05	0.430
CPZ baseline	677.78±425.99	577.63±450.65	0.116	548.88±312.08	619.76±690.90	0.695
Clinical and functional variables (M±SD)						
PANSS positive	19.32±8.44	16.81±7.22	**0.021**	21.00±9.01	16.17±5.86	**0.029**
PANSS negative	18.61±7.90	19.94±7.66	0.217	14.11±7.78	15.70±5.91	0.428
PANSS general	38.74±11.80	36.21±11.68	0.120	37.94±14.79	36.27±12.21	0.672
PANSS total	76.67±23.30	72.96±22.86	0.245	73.06±26.94	68.13±21.07	0.484
YMRS	9.29±9.89	6.33±8.53	**0.030**	17.22±15.14	8.87±9.85	**0.025**
MADRS	11.93±9.18	12.83±9.30	0.479	13.72±11.33	14.23±12.44	0.887
FAST	27.30±16.67	29.77±15.53	0.266	22.39±16.93	23.50±13.86	0.806
Cognitive measures (M±SD)						
Attention	88.87±7.72	90.11±9.59	0.343	87.56±11.51	88.00±10.14	0.894
Verbal memory	133.59±47.57	136.24±49.63	0.701	136.67±60.80	136.37±46.67	0.985
Working memory	77.51±14.65	79.39±16.04	0.384	76.14±16.19	79.37±19.35	0.556
Executive function	122.02±42.79	128.32±45.44	0.321	132.34±36.75	130.80±36.87	0.896
GCI	293.14±47.07	297.53±52.69	0.565	297.12±56.74	295.11±48.23	0.905
Cognitive reserve and premorbid adjustment (M±SD)						
CR	73.53±10.50	75.25±12.17	0.276	78.59±13.76	78.32±16.21	0.954
PAS	24.92±13.48	23.84±13.39	0.571	18.29±15.74	18.97±11.49	0.868

Abbreviations: M=Mean, SES=Socioeconomic status, CPZ= Chlorpromazine equivalents, PANSS= Positive and Negative Symptom Scale, YMRS= Young Mania Rating Scale, MADRS= Montgomery-Asberg Depression Rating Scale, FAST=Functioning Assessment Short Test, GCI= Global Cognition Index, CR= Cognitive Reserve, PAS= Premorbid Adjustment Scale. Significant differences ($p<0.05$) marked in bold.

Table 3. Linear regression with cognitive reserve in patients with non-affective and affective first episode of psychosis at baseline and at 2-year follow-up

	Cannabis users					Non cannabis users				
Non-affective first episode of psychosis										
Baseline	**(n=97)**					**(n=114)**				
Functional Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*p*
FAST	0.043	-0.334	0.179	-0.208	0.065	0.022	-0.179	0.123	-0.148	0.149
Clinical Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
PANSS positive	0.001	0.021	0.093	0.026	0.823	0.006	-0.047	0.060	-0.080	0.433
PANSS negative	0.043	-0.161	0.086	-0.208	0.065	0.057	-0.153	0.064	-0.238	**0.019**
PANSS general	0.004	-0.075	0.132	-0.065	0.572	0.007	-0.085	0.100	-0.086	0.400
PANSS total	0.008	-0.215	0.265	-0.092	0.420	0.022	-0.285	0.196	-0.148	0.149
YMRS	0.013	-0.101	0.099	-0.115	0.311	<0.001	0.004	0.063	0.007	0.948
MADRS	0.078	-0.261	0.102	-0.279	**0.013**	0.014	-0.090	0.077	-0.119	0.245
Cognitive measures	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
Verbal memory	0.157	1.856	0.490	0.397	**<0.001**	0.124	1.469	0.400	0.353	**<0.001**
Executive function	0.002	-0.168	0.491	-0.039	0.734	0.005	0.273	0.384	0.073	0.478
Attention	0.157	-0.293	0.078	-0.396	**<0.001**	0.067	-0.207	0.079	-0.258	**0.011**
Working memory	0.259	0.740	0.142	0.509	**<0.001**	0.220	0.620	0.120	0.469	**<0.001**
GCI	0.130	1.704	0.502	0.361	**0.001**	0.134	1.607	0.419	0.366	**<0.001**
Follow-up	**(n=19)**					**(n=110)**				
Functional Variables	R^2	B	S.E.	Beta	p	R^2	B	S.E.	Beta	**p**
FAST	0.040	-0.248	0.191	-0.201	0.202	0.084	-0.411	0.184	-0.290	**0.030**
Clinical Variables	R^2	B	S.E.	Beta	p	R^2	B	S.E.	Beta	**P**
PANSS positive	0.004	0.021	0.049	0.066	0.677	0.069	-0.093	0.046	-0.263	**0.050**
PANSS negative	0.013	-0.063	0.088	-0.112	0.480	0.085	-0.155	0.069	-0.291	**0.030**
PANSS general	0.013	-0.076	0.104	-0.115	0.469	0.065	-0.192	0.099	-0.255	0.058
PANSS total	0.008	-0.118	0.213	-0.087	0.582	0.086	-0.440	0.195	-0.293	**0.028**
YMRS	0.011	0.028	0.043	0.103	0.517	0.002	-0.007	0.023	-0.039	0.775
MADRS	0.034	-0.112	0.094	-0.185	0.240	0.073	-0.142	0.069	-0.269	**0.045**
Cognitive measures	R^2	B	S.E.	Beta	p	R^2	B	S.E.	Beta	**P**
Verbal memory	0.056	1.029	0.670	0.236	0.133	0.114	1.351	0.513	0.337	**0.011**
Executive function	<0.001	0.027	0.596	0.007	0.964	0.019	0.529	0.517	0.138	0.311
Attention	0.344	-0.596	0.130	-0.587	**<0.001**	0.130	-0.325	0.114	-0.361	**0.006**
Working memory	0.168	0.543	0.191	0.410	**0.007**	0.215	0.722	0.188	0.464	**<0.001**
GCI	0.034	0.812	0.685	0.184	0.243	0.127	1.648	0.588	0.357	**0.007**
Affective first episode of psychosis										
Baseline	**(n=18)**					**(n=30)**				
Functional Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*p*
FAST	0.035	-0.154	0.257	-0.186	0.562	0.011	0.081	0.166	0.104	0.627
Clinical Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
PANSS positive	0.059	-0.151	0.191	-0.242	0.448	0.090	-0.112	0.076	-0.301	0.153
PANSS negative	0.032	0.096	0.167	0.179	0.577	0.057	-0.088	0.076	-0.239	0.261
PANSS general	0.005	0.075	0.348	0.068	0.833	0.146	-0.272	0.140	-0.382	0.066
PANSS total	<0.001	0.020	0.621	0.010	0.975	0.142	-0.471	0.247	-0.377	0.069
YMRS	0.159	-0.390	0.283	-0.399	0.199	0.111	-0.182	0.110	-0.334	0.111
MADRS	0.010	0.066	0.214	0.098	0.763	0.017	0.108	0.174	0.131	0.541
Cognitive measures	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
Verbal memory	0.644	3.096	0.727	0.803	**0.002**	0.213	1.408	0.577	0.461	**0.023**
Executive function	0.003	-0.140	0.767	-0.058	0.859	0.003	0.131	0.481	0.058	0.788
Attention	0.055	-0.113	0.148	-0.235	0.462	0.218	-0.309	0.125	-0.467	**0.021**
Working memory	0.376	0.759	0.310	0.613	**0.034**	0.134	0.432	0.234	0.366	0.078
GCI	0.560	2.804	0.786	0.748	**0.005**	0.162	1.267	0.613	0.403	0.051
Follow-up	**(n=9)**					**(n=20)**				
Functional Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*p*

FAST	0.003	0.056	0.451	0.050	0.906	0.454	-0.904	0.265	-0.674	**0.004**
Clinical Variables	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
PANSS positive	0.198	-0.046	0.038	-0.445	0.270	0.048	-0.062	0.073	-0.219	0.415
PANSS negative	0.255	-0.145	0.101	-0.505	0.202	<0.001	-0.006	0.098	-0.017	0.949
PANSS general	0.176	-0.126	0.112	-0.420	0.301	0.020	0.076	0.142	0.141	0.602
PANSS total	0.222	-0.318	0.243	-0.471	0.239	<0.001	0.008	0.297	0.007	0.980
YMRS	0.339	-0.059	0.034	-0.582	0.130	0.023	-0.079	0.137	-0.153	0.573
MADRS	0.083	-0.073	0.099	-0.287	0.490	0.012	0.044	0.105	0.111	0.682
Cognitive measures	R^2	B	S.E.	Beta	*p*	R^2	B	S.E.	Beta	*P*
Verbal memory	0.716	2.849	0.733	0.846	**0.008**	0.541	2.256	0.555	0.736	**0.001**
Executive function	0.009	0.213	0.911	0.095	0.823	0.001	-0.056	0.571	-0.026	0.923
Attention	0.317	-0.211	0.126	-0.563	0.146	0.063	-0.205	0.211	-0.252	0.347
Working memory	0.344	0.714	0.403	0.586	0.127	0.424	1.051	0.327	0.651	**0.006**
GCI	0.727	2.696	0.675	0.852	**0.007**	0.582	2.373	0.537	0.763	**0.001**

Abbreviations: B= The unstandardized beta, S.E.= The standard error for the unstandardized beta, FAST=Functioning Assessment Short Test, PANSS= Positive and Negative Symptom Scale, YMRS= Young Mania Rating Scale, MADRS= Montgomery-Asberg Depression Rating Scale; GCI= Global Cognition Index. Significant differences ($p<0.05$) marked in bold.

Conflict of interest

E. Vieta has received research support from or served as consultant, adviser or speaker for AB-Biotics, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Suibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

M. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of AB-Biotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Roviand Takeda.

A. González-Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, Takeda, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, and the European Framework Program of Research.

I. Corripio has received research grants and served as a consultant, advisoror speaker for the companies Otsuka and Ferrer.

R. Rodriguez-Jimenez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/ BMD-2422 AGES; S2017/BMD-3740), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini.

I. Baeza has received honoraria or travel support to attend conferences from Angelini, Janssen and Otsuka-Lundbeck, and research support from Instituto de Salud Carlos III.

C. De-la-Camara received financial support to attend scientific meetings from Janssen, Almirall, Lilly, Lundbeck, Rovi, Esteve, Novartis, Astrazeneca, Pfizer and Casen Recordati.

J.A.Ramos-Qurioga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió, Raffo in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice

and Eli- Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

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

Author Statement

Contributors

SA, NV, CV and GM conceived the study, with substantial contributions from the other authors. SA and NV did the literature search and wrote the first draft. All authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Acknowledgments

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. Una 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 (2017SGR1355). Departament de Salut de la Generalitat de Catalunya, en la convocatoria corresponent a l'any 2017 de concessió de subvencions del Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020, modalitat Projectes de recerca orientats a l'atenció primària, amb el codi d'expedient SLT006/17/00345. MB is also grateful for the support of the Institut de Neurociències, Universitat de Barcelona.

SA has been supported by a Sara Borrell contract (CD20/00177), funded by Instituto de Salud Carlos III (ISCIII) and co-funded by European Social Fund "Investing in your future".

The study has been supported by a BITRECS project conceded to NV. BITRECS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754550 and from "La Caixa" Foundation.

EV thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283) integrated into the Plan Nacional de I+D+I y cofinanciado por el 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) and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

AGP thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI18/01055), 321218ELCY IT1232-19 Basque Government, Excellent Groups UPV/EHU, 2017111104 Basque Government, Counsel of Health.

IB thanks to Instituto de Salud Carlos III for her support (INT19/0021).

We also would like to thank the authors of the PEPs group who participated in the development of this manuscript, namely, Madero S [1], Forte MF [1], Merchán-Naranjo J [2,10], Ayora M [2,10], Roldán A [2,11], Alonso-Solís A [2,11], González-Ortega I [2,8,9,16], Zorrilla I [2,8,9], De-la-Cámara C [2,17], Santabárbara J [2,18], Sanjuan J [2,19], Escartí MJ [2,19], Martínez-Sadurní L [13], Trabsa A [13], Sparacino G [20], Garriga M [2,3], Castro-Fornieles J [2,12], Baeza I [2,12], Contreras F [2,21], Saiz-Masvidal C [21,22], González-Blanco L [2,23], Sáiz PA [2,23], Gutierrez M [2,24], Sanchez-Pastor L [25], Rodriguez-Jimenez R [2,25,26], Usall J [27], Butjosa A [2,27], Pomarol-Clotet E [2,28], Sarró S [2,28,29], Ibáñez A [2,30], Lucía Moreno-Izco [5,6], Balanzá-Martinez V [2,31].

PEPs Group additional affiliations:

[16] The National Distance Education University (UNED), Vitoria, Spain.

[17] Department of Medicine and Psychiatry. Universidad de Zaragoza, Instituto de Investigación Sanitaria (IIS) Aragón, Zaragoza, Spain.

[18] Hospital Clínico Universitario and Instituto de Investigación Sanitaria (IIS) Aragón, Department of Preventive Medicine and Public Health. Universidad de Zaragoza, Zaragoza, Spain.

[19] Department of Psychiatry, Hospital Clínico Universitario de Valencia, School of Medicine, Universidad de Valencia, Biomedical Research Institute INCLIVA, Valencia, Spain.

[20] Department of Health Sciences, Università degli Studi di Milano, Milan, Italy.

[21] Bellvitge Biomedical Research Institute IDIBELL, Department of Psychiatry- Bellvitge University Hospital, Hospitalet de Llobregat- Barcelona, Spain.

[22] University of Barcelona, Department of Clinical Sciences- School of Medicine, Barcelona, Spain.

[23] Department of Psychiatry, University of Oviedo; Instituto de Investigación Sanitaria del Principado de Asturias (ISPA); Mental Health Services of Principado de Asturias (SESPA), Oviedo, Spain.

[24] Araba University Hospital, Bioaraba Research Institute, Vitoria, Spain.

[25] Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain.

[26] CogPsy Group, Universidad Complutense de Madrid (UCM), Madrid, Spain.

[27] Institut de Recerca Sant Joan de Déu, Esplugues del Llobregat, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain.

[28] FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain.

[29] School of Medicine, Universitat Internacional de Catalunya, Barcelona, Spain

[30] Department of Psychiatry, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, Madrid, Spain.

[31] Department of Medicine, University of Valencia, Valencia, Spain.

Role of the funding source

This study received economic support from the Spanish Ministry of Economic Affairs and Competitiveness, the Carlos III Health Care Institute (Grant Number PI08/0208; PI11/00325; PI14/00612), the European Regional Development Fund, the European Union, “Una manera de hacer Europa/ A Way of Shaping Europe”, and CIBERSAM; Departament de Salut de la Generalitat de Catalunya, en la convocatoria corresponent a l’any 2017 de concessió de subvencions del Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020, modalitat Projectes de recerca orientats a l’atenció primària, amb el codi d’expedient SLT006/17/00345.

Introduction

Cognitive reserve (CR) has been classically defined as the ability of the brain to cope with brain damage in order to delay the onset of clinical manifestations of major disease and minimize their expression (Stern, 2002). In the field of neuropsychiatric disorders, higher CR has been considered as a protective factor in individuals suffering from psychiatric diseases (Barnett et al., 2016; Amoretti and Ramos-Quiroga, 2021). It was reported that CR was associated with later age at onset, higher insight, reduced clinical symptoms severity, better cognitive performance and better psychosocial functioning in people with first episode of psychosis (FEP), schizophrenia and bipolar disorder (Barnett et al., 2006; de la Serna et al., 2013; Forcada et al., 2015; Anaya et al., 2016; Amoretti et al., 2016; Herrero et al., 2020; Camprodon-Boadas et al., 2020; González-Ortega et al., 2020; Lin et al., 2020).

It has been shown that there are several predictors of poor outcome after a FEP, including being male, higher negative symptom severity, younger age at onset, longer duration of untreated psychosis (DUP), non-adherence to medication, poorer premorbid adjustment, cannabis use at onset and continued cannabis use following onset of psychosis (Malla et al., 2006; González-Pinto et al., 2008, 2011; Alvarez-Jimenez et al., 2012; Leeson et al., 2012; Verma et al., 2012; Schoeler et al., 2016; Patel et al., 2016). In addition, the differences between affective and non-affective psychosis are well known (Torrent et al., 2018) and it has been shown that affective FEP showed a higher CR compared to those with a non-affective FEP (Amoretti et al., 2018). A recent study has explored the possible mediating effects of CR on the relationship between cognitive performance or negative symptoms and functional outcome in non-affective FEP (Amoretti et al., 2020). The results obtained suggest that at 2-year follow-up CR has a mediatory effect on attention, verbal memory and negative symptoms measured at baseline. Thus, it may be useful to evaluate CR in FEP patients as it can help in the prediction of long-term functioning.

Concerning the relationship between drug abuse and CR, a study by Leeson and colleagues (Leeson et al., 2012) examined the effect of cannabis use and CR (assessed with premorbid intellectual quotient (IQ)) on age at onset and psychosis outcomes. They found that the cannabis-users had higher CR and better psychosocial functioning than the non-users.

To the best of our knowledge, there are fewer studies analyzing whether there are differences between cannabis users and non-users in terms of the impact of CR in the long-term in FEP patients. Moreover, while cannabis use has been studied in first-episode schizophrenia, there

are no studies analyzing whether there are differences between affective and non-affective FEP patients in terms of the association between CR and cannabis consumption, nor have patients been compared with healthy controls (HC).

Aims of the Study

The aim was to analyze the differences in clinical presentation according to the use of cannabis (cannabis users vs non-users) among patients suffering from a non-affective vs affective FEP, compare it with HC and investigate the effect exerted by the association of CR and cannabis use on longitudinal outcomes. Particularly, the study explores whether CR can be considered as acting as a mediator between cognitive domains or clinical status and functionality for cannabis users and non-users, in the three subgroups (non-affective FEP, affective FEP and HC).

Material and Methods

Sample

The sample of this study came from the multicenter, naturalistic and longitudinal project "Phenotype-genotype interaction. Application of a predictive model in first psychotic episodes" (Bernardo et al., 2013, 2019), under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM) (Salagre et al., 2019).

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

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. It was approved by the ethics committees at each participating center. Each individual gave written informed consent prior to their inclusion in the study.

Assessments

1. Clinical and sociodemographic assessment

Sociodemographic and clinical data for all participants were assessed at baseline and at 2-year follow-up. Antipsychotic mean doses were measured by chlorpromazine equivalents (CPZ) based on international consensus (Gardner et al., 2010). 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 (Kokkevi and Hartgers, 1995). It assesses history (age at first use, years of frequent use) and present cannabis consumption (daily, weekly and monthly use for the last 3 months). Early first use of cannabis has been defined as taking place at or before 15 years of age, similarly to other authors (Mané et al., 2017).

Diagnosis was determined by experienced clinicians using the Structured Clinical Interview for DSM (SCID-I) (First et al., 1997) according to DSM-IV criteria. 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". In order to ensure diagnostic stability, the diagnoses of the patients who completed the study were determined based on information gathered at the two-year follow-up visit.

A psychopathological assessment was carried out with the Spanish versions of the following scales: 1) Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994); 2) Montgomery-Asberg Depression Rating Scale (MADRS) (Lobo et al., 2002); and 3) Young Mania Rating Scale (YMRS) (Colom et al., 2002).

2. Functional assessment

The overall functional outcome was assessed by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007; Amoretti et al., 2021).

Premorbid adjustment was assessed with The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Only childhood and early adolescence life periods have been taken into account since they are the two periods answered by all the participants.

3. Neuropsychological assessment

All participants were tested with a comprehensive neuropsychological battery exploring different cognitive domains: Sustained attention, Verbal Learning and Memory, Working

Memory and Executive Functions (see **Supplementary Information 1**). A global cognition index (GCI) was obtained from the aforementioned cognitive domains. The neuropsychological assessments were performed in the second month of evaluation in order to ensure the clinical stability of patients and were repeated during the two-year follow-up visit.

4. Cognitive reserve assessment

The following evaluation was carried out to measure each proxy at baseline: 1. The estimated premorbid IQ was calculated with the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III)(Wechsler, 1997); 2. Education was assessed taking into account the number of years of obligatory education that subjects had completed as well as parents' educational level and lifetime school performance; 3. Lifetime participation in leisure, social and physical activities was assessed by PAS scale (scholastic performance) and by FAST scale, which allows us to assess specific life-domains such as interpersonal relationships and leisure time. All the information about how the PCA was performed can be found elsewhere (Amoretti et al., 2018).

Statistical Analysis

Patients and HC were divided in "current cannabis users", defined as those smoking cannabis in the past 30 days and those who did not "no current cannabis users". In order to provide information on the prevalence of cannabis users among FEP, past users (defined as those that used cannabis in lifetime but not in the last 30 days) and individuals that never used cannabis were also identified. Finally, cannabis users were also classified into two groups according to the age of first use (before/after 15 years of age).

A Principal Components Analysis (PCA) was performed to create a "Cognitive reserve score" for each subject with the three main proxies. In order to summarize the information about the principal cognitive domains, a "Global Cognition Index" was created for each subject with PCA analysis. Descriptive analyses were conducted using chi-square for categorical variables and Student's t-test for continuous variables. Demographic, clinical and neuropsychological differences between the groups were examined using unpaired t-tests and chi-square. To compare the performance at baseline and two-year follow-up, a repeated measures analysis of variance (ANOVA) was used.

Similarly to previous studies (Amoretti et al., 2016), linear regression analysis models were carried out to assess the predictive value of CR. In a second step, the analysis was carried out

controlling for possible confounders (CPZ, DUP, CGI, tobacco and cannabis in patients and only tobacco and cannabis in the HC group).

The mediation analyses were performed according to the principles of Baron and Kenny (Baron and Kenny, 1986), based on four steps: 1) The independent variable (clinical and cognitive domains) was significantly related to the dependent variable (functioning) (path c); 2) The independent variable was significantly related to the proposed mediator (CR) (path a); 3) The proposed mediator was significantly related to the dependent variable (path b); 4) The independent variable was not significantly related to the dependent variable when controlling for the effects of the proposed mediator (path c') (see **Figure 1**). Hence, if the independent variable is no longer significant when the mediator is controlled, the finding supports full mediation. If the independent variable is still significant, the finding supports partial mediation. These analyses were carried out in both cannabis users and non-users to explore whether or not there were differences between them.

Results

Sociodemographic characteristics of the sample

A total of 259 FEP patients (211 non-affective and 48 affective) and 205 HC were enrolled in this study. At two-year follow-up 158 patients and 140 HC were re-evaluated. The rest of the sample dropped out of the study, mostly due to a loss of follow-up or refusal of re-evaluation. Those patients who were assessed at follow-up (n=158) were indistinguishable from those who were not (n=101) in terms of age (t=0.009, *p*=0.993), gender (x^2=0.090, *p*=0.779), age at first presentation (t=-0.305, *p*=0.761), SES (x^2=6.157, *p*=0.291), tobacco (x^2=0.102, *p*=0.432) and cannabis use (x^2=1.387, *p*=0.163), DUP (t=1.652, *p*=0.100), PANSS-P (t=1.713, *p*=0.088), general PANSS score (t=1.630, *p*=0.104), total MADRS score (t=1.692, *p*=0.092), YMRS (t=1.295, *p*=0.196), FAST (t=0.579, *p*=0.563), CPZ (t=-0.432, *p*=0.666), PAS (t=1.195, *p*=0.233), attention (t=0.268, *p*=0.789), working memory (t=-0.872, *p*=0.384) and executive function (t=0.787, *p*=0.432). However, these two groups differed in terms of negative symptoms (t=2.120, *p*=0.035) and total PANSS score (t=2.137, *p*=0.034), CR (t=-2.939, *p*=0.004) and verbal memory (t=-2.266, *p*=0.024), showing higher negative symptoms, lower CR and worse verbal memory performance those who were assessed only at baseline.

In HC, those who were assessed at follow-up (n=140) were indistinguishable from those who were not (n=65) in terms of age (t=-1.069, *p*=0.287), gender (x^2=1.459, *p*=0.147), SES (t=10.578, p=0.060), tobacco (x^2=0.102, *p*=0.432) and cannabis use (x^2=1.387, *p*=0.163), FAST (p=1.984, *p*=0.051), PAS (t=0.210, *p*=0.834), attention (t=-0.813, *p*=0.417), working memory

(t=-0.166, *p*=0.868), verbal memory (t=-2.051, *p*=0.064) and executive function (t=1.475, *p*=0.142). However, these two groups differed in terms of CR (t=-3.677, *p*<0.001), showing a lower CR those who were assessed only at baseline.

A summary of the baseline sociodemographic and clinical characteristics of FEP patients and HC is shown in **Table 1**. After two years of follow-up, the severity of clinical symptoms improved (values of partial eta squared range from 0.204 to 0.415, medium to large effect sizes), as did cognitive (η2 ranges from 0.056 to 0.313) and functional (η2=0.135) scores. Affective patients had a higher CR than non-affective patients (p=0.017).

There were no differences between patients and HC in terms of age (p=0.078) and gender (p=0.328). However, we found significant differences in SES (p=0.001), PAS (p<0.001), CR (p<0.001), and all cognitive domains and functioning at baseline and follow-up (p<0.001). A greater proportion of patients reported tobacco and cannabis use at baseline (p<0.001), with higher monthly cannabis use (p<0.001). However, at follow-up they differed only in tobacco use (p=0.002), and not in cannabis use (p=0.293) since the percentage of cannabis users reduces from 44% to 15% from baseline to follow-up. They do not also differ in monthly cannabis use at follow-up (p=0.354).

Consumption pattern

At baseline, the 19% of HC used cannabis. Of the 38 HC who used cannabis at baseline, 24 of them maintained their use, 6 stopped and 8 started to consume it during the follow-up period. There were no differences in any measure between those who stopped and those who continued using cannabis. Self-reported monthly cannabis use at baseline and at follow-up was not correlated with any measure.

A percentage as high as 45% of non-affective FEP consumed cannabis at baseline, 12% were lifetime (but not actual) users and 43% had never used cannabis. Of the 97 non-affective FEP patients who used cannabis at baseline, 17 of them maintained their use (18%), 42 stopped using cannabis (43%), and 2 started to consume it (2%) during the follow-up period. There were no differences between those who stopped and those who continued using cannabis. Self-reported monthly cannabis use at baseline was not correlated with any measure. Monthly cannabis use at follow-up was associated with better working memory performance (r=0.767, p=0.004).

A smaller percentage of affective FEP patients (37.5%) consumed cannabis at baseline compared to non-affective FEP, and a higher percentage of affective patients (58.3%) reported

never used cannabis. Of the 18 who reported cannabis use at baseline, 9 of them maintained their use (50%) and 4 stopped using cannabis (22%). There were no differences between those who stopped and those who continued using at baseline, except for CPZ (p=0.004), which was lower in patients who stopped using cannabis. Self-reported monthly cannabis use at baseline was not correlated with any clinical, functional or cognitive outcome. Furthermore, monthly cannabis use at follow-up was associated with CR (r=-0.811, p=0.050), psychosocial functioning (r=0.880, p=0.049), positive, negative and general PANSS score (r=0.856, p=0.029; r=0.866, p=0.026 and r=0.898, p=0.015).

Cannabis use in healthy controls

In the HC group, there were more males who reported cannabis use than females (84%, x^2=7.992, p=0.003). Cannabis users showed a better performance on executive functioning (156.50±30.15 vs. 142.65±29.27, p=0.013). At follow-up there were no differences between those who used cannabis at two years of follow-up and those who did not, except for gender. Self-reported monthly cannabis use at baseline and at follow-up was not correlated with any cognitive measure. CR was neither associated with age of first use of cannabis (p=0.505) nor with years of frequent use (p=0.939).

Cannabis use in patients

At baseline, the 80% of non-affective FEP patients who reported cannabis use were males. Those non-affective FEP patients with cannabis use were younger, with more positive and manic symptoms compared to those with non-affective FEP without cannabis use (see **Table 2**). There were differences between those who have never used cannabis and those who have used (either in the past or currently) in gender, positive and manic symptoms. Those patients with an early age at first cannabis use (n=43) were younger (p=0.001), with a longer DUP (p=0.022), worse working memory performance (p=0.010) and GCI (p=0.031) and a lower CR compared to those with a late age at first use (p=0.016). At follow-up, those patients that reported cannabis use showed more manic symptoms (p=0.003) (see **Supplementary Table 1**).

In affective patients, there were no differences between those who reported cannabis use and those who did not in terms, except for positive and manic symptoms at baseline. There were no significant differences between those who had never used cannabis and those who had used (either in the past or currently), except for gender. Those patients with an early age at first cannabis use (n=10) experienced a FEP at younger age (p=0.030) compared to those with a

later age at onset, without differences in other variables. At follow-up, those patients that reported cannabis use showed lower CR and more manic and positive symptoms.

Predictive value of CR on clinical, functional and cognitive variables

In HC cannabis users, the CR was able to predict working memory at baseline (R^2=0.201, B=0.546, p=0.015) and attention at follow-up (R^2=0.173, B=-0.286, p=0.049). This prediction persists after controlling for a possible confounder just in working memory (p<0.001). In those without cannabis use, the CR was able to predict verbal memory (R^2=0.095, B=0.913, p<0.001), attention (R^2=0.032, B=-0.148, p=0.030), working memory (R^2=0.082, B=0.422, p<0.001) and CGI (R^2=0.079, B=0.925, p=0.001) at baseline. These predictions persist after controlling for a possible confounder (tobacco use). At follow-up the CR was not able to predict any measure.

In cannabis users with non-affective FEP, those with high CR had a later age of onset (r=0.328, p=0.004), later age at first use of cannabis (r=0.251, p=0.006) and a significantly better performance in attention (r=-0.428, p<0.001), working memory (r=0.535, p<0.001), verbal memory (r=0.380, p<0.001) and GCI (r=0.361, p=0.001) at baseline. At follow-up high CR was related to better performance in attention (r=-0.561, p<0.001) and working memory (r=0.401, p=0.004). After performing a regression analysis, we have observed that in cannabis users, the CR was associated with age at onset, depressive symptoms at baseline and different cognitive domains at baseline (verbal memory, attention, working memory and GCI) and only attention and working memory at follow-up. This prediction persists after controlling for possible confounders (DUP, CPZ and tobacco use) (see **Table 3**). In contrast, in those non-affective FEP patients without cannabis use, high CR was associated with a better psychosocial functioning (r=-0.191, p=0.042), lower negative symptoms (r=-0.288, p=0.003) and total PANSS (r=-0.190, p=0.043), lower antipsychotic dose (r=-0.228, p=0.021) and better cognitive performance in attention (r=-0.248, p=0.013), working memory (r=0.460, p<0.001) and verbal memory (r=0.341, p<0.001). At follow-up, higher CR was associated with positive (r=-0.263, p=0.023), negative (r=-0.306, p=0.008) and total symptoms on the PANSS scale (r=-0.257, p=0.026). It was also related to better performance in attention (r=-0.337, p=0.007), working memory (r=0.517, p<0.001), verbal memory (r=0.406, p=0.001) and GCI (r=0.363, p=0.005). The CR was able to predict negative symptoms and all cognitive domains except executive functions at baseline and at follow-up. Moreover, at follow-up the CR predicts functioning and depressive symptoms, as well as positive and total symptoms on the PANSS scale. After controlling for possible confounders (DUP, CPZ and tobacco use), this prediction persists in all outcomes.

In affective FEP patients, those with cannabis use who had high CR had a significantly better performance in working memory (r=0.536, p=0.022), verbal memory (r=0.727, p=0.001) and GCI (r=0.631, p=0.009) and lower dose of antipsychotics (r=0.659, p=0.004) at baseline and better performance in verbal memory (r=0.833, p=0.005) and GCI (r=0.828, p=0.011) at follow-up. After performing a regression analysis, the CR was able to predict verbal memory, working memory, and GCI at baseline and only verbal memory and GCI at follow-up (see **Table 3**). These predictions persist after controlling for possible confounders. In contrast, for those patients without cannabis use, high CR was associated with a lower positive, general and total PANSS score (r=-0.380, p=0.038; r=-0.470, p=0.009 and r=-0.436, p=0.016, respectively) and lower manic symptoms (r=-0.400, p=0.028) at baseline and with better psychosocial functioning (r=-0.667, p=0.001) and better performance in working memory (r=0.483, p=0.023), verbal memory (r=0.619, p=0.003) and GCI (r=0.637, p=0.006) at follow-up. The CR was able to predict verbal memory and attention at baseline, and psychosocial functioning, verbal memory, working memory and GCI at follow-up.

Mediators of functional outcome

In those HC who reported cannabis use, the effect of working memory on functioning at baseline was not mediated by CR (see **Supplementary Table 2**).

In non-affective patients who reported cannabis use, the effect of clinical variables or cognitive performance on functioning was not mediated by CR at baseline nor at follow-up (see **Supplementary Table 3-4**). There were clinical variables associated with functioning, but CR was not related to them. One was related to CR but not to functioning and there were some variables that were not associated with any of these measures (see **Supplementary Information 2**). In non-affective FEP patients without cannabis use at baseline, the effect of negative and total PANSS on functioning was not mediated by CR. At two-year follow-up, CR partially mediated the relationship between verbal memory and functioning. However, the effects of positive, negative and total PANSS scores on functioning were not mediated by CR.

In affective patients who reported cannabis use, there were clinical variables associated with functioning, but CR was not related to them and variables related to CR were not associated with functioning. Therefore, no mediation analysis could be conducted. In those affective patients who did not report cannabis use, the effect of general symptoms of PANSS on functioning at baseline was not mediated by CR. However, the CR mediates the effect of working memory assessed at follow-up on functioning. In other words, working memory was no longer significant when the mediator (CR) was controlled, indicating that the relationship

between working memory and functioning (both assessed at follow-up) was totally mediated by CR. A summary of the results are shown in **Figure 2**.

Discussion

Two main findings emerged from the present study. Non-affective FEP patients with cannabis use were males, younger, with more positive and manic symptoms compared to those with non-affective FEP without cannabis use. Affective patients with cannabis use differ from those without cannabis on positive and manic symptoms. CR played a differential role in the outcome of psychoses according to being a cannabis user or not. In particular, in both groups of patients, regardless of whether the patients consumed cannabis, CR was associated with better cognitive performance. However, only in non-affective FEP without cannabis use, CR was able to predict positive, negative and depressive symptoms and psychosocial functioning at follow-up. Similarly, only in affective patients without cannabis use, CR was able to predict psychosocial functioning at follow-up. Indeed, CR mediates the relationship between some cognitive domains and functioning at follow-up only in patients without cannabis use.

Control subjects show a higher CR level than the patients, and the group with an affective FEP shows a higher CR compared to those with a non-affective FEP. These results are in line with previous studies (de la Serna et al., 2013; Forcada et al., 2015; Amoretti et al., 2018). However, unexpectedly, we did not find differences between cannabis users and non-users in terms of CR, premorbid adjustment or cognitive performance, neither in patients nor in controls. Previous literature has shown that patients who use cannabis constitute a subgroup of patients with better premorbid adjustment, better cognitive function and greater CR than other psychotic patients (Schnell et al., 2009; Rodríguez-Sánchez et al., 2010; Cunha et al., 2013; Yücel et al., 2012; Maldonado and Torrens, 2020). Nonetheless, there are also studies that observed no differences in cognition (Bugra et al., 2013), symptoms, premorbid adjustment or antipsychotic medication (Leeson et al., 2012). In fact, a recent meta-analysis indicates that cannabis use is not generally associated with neurocognitive functioning in patients with FEP (Sánchez-Gutiérrez et al., 2020). There are other possible explanations for the inconsistency in results. There are studies focused on psychosis in general, including affective psychoses, while others were focused specifically on schizophrenia or on FEP. Some studies focusing on a history of lifetime use may include subjects who have used it only at relatively specific moments or who have not used it for years, while others focus on current consumption.

In line with the literature, we found evidence that CR was associated with better cognitive performance (de la Serna et al., 2013; Amoretti et al., 2020), regardless of whether the patients consumed cannabis and regardless of whether the diagnosis was affective or non-affective FEP. However, the effect exerted by CR on clinical symptoms and functionality was different, depending on whether or not there was cannabis use. Specifically, in non-affective FEP with cannabis use, we observed a correlation between age at onset and CR (Leeson et al., 2012) and in non-users with functionality, negative symptoms and antipsychotics level (Amoretti et al., 2016, 2018). In affective patients, those with high CR and cannabis use had a lower dose of antipsychotic and in those without cannabis use, higher CR was associated with lower severity of positive and manic symptoms at baseline (Amoretti et al., 2018) and higher psychosocial functioning at follow-up. Thus, in both diagnoses, it seems that CR exerted an effect on clinical and functional outcomes particularly in those patients without cannabis use. CR seems to be more related to negative symptoms in non-affective patients and to positive and manic symptoms in affective patients.

Regarding the capacity of CR, in non-affective FEP without cannabis use, CR was able to predict positive, negative and depressive symptoms, functioning and all cognitive domains except executive functioning at follow-up. However, in those with cannabis use CR only predicted attention and working memory at follow-up. In affective patients without cannabis use CR was able to predict functioning, verbal memory, working memory and GCI at follow-up and in those with cannabis use CR predicted verbal memory and GCI. Therefore, again, not only in the association but also in the prediction at two-year follow-up, CR exerted a greater effect in those subjects without cannabis use, especially in the clinical and functional course. These results may be due to the fact that although higher CR has been considered as a protective factor in individuals suffering from psychiatric diseases (Barnett et al., 2006), cannabis use may have more impact on clinical and functional outcomes than CR (Seddon et al., 2016).

Finally, in terms of mediation procedure, at baseline the path between domains of cognitive performance or clinical symptoms on psychosocial functioning was not mediated by CR, suggesting that the clinical status at that time contributed strongly in defining functioning at baseline. These results suggest that at baseline, patients showed a prominent functional impairment, probably as a consequence of clinical symptoms (Amoretti et al., 2020; Barnes and Pant, 2005). At two-year follow-up, FEP improved their functioning, clinical and neurocognitive performance. In non-affective FEP with cannabis use, CR did not have a mediatory effect either, indicating that attention and working memory in these patients have a

strong association with functioning at follow-up. As a result, it would be recommended to evaluate and even enhance attention and working memory in this subpopulation (Penadés et al., 2012). These results are in line with previous studies in which attention and working memory were identified as the main cognitive predictors of functional outcome (González-Blanch et al., 2010; Fu et al., 2017). In those non-affective FEP patients without cannabis use, CR partially mediated the relationship between verbal memory and functioning at follow-up. In this case, CR could be considered an important aspect to take into account when predicting functionality. Similarly, in affective FEPs without cannabis use, CR mediated the effect of working memory on functioning at follow-up. Thus, based on these results, we consider that, in non-cannabis users, the implementation of early interventions centered on CR stimulation could be beneficial for the prevention or reduction of the impact of illness. Instead, in cannabis users an early intervention to reduce cannabis use can be suggested.

This study has certain limitations, which must be taken into account. Firstly, 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 (especially in CR). The small sample size, particularly of the affective psychosis FEP, hampers the generalizability of the findings, thus further research should be conducted to validate them. Secondly, a limitation present in all CR studies undertaken on a psychiatric population is that there is no consensus in measuring CR as a construct, which makes it difficult to optimally compare studies. Finally, cannabis use was self-reported by participants, without using an objective measure such as urine drug screen.

In conclusion, CR seems to be a protective factor, especially in those FEP without cannabis use, and its characterization could considerably improve our understanding of individual differences and be a useful stratification tool in FEP patients, thus enabling the implementation of personalized interventions.

References

Alvarez-Jimenez, M., Priede, A., Hetrick, S.E., Bendall, S., Killackey, E., Parker, A.G., McGorry, P.D., Gleeson, J.F., 2012. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr. Res. 139(1-3), 116-28. doi: 10.1016/j.schres.2012.05.007.

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. Eur. Neuropsychopharmacol. 26(10), 1638-1648. doi: 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., Panadés, R., Sánchez-Torres, A.M., Cuesta, M., Bernardo, M., PEPsGroup., 2018. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. Acta Psychiatr. Scand. 138(5), 411-55. doi: 10.1111/acps.12949.

Amoretti, S., Ramos-Quiroga, J.A., 2021. Cognitive reserve in mental disorders. Eur. Neuropsychopharmacol. 49, 113-115. doi: 10.1016/j.euroneuro.2021.04.011.

Amoretti, S., Mezquida, G., Rosa, A.R., Bioque, M., Cuesta, M.J., Pina-Camacho, L., Garcia-Rizo, C., Barcones, F., González-Pinto, A., Merchán-Naranjo, J., Corripio, I., Vieta, E., Baeza, I., Cortizo, R., Bonnín, C.M., Torrent, C., Bernardo, M., PEPs Group., 2021. The Functioning Assessment Short Test (FAST) applied to first-episode psychosis: psychometric properties and severity thresholds. Eur. Neuropsychopharmacol. 47, 98-111. doi: 10.1016/j.euroneuro.2021.02.007.

Amoretti, S., 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., PEPs Group. 2020.The impact of cognitive reserve, cognition and clinical symptoms on psychosocial functioning in first-episode psychoses. Psychol. Med. 1-12. doi: 10.1017/S0033291720002226.

Anaya, C., Torrent, C., Caballero, F.F., Vieta, E., Bonnín, C.M., Ayuso-Mateos, J.L., CIBERSAM Functional Remediation Group., 2016. Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. Acta Psychiatr. Scand. 133(5), 386-398. doi: 10.1111/acps.12535.

Barnes, T.R.E., Pant, A., 2005. Long-term course and outcome of schizophrenia. Psychiatry, 4(10), 29-32. doi: 10.1383/psyt.2005.4.10.29.

Barnett, J., Salmond, C., Jones, P., Sahakian, B.J., 2006. Cognitive reserve in neuropsychiatry. Psychol. Med. 36(8), 1053-1064. doi: 10.1017/S0033291706007501.

Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. 51(6), 1173-1182. doi: 10.1037/0022-3514.51.6.1173.

Bernardo, M., Bioque, M., Parellada, M., Saiz, J., Cuesta, M.J., Llerena, A., Sanjuán, J., Castro-Fornieles, J., Arango, C., Cabrera, C., PEPs Group., 2013. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). Rev. Psiquiatr. Salud Ment. 6(1), 4-16. doi: 10.1016/j.rpsm.2012.11.001.

Bernardo, M., Cabrera, B., Arango, C., Bioque, M., Castro-Fornieles, J., Cuesta, M.J., Lafuente, A., Parellada, M., Saiz-Ruiz, J., Vieta, E., 2019. One decade of the first episodes project (PEPs): Advancing towards a precision psychiatry. Rev. Psiquiatr. Salud Ment. 12(3), 135-140. doi: 10.1016/j.rpsm.2019.03.001.

Bugra, H., Studerus, E., Rapp, C., Tamagni, C., Aston, J., Borgwardt, S., Riecher-Rössler, A., 2013. Cannabis use and cognitive functions in at-risk mental state and first episode psychosis. Psychopharmacology (Berl). 230(2), 299-308. doi: 10.1007/s00213-013-3157-y.

Camprodon-Boadas, P., de la Serna, E., Baeza, I., Puig, O., Ilzarbe, D., Sugranyes, G., Borras, R., Castro-Fornieles, J., 2020. Cognitive reserve in patients with first-episode psychosis as outcome predictor at 5-year follow-up. Eur. Child Adolesc. Psychiatry. doi: 10.1007/s00787-020-01668-4.

Cannon-Spoor, H., Potkin, S., Wyatt, R., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8(3), 470-484. doi: 10.1093/schbul/8.3.470.

Colom, F., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Reinares, M., Torrent, C., Goikolea, J.M., Banús, S., Salamero, M., 2002. [Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale]. Med. Clin. (Barc). 119(10), 366-371. doi: 10.1016/s0025-7753(02)73419-2.

Cunha, P.J., Rosa, P.G., Ayres Ade, M., Duran, F.L., Santos, L.C., Scazufca, M., Menezes, P.R., dos Santos, B., Murray, R.M., Crippa, J.A., Busatto, G.F., Schaufelberger, M.S., 2013. Cannabis use, cognition and brain structure in first-episode psychosis. Schizophr. Res. 147(2-3), 209-215. doi: 10.1016/j.schres.2013.04.009.

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. Schizophr. Res. 143(1), 125-131. doi: 10.1016/j.schres.2012.10.026.

First, M., Spitzer, R., Gibbon, M., Williams, J., 1997. Structured clinical interview for DSM-IV axis I disorders-clinician (SCID-I). Washington DC. American Psychiatric Press.

Forcada, I., Mur, M., Mora, E., Vieta, E., Bartrés-Faz, D., Portella, M., 2015. The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. Eur. Neuropsychopharmacol. 25(2), 214-222. doi: 10.1016/j.euroneuro.2014.07.018

Fu, S., Czajkowski, N., Rund, B.R., Torgalsbøen, A.K., 2017. The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia. Schizophr. Res. 190, 144-149. doi: 10.1016/j.schres.2017.03.002.

Gardner, D., Murphy, A., O'Donnell, H., Centorrino, F., Baldessarini, R.J., 2010. International consensus study of antipsychotic dosing. Am. J. Psychiatry. 167(6), 686-693. doi: 10.1176/appi.ajp.2009.09060802.

González-Blanch, C., Perez-Iglesias, R., Pardo-García, G., Rodríguez-Sánchez, J.M., Martínez-García, O., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2010. Prognostic value of cognitive functioning for global functional recovery in first-episode schizophrenia. Psychol. Med. 40(6), 935-944. doi: 10.1017/S0033291709991267.

González-Ortega, I., González-Pinto, A., Alberich, S., Echeburúa, 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., PEPs Group., 2020. Influence of social cognition as a mediator between cognitive reserve and psychosocial functioning in patients with first episode psychosis. Psychol. Med. 50(16), 2702-2710. doi: 10.1017/S0033291719002794.

González-Pinto, A., Alberich, S., Barbeito, S., Gutierrez, M., Vega, P., Ibáñez, B., Haidar, M.K., Vieta, E., Arango, C.,. 2011. Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. Schizophr. Bull. 37(3), 631-639. doi: 10.1093/schbul/sbp126.

González-Pinto, A., Vega, P., Ibáñez, B., Mosquera, F., Barbeito, S., Gutiérrez, M., Ruiz de Azúa, S., Ruiz, I., Vieta, E., 2008. Impact of cannabis and other drugs on age at onset of psychosis. J. Clin. Psychiatry. 69(8), 1210-1216. doi: 10.4088/jcp.v69n0802.

Herrero, P., Contador, I., Stern, Y., Fernández-Calvo, B., Sánchez, A, Ramos, F., 2020. Influence of cognitive reserve in schizophrenia: A systematic review. Neurosci. Biobehav. Rev. 108, 149-159. doi: 10.1016/j.neubiorev.2019.10.019.

Kokkevi, A., Hartgers, C., 1995. European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. Eur. Addict. Res. 1, 208-210. doi:10.1159/000259089.

Leeson, V., 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. Schizophr. Bull. 37(4), 768-777. doi: 10.1093/schbul/sbp143.

Lin, X., Lu, D., Zhu, Y., Luo, X., Huang, Z., Chen, W., 2020. The effects of cognitive reserve on predicting and moderating the cognitive and psychosocial functioning of patients with bipolar disorder. J. Affect. Disord. 260, 222-231. doi: 10.1016/j.jad.2019.09.019.

Lobo, A., Chamorro, L., Luque, A., Dal-Re, R., Badia, X., Baro, E., 2002. [Validation of the Spanish versions of the Montgomery-Asberg depression and Hamilton anxiety rating scales]. Med. Clin. (Barc). 118, 493-499. doi: 10.1016/s0025-7753(02)72429-9.

Maldonado, R., Torrens, M., 2020. Cannabis research: Risks of recreational use and potential medical applications. Eur. Neuropsychopharmacol. 36, 167-168. doi: 10.1016/j.euroneuro.2020.06.009.

Malla, A., Norman, R., Schmitz, N., Manchanda, R., Béchard-Evans, L., Takhar, J., Haricharan, R., 2006. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol. Med. 36(5), 649-658. doi: 10.1017/S0033291706007379.

Mané, A., Bergé, D., Penzol, M.J., Parellada, M., Bioque, M., Lobo, A., González-Pinto, A., Corripio, I., Cabrera, B., Sánchez-Torres, A.M., Saiz-Ruiz, J., Bernardo M., PEPs Group. (2017). Cannabis use, COMT, BDNF and age at first-episode psychosis. Psychiatry Res. 250, 38-43. doi: 10.1016/j.psychres.2017.01.045.

Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., Bhattacharyya S., 2016. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. BMJ Open. 6(3) e009888. doi: 10.1136/bmjopen-2015-009888.

Penadés, R., Catalán, R., Salamero, M., Boget, T., Puig, O., Guarch, J., Gastó, C., 2006. Cognitive remediation therapy for outpatients with chronic schizophrenia: a controlled and randomized study. Schizophr. Res. 87(1-3), 323-331. doi: 10.1016/j.schres.2006.04.019.

Peralta, V., Cuesta, M., 1994. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res. 53(1), 31-40. doi: 10.1016/0165-1781(94)90093-0.

Rodríguez-Sánchez, J.M., Ayesa-Arriola, R., Mata, I., Moreno-Calle, T., Perez-Iglesias, R., González-Blanch, C., Periañez, J.A., Vazquez-Barquero, J.L., Crespo-Facorro, B., 2010. Cannabis use and cognitive functioning in first-episode schizophrenia patients. Schizophr. Res. 124(1-3), 142-151. doi: 10.1016/j.schres.2010.08.017.

Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E. (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Ment. Health. 7, 5. doi: 10.1186/1745-0179-3-5.

Salagre, E., Arango, C., Artigas, F., Ayuso-Mateos, J.L., Bernardo, M., Castro-Fornieles, J., Bobes, J., Desco, M., Fañanás, L., González-Pinto, A., Haro, J.M., Leza, J.C., Mckenna, P.J., Meana, J.J., Menchón, J.M., Micó, J.A., Palomo, T., Pazos, Á., Pérez, V., Saiz-Ruiz, J., Sanjuán, J., Tabarés-Seisdedos, R., Crespo-Facorro, B., Casas, M., Vilella, E., Palao, D., Olivares, J.M., Rodriguez-Jimenez, R., Vieta, E., 2019. CIBERSAM: Ten years of collaborative translational research in mental disorders. Rev. Psiquiatr. Salud Ment., 12(1), 1-8. doi: 10.1016/j.rpsm.2018.10.001.

Sánchez-Gutiérrez, T., Fernandez-Castilla, B., Barbeito, S., González-Pinto, A., Becerra-García, J.A., Calvo, A., 2020. Cannabis use and nonuse in patients with first-episode psychosis: A systematic review and meta-analysis of studies comparing neurocognitive functioning. Eur. Psychiatry. 63(1), e6. doi: 10.1192/j.eurpsy.2019.9.

Schnell, T., Koethe, D., Daumann, J., Gouzoulis-Mayfrank, E., 2009. The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacology (Berl). 205(1), 45-52. doi: 10.1007/s00213-009-1512-9.

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry, 3(3), 215-225. doi: 10.1016/S2215-0366(15)00363-6.

Seddon, J.L., Birchwood, M., Copello, A., Everard, L., Jones, P.B., Fowler, D., Amos, T., Freemantle, N., Sharma, V., Marshall, M., Singh, S.P., 2016. Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study. Schizophr. Bull. 42(3), 619-625. doi: 10.1093/schbul/sbv154.

Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8(3), 448-460. doi: 10.1017/S1355617702813248

Torrent, C., Reinares, M., Martinez-Arán, A., Cabrera, B., Amoretti, S., Corripio, I., Contreras, F., Sarró, S., González-Pinto, A., Lobo, A., Cuesta, M.J., Sánchez-Torres, A., Bergé, D., Castro-Fornieles, J., Moreno, C., Bernardo, M., Vieta, E., PEPS group., 2018. Affective versus non-affective first episode psychoses: A longitudinal study. J. Affect. Disord. 238, 297-304. doi: 10.1016/j.jad.2018.06.005.

Verma, S., Subramaniam, M., Abdin, E., Poon, L.Y., Chong, S.A., 2012. Symptomatic and functional remission in patients with first-episode psychosis. Acta Psychiatr. Scand. 126(4), 282-289. doi: 10.1111/j.1600-0447.2012.01883.x.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale - III (WAIS-III). San Antonio, TX: The Psychological Association.

Yücel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr. Bull. 38(2), 316-330. doi: 10.1093/schbul/sbq079.