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Original article

Assessing cognitive reserve outcomes and biomarkers in first episode of psychosis: Rationale, objectives, protocol and preliminary results of the CRASH Project

Evaluación del impacto de la reserva cognitiva y los biomarcadores en el primer episodio de psicosis: justificación, objetivos, protocolo y resultados preliminares del proyecto CRASH

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ABSTRACT

Introduction: Cognitive reserve (CR) has proved to predict clinical, cognitive and functional outcomes. Despite this, it is necessary to shed greater light on the identification of factors associated with CR in first psychotic episodes (FEP). The aim of this article was to describe the rationale, objectives, protocol, and preliminary results for a new project of CR.
Material and methods: The CRASH Project is a coordinated, multicenter and multimodal study of patients with a FEP with a one-year prospective longitudinal follow-up. This project is funded by the *Departament de Salut* of the *Generalitat de Catalunya* and file code SLT006/17/00345. The project was structured in four modules, each focusing on a different outcome measure: (1) General and Basic; (2) Neuroimaging; (3) Neurocognition; and (4) Biological.
Results: A total of 90 FEP patients and 100 healthy controls were enrolled in this study. There were no differences between patients and HC in terms of age ($p = 0.104$), gender ($p = 0.140$) and socioeconomic status ($p = 0.104$). However, at inclusion, we found significant differences in functioning ($p < 0.001$), CR ($p < 0.001$), and all cognitive domains except executive functioning. Patients were clinically stable at inclusion.

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Conclusions: The results obtained by this project are hoped to contribute as much towards the understanding of the illness' physiopathology as towards the generation of new treatment designs and therapeutic strategies that allow for a personalized management according to each individual's profile, which includes CR as well as clinical characteristics.

Introduction

It is estimated that approximately three in every 100 people experience a psychotic episode at some point in their lifetime.[1] Isolated psychotic episodes, which resolve themselves and do not develop into a full psychotic disorder, do exist. However, up to 80% of patients suffer from a psychotic relapse within five years of the first episode of psychosis (FEP),[2] hence the importance of adequate diagnosis and treatment in preventing relapses. The illness course is highly variable due to, amongst other factors, the lack of specificity of the first symptoms, as well as the associated comorbidity with substance abuse, anxiety, lack of illness awareness, lack of treatment adherence or cognitive decline. Various factors have been reported as possible determinants of a FEP prognosis. Those which have attracted the greatest interest have been the duration of untreated psychosis (DUP), premorbid adaptation, comorbid substance consumption, the predominance of negative symptoms and cognitive alterations.[3–7] A clear association has also been established between the abandonment of antipsychotic medication and the risk of relapse, hospitalization and the appearance of resistance to treatment.[8]

The DUP is the time that passes between the beginning of a psychotic disorder and its recognition and therapeutic intervention. It is related to resistance to treatment[9] and to a low level of symptomatic and functional recovery.[10–12] The DUP tends to be considered difficult to measure since the information is extracted retrospectively by means of clinical interviews and it usually means that the informant's help is required. The same problem is encountered in the measurement of premorbid adjustment, that is to say the subject's social, interpersonal, academic and professional functioning before the appearance of psychotic symptoms, since that relies on the memory of the evaluated person and their informants. Premorbid adjustment is related to the presence of negative symptoms, psychosocial functioning, relapse rate and response to treatment.[10,13–17]

Among other factors associated with a better or worse prognosis in FEP, substance use is present in a substantial proportion of patients with FEP and it is higher than in the general population. Colizzi and collaborators reported that in the premorbid phase, up to 65.4% of FEP patients reported cannabis use, 53.2% nicotine dependence, 40.5% problems with alcohol and 36.6% the use of stimulants.[18] Psychotic disorders resulting from substance use have been linked to worse prognosis, with greater unfulfillment and abandonment of treatment, as well as lower remission rates.[19,20] Negative symptoms play a crucial role in the recovery process[21] and they are particularly important due to their association with functionality[22,23] and worse prognosis.[24] In fact, patients with persistent negative symptoms are characterized by a high DUP, a poor premorbid adjustment and a tendency towards worse cognitive performance.[25] Finally, there is a clear association between cognitive deficits and poor functionality, including the fulfilment of basic everyday activities, the acquisition of social abilities, resolution of social problems and occupational functioning.[26,27] Cognitive alterations have been observed from the premorbid phase onwards, before the appearance of the illness' positive symptoms.[28]

One concept which has been clearly related to cognition and which has gained ground during recent years in psychiatric disorders, and especially in psychotic disorders, is cognitive reserve (CR). This term emerged from the context of dementias, then extending itself to other chronic neurodegenerative illnesses such as the human immunodeficiency virus or multiple sclerosis,[29] and currently there is a wide interest in it in the area of psychiatry.[30] CR refers to the hypothetical capacity of an adult brain to deal with a specific pathology and minimize symptomatology,[31] and it is fundamentally determined by genetic factors and neurodevelopment. However, it can vary according to the environment and exposition to certain environmental factors such as education, lifestyle and mental and physical activities.[32] Recent studies on FEP populations show that CR has an impact on clinical evolution, especially on those with a negative functional and cognitive symptomatology within this population.[33–38] Nevertheless, a deeper knowledge of the physiology of cognitive reserve and of FEP is considered necessary since the study of different biomarkers related to these concepts could help to elucidate the progression of the pathogenesis and provide potential targets for better therapeutic strategies. In this sense, the inflammatory processes, as well as structural neuroimaging have been considered areas of interest and promise in research focused on biomarkers.

Recent literature suggests that serious mental disorders are associated with inflammatory processes,[39] mainly in psychotic disorders,[40] and it is suggested that several cytokines involved in these processes should be the center of attention for new research in order to define biological markers of progression and the course of the disorder.[41] For FEP, in the initial stages of the illness research has found unsettled anti-inflammatory activity to bear influence on progressive inflammatory processes[42] and has associated this with cognitive dysfunction.[43,44] Oxidative stress also plays an important role in many neuropsychiatric illnesses including schizophrenia[45] and, together with nitrosative processes, has been associated with cognitive function in schizophrenia and FEP.[46,47] It seems as though all of these markers can vary according to patients' clinical status.[48]

Regarding the most commonly found biomarkers in structural neuroimaging studies in FEP, a decline in the volume of grey matter and abnormalities in white matter are shown, as well as an increase in the volume of ventricles.[49,50] FEP studies seem to indicate that the most robust structural alterations that can be identified as biomarkers of schizophrenia are decreases in grey matter in temporo-insular regions and the anterior cingulate cortex.[51] As far as neuroimaging and CR studies are concerned, in a population with dementia, the component variables of the concept of CR exert influence on cerebral structure,[52,53] demonstrating that those subjects with greater CR accumulate more pathology, which means that they require more neuroanatomical changes in order to present cognitive decline.[54] In healthy subjects it has been observed that greater CR has been associated with a greater volume of grey matter in the regions of the brain that are involved in motor and cognitive functions, and with less functional connectivity in a resting state.[55] However, there is only one publication on serious mental disorders (which include psychotic, bipolar and major depressive disorders) in which it has been observed that a greater CR alters the relationship between brain pathology and clinical presentation for patients with bipolar disorder.[56] Furthermore, one limitation, present in all studies about CR in serious mental disorders, is that the level of CR has been estimated using heterogeneous methods

since no standardized measures were available for this population. For this reason, in 2019 the psychometric properties of the *Cognitive Reserve Assessment Scale in Health* (CRASH) were developed and examined. The scale was designed to measure cognitive reserve in people with a serious mental disorder.[57]

Studies into the impact that CR, biomarkers and other relevant variables have can help in taking fundamental care decisions. The aim of this article was to describe the rationale, objectives, protocol, and preliminary results for a new project of CR.

Material and methods

Sample

Subjects with a FEP and healthy controls (HC) were included in the CRASH Project. All participants were recruited from three centers: Hospital Clinic of Barcelona, Mútua Terrassa University Hospital and Bellvitge University Hospital, which belong to the CIBERSAM Network in Spain.[58,59]

The inclusion criteria for patients were: (1) aged between 18 and 45 years old at the time of first evaluation; (2) presence of psychotic symptoms such as delusions, hallucinations, disorganized speech and behavior of less than five years' duration; (3) speak Spanish correctly and (4) signed informed consent. Exclusion criteria were: (1) mental retardation, understood not only as estimated Intelligent Quotient (IQ) <70, but also malfunctioning and problems with adaptive process; (2) history of head trauma with loss of consciousness and/or; (3) organic disease with mental repercussions. Since this was a naturalistic study, there were no guidelines for the administered treatment.

The patients matched with HC on age (±10%), gender and parental socioeconomic status (±1 level). The exclusion criteria for HC 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 a history of psychotic disorder.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and Research Ethics Committee (HCB/2017/079, PR427/17 and Acta04/2018).

Study design and objectives of the CRASH project

The CRASH Project is a coordinated, multicenter and multimodal study of patients with a FEP with a one-year prospective longitudinal follow-up. This project is funded by the *Departament de Salut* of the *Generalitat de Catalunya*, as part of the 2018 call for grants for the Strategic Plan for Research and Innovation in Health (PERIS) 2016–2020, modality "Research projects oriented to primary care" and file code SLT006/17/00345.

The objective of the CRASH Project is the identification potential markers (including CR, cognitive and clinical variables, functioning, neuroimaging and inflammatory biomarkers) in order to develop strategies which allow for the adequate stratification of patients, as well as to predict the course of illness and response to treatment in FEP. The specific objectives of the current project are: (a) to define neuroimaging, inflammatory, neuropsychological, clinical, diagnostic and CR-related profiles; (b) to replicate previous findings related to the predictive value of CR as a variable that affects the evolution of patients with a FEP; (c) to use CR and other relevant variables in order to elaborate a predictive model of the appearance of relapse; (d) to define neuropsychological profiles that are related to clinical, diagnostic and global functioning variables in this cohort of patients with FEP according to CR; (e) to study the relationship between CR and brain structure as well as its implication in prognosis; (f) to analyze biomarkers and the mediatory role of CR as variables related to therapeutic response and its association with other clinical outcome variables (relapse, treatment adherence, hospital readmission etc.).

The project was structured in four modules, each focusing on a different outcome measure: (1) General and Basic; (2) Neuroimaging; (3) Neurocognition; and (4) Biological.

Assessments

The study design began by identifying the factors related to CR and to early and long-term outcome of FEP. To explore which instruments would be best suited to assess these factors, initially an in-depth review of the scientific literature and existing measures used in this population was carried out. Once the first draft of the assessment protocol was prepared, it was discussed with external consultants and with all the centers to ensure a refined measurement and to reduce unnecessary or redundant measures. All scales were administered by expert clinicians, except those that were self-administered. Psychopathological, functional and neuropsychological assessments were performed at baseline (T0) and repeated in the one-year follow-up visit (T1). Blood sample was collected at T0 and T1. Structural magnetic resonance imaging was also acquired at T0 and T1. The assessment procedure (T0 and T1) was common for HC, with the exception of acquisition of neuroimaging which was only acquired at T0.

The modules are discussed in detail below.

General module

This module includes information about sociodemographic and environmental factors, diagnostic interview, CR, premorbid adjustment, clinical and functional outcomes and other prognostic factors.

Diagnostic interview. The first step in this project was to confirm the diagnosis of psychotic disorder. For this, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[60] was used. A complete personal and family history was also performed.

Sociodemographic and environmental factors. At baseline, a complete evaluation was performed. Sociodemographic data was systematically obtained for all participants and included: age, gender, marital status, current living situation, education, employment situation and parental socioeconomic status (SES), determined using Hollingshead's Two-Factor Index of Social Position.[61] The Childhood Trauma Questionnaire (CTQ)[62] was used to assess five sub-scales: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect.

Assessments of obstetric complications were recorded using the Lewis–Murray Scale of Obstetric Data[63] and subjects' urbanicity was also recorded. In both evaluations the weight, height, body mass index, blood pressure and abdominal perimeter were also obtained, with the aim of monitoring physical health indicators. The Short Form 36 (SF36) Health Survey Questionnaire[64] was used to measure eight multi-item variables: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health. Finally, a systematic register of drug misuse habits was performed at baseline and follow-up visits.

Cognitive reserve and premorbid adjustment. To assess CR, the Cognitive Reserve Questionnaire (CRQ)[65] and Cognitive Reserve Assessment Scale in Health (CRASH)[57] were used. In both scales, the higher the score, the greater the CR.

The Premorbid Adjustment Scale (PAS)[66] was applied to assess premorbid adjustment retrospectively. Higher scores on the test indicate worse premorbid adjustment.

Clinical status and global functioning. In order to retrospectively characterize and date the initial symptoms of psychotic illness the Symptom Onset in Schizophrenia (SOS) inventory was used.[67] The DUP was calculated as the number of days elapsed between the first manifestations of psychotic symptoms and the initiation of adequate treatment for psychosis.

A psychopathological assessment was carried out at inclusion and after one year of follow-up with the Spanish validated versions of the following scales: the Positive and Negative Syndrome Scale (PANSS)[68,69] for positive and negative symptoms, the Brief Negative Symptom Scale (BNSS)[70,71] for negative symptoms, the Hamilton Depression Rating Scale (HDRS)[72,73] for depressive symptoms, the Young Mania Rating Scale (YMRS)[74,75] for manic symptoms, and the Clinical Global Impression Scale (CGI)[76] for symptom severity. On each scale, the items were summed to obtain a total score. Higher scores indicate greater severity.

The overall functional outcome was assessed by The Global Assessment of Functioning (GAF).[77] The GAF is a scale designed to assess the severity of symptoms and the level of functioning. Higher scores correspond to better functioning.

In both assessments during the project, information about pharmacological treatments and dosage were collected.

Other prognostic factors. The Spanish version of the Strauss and Carpenter Prognostic Scale for Schizophrenia[78,79] was used to evaluate the prognosis. The Scale to Assess Unawareness in Mental Disorder (SUMD) was used to evaluate insight.[80,81] The Scale of the Udvalg for Kiniske Undersogelser (UKU)[82] was used to evaluate adverse drug reactions (general side effects of psychotropic drugs). Finally, the Morisky Green Levine Medication Adherence Scale[83] was administered to measure patients' adherence to drug treatment. The latter includes four questions with yes/no response options (Always forget to take medicines; Always careless about taking medicines; Stop taking medicines when feeling better; Stop taking medicines when feeling worse).

Neuroimaging module

Structural Magnetic Resonance Imaging (sMRI), Functional (resting state) and Diffusion Tension Imaging (DTI-MRI) were performed at Hospital Clinic of Barcelona. MRI scans were acquired at baseline and at 1-year follow-up in FEP patients and just at baseline in HC. Sequences were acquired in axial orientation for each subject, a T1-weighted 3D gradient echo (matrix = 256 × 256, 160 slices; voxel size 1 mm × 1 mm × 1.5 mm) and a T2-weighted Turbo-Spin-Echo (matrix = 256 × 256, 45 slices; voxel size 1 mm × 1 mm × 3.3 mm).

Neurocognition module

The neuropsychological battery employed in this study was designed to address different cognitive domains by means of standardized neuropsychological tests that have proven sensibility and specificity. These tests have been used previously in the cognitive assessment of this type of patient.[84,85] The neuropsychological assessment was made at baseline and at one-year follow-up in patients and controls. They were administered by specialized neuropsychologists.

In order to estimate global functioning in the form of IQ, vocabulary and block design subtests from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV)[86] were used. Different cognitive domains were assessed with the following instruments:

- To assess verbal memory, the Spanish version of California Verbal Learning Test (CVLT)[87,88] was used.
- Visual memory was tested with the Wechsler Memory Scale, third edition (WMS-IIII).[89]
- Processing speed was assessed with the Trail Making Test (Form A)[90] and the Coding Subtest of the WAIS-IV.
- Working memory was assessed by the Digit Span Subtest and the Letter-Number Sequencing Subtest of the WAIS-IV.[86]
- Sustained attention was tested with the Continuous Performance Test–II (CPT-II).[91]
- Verbal fluency was assessed with the Controlled Oral Word Association Test, FAS-Test[92] and Test Barcelona, Animal Words.[93]
- Executive functions were evaluated using the Stroop Test word–color interference effect[94] (interference) and the Tower of London test[95] (planning).
- Social cognition was tested with the Mayer–Salovey–Caruso Emotional Intelligence Test MSCEIT.[96]

Higher scores correspond to better performance in all cognitive domains except for attention.

Biological module

The main purpose of this module was to conduct an extensive analysis of the plasma biomarkers involved in oxidative stress (total antioxidant status and glutathione levels), inflammatory and anti-inflammatory interleukins, and lymphocytes and monocytes cell subpopulations potentially involved in a first episode of psychosis. 10 mL of peripheral blood from all participants were collected at baseline and at follow-up in K2 EDTA BD Vacutainer EDTA tubes. The blood samples were centrifuged at 1800 rpm for 10 min at 4 °C. The plasma was separated and stored at −70 °C until measurement. Genomic DNA was extracted using the MagNA Pure LC DNA Isolation Kit and a MagNA Pure LC 2.0 instrument (Roche Diagnostics GmbH, Mannheim, Germany) and DNA concentration and quality were measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Surrey, CA). Additionally, a total of 2.5 μg of genomic DNA was sent for genome-wide genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

Data analysis

Data were analyzed using SPSS, version 25. Descriptive analyses were conducted using chi-square for categorical variables and Student's test for continuous variables. Group differences were examined using unpaired *t*-tests for normally distributed variables, or using Mann–Whitney *U* tests for non-normal data.

A Principal Components Analysis (PCA) was performed to avoid redundant information of separate test cognitive variables and reduce measures to a few principal domains. The neurocognitive assessment was represented by eight cognitive domains: verbal memory, visual memory, executive function and inhibition, sustained attention, working memory, verbal fluency and processing speed (see Supplementary Table 1).

Preliminary results

A total of 90 FEP patients and 100 HC were enrolled in this study, with one-year follow-up evaluations still ongoing. A summary of the baseline sociodemographic and clinical characteristics of FEP patients and HC is shown in Table 1. There were no differences between patients and HC in terms of age ($p = 0.104$), gender ($p = 0.140$) and socioeconomic status ($p = 0.104$). However, at inclusion, we found significant differences in functioning ($p < 0.001$),

Table 1
Differences between patients and healthy controls.

	Patients ($n = 90$)	Healthy controls ($n = 100$)	t or x^2	p
Sociodemographic variables				
Gender: male *N* (%)	53 (59)	50 (50)	1.51	0.140
Age ($M \pm SD$)	26.13 ± 6.35	27.72 ± 6.97	−1.63	0.104
SES (%)				
High	31 (25)	32 (32)		
Medium–high	17 (19)	13 (13)		
Medium	12 (14)	27 (27)	7.67	0.104
Medium–low	16 (18)	21 (21)		
Low	13 (15)	7 (7)		
Functional variables ($M \pm SD$)				
GAF	66.24 ± 12.03	85.27 ± 10.16	−10.82	**<0.001**
Cognitive reserve ($M \pm SD$)				
CRASH	42.22 ± 15.08	51.62 ± 11.46	−4.61	**<0.001**
Cognitive measures ($M \pm SD$)				
Verbal memory	187.29 ± 60.55	231.20 ± 38.47	−5.71	**<0.001**
Sustained attention	145.61 ± 15.61	137.38 ± 16.43	2.79	**0.006**
Working memory	65.72 ± 20.82	74.31 ± 21.78	−2.60	**0.010**
Executive function (Planning)	231.58 ± 32.12	235.14 ± 42.74	−0.54	0.588
Executive function (Inhibition)	50.91 ± 8.50	53.25 ± 13.80	−1.27	0.207
Visual memory	86.30 ± 24.44	109.04 ± 19.76	−6.19	**<0.001**
Processing speed	44.16 ± 10.45	48.54 ± 6.76	−3.27	**0.001**
Verbal fluency	73.22 ± 15.61	84.52 ± 13.58	−4.99	**<0.001**

Abbreviations: *M* = mean, SES = socioeconomic status, GAF = Global Assessment of Functioning, CRASH = Cognitive Reserve Assessment Scale in Health. Significant differences ($p < 0.05$) marked in bold.

CR ($p < 0.001$), and all cognitive domains except executive functioning (planning and inhibition, $p = 0.588$ and 0.207, respectively). Regarding clinical status of patients, patients obtained a mean score of 9.56 ± 3.82 in the positive PANSS, 13.40 ± 5.93 in the negative symptoms, 5.05 ± 5.37 in the depressive symptoms scale (HDRS) and 1.14 ± 2.23 in the manic symptoms scale (YMRS). Thus, patients were clinically stable at inclusion.

Discussion

The main purpose of the present article is to report the rationale, the design, the assessment adopted, and the preliminary results of the CRASH Project.

In recent years, the literature shows an increasing interest in the study of CR and its prognostic implications for serious mental illnesses. Despite this, it is necessary to shed greater light on the identification of factors associated with CR in first psychotic episodes. The current project aims to characterize cognitive reserve and its association with clinical variables, functioning, neuroimaging and inflammatory biomarkers. It is expected to generate knowledge which will increase the diagnostic and prognostic value of CR by generating personalized interventions. Until now, the clinical heterogeneity of FEP and the methodological variability of the studies conducted have not allowed biomarkers to be established accurately, a fact which again highlights the importance of studying the FEP population. Knowing the strategies which best help patients in the initial stages of illness is, moreover, highly translational and can imply considerable economic savings. Furthermore, this insight can allow us to approach interventions in a way that is individualized and adapted to patients' characteristics, which is expected to improve the prognosis of people with a FEP.

When this project was designed, the inclusion criteria were purposefully unrestrictive to include real-world patients with a FEP. For example, the use of substances such as cannabis or alcohol was not established as an exclusion criterion. The reason for this is that a high percentage of people with a FEP consume substances and it is both a risk factor for a FEP and for a poorer prognosis. Including them in the study will allow for the exploration of whether those who consume substances, despite having a high level of cognitive reserve, maintain a worse prognosis. If not, there may be differences between the accumulated CR of patients who consume and those who do not. Another example is not excluding any type of medication or treatment. With this naturalistic design it is expected to obtain results applicable to daily clinical practice.

In the coming articles, in which the information obtained via the different modules is combined, we will hopefully obtain a global vision of the main factors that are related to CR and the prognosis of the FEP population. Furthermore, each of the components of CR (Education, Occupation, Intellectual and Leisure Activities) will also be described in order to analyze their association with prognostic variables such as the clinical, functional or cognitive state of patients and the different biomarkers. In fact, there is a considerable interest in evaluating the impact that intervention in modifiable components of CR like leisure activities and lifestyle may have. They could have very positive effects on CR, especially within the first years of the illness, thus minimizing the impact that the disorder itself can exert on both neuropsychological and functional levels. For this reason, a psychological approach has been designed, developed and is currently being implemented in parallel to this project at the Hospital Clinic of Barcelona.[97] It aims to enhance CR in the children of patients with schizophrenia, bipolar disorder and FEP (PI17/01066; PI18/00805; PI20/00344) and ultimately value the efficiency of such an intervention. The data from all of the projects together will provide more complete information about the nature and impact of CR for FEP patients.

This project has certain limitations. To start with, one limitation which is shared with all longitudinal studies is the loss of subjects between baseline and follow-up visits. To try to reduce this loss, personal contact was established with the patients and their families when organizing the visits. Additionally, for this study the follow-up of some subjects was during the Coronavirus disease 2019 (COVID-19) pandemic, which meant that some participants were more reticent to maintain follow-up visits than would be expected in normal conditions. Moreover, one inherent limitation in clinical and neuropsychological assessments lies in the differences between observers. For this reason, semi-structured clinical interviews were included and periodical meetings were held to reduce the differences between neuropsychological assessors.

Although the naturalistic design brings certain strengths to the project, it has the limitation of not having controlled pharmacological treatment. This fact could mean that some variables can be influenced by treatment and should be controlled (for example, cognitive performance). Notwithstanding, the fact that pharmacological treatment was not limited means that this project offers us data about the usual treatment received by people with a FEP, and that results derived may be generalizable to a real-world setting.

Despite the aforementioned limitations, this is an innovative project which analyzes a large quantity of clinical, functional, cognitive, neuroimaging and biomarker variables which can allow for a deeper understanding of the concept of CR and its impact on the evolution of patients with a FEP.

In conclusion, the results obtained by this project are hoped to contribute as much towards the understanding of the illness' physiopathology as towards the generation of new treatment designs and therapeutic strategies that allow for a personalized management according to each individual's profile, which includes cognitive reserve as well as clinical characteristics.

Data availability statement

The data that support the findings of this study are available on request from the corresponding authors.

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Conflicts of interest

M. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board (unrelated to the present work) of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Otsuka, Menarini and Takeda.

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpsm.2022.03.001.

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