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# Relapse, cognitive reserve, and their relationship with cognition in first episode schizophrenia: a 3-year follow-up study.

--Manuscript Draft--

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| **Abstract:** | Schizophrenia is frequently characterized by the presence of multiple relapses. Cognitive impairments are core features of schizophrenia. Cognitive reserve (CR) is the ability of the brain to compensate for damage caused by pathologies such as psychotic illness. As cognition is related to CR, the study of the relationship between relapse, cognition and CR may broaden our understanding of the course of the disease. We aimed to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. Ninety-nine patients with a remitted first episode of schizophrenia or schizophreniform disorder were administered a set of neuropsychological tests to assess premorbid IQ, attention, processing speed, working memory, verbal and visual memory, executive functions and social cognition. They were followed up for 3 years (n=53) or until they relapsed (n=46). Personal and familial CR was estimated from a principal component analysis of the premorbid information |

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|---|---|
| | gathered. Linear mixed-effects models were applied to analyse the effect of time and relapse on cognitive function, with CR as covariate. Patients who relapsed and had higher personal CR showed less deterioration in attention, whereas those with higher CR (personal and familial CR) who did not relapse showed better performance in processing speed and visual memory. Taken together, CR seems to ameliorate the negative effects of relapse on attention performance and shows a positive effect on processing speed and visual memory in those patients who did not relapse. Our results add evidence for the protective effect of CR over the course of the illness. |

Cover Letter

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Dr. Eduard Vieta
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Dear Editor:

Thank you for the opportunity of reviewing the manuscript. We have responded to the reviewer's queries and made the correspondent changes in the manuscript.

Sincerely,

Dr. Manuel J. Cuesta.

Reviewers' comments:

Reviewer 1: Review of ENP-2022-207 by Scot Purdon

Dr. Purdon, thank you very much for your comments. We have responded to your queries as follows.

A very well written introduction to how one's cognitive reserve (CR) may interact with relapse to attenuate cognitive deficits in FEP individuals, approximately half of whom entered their 2nd episode over the course of this 3 year study. This is an ambitious undertaking and the authors here report on two modules of their six module investigation.

A few surprises in the results here, namely, main effects of relapse in the absence of an interaction with CR were only observed for Verbal Memory. From table 2 it is apparent that the relapse group had lower Verbal Memory scores at baseline, and then both groups showed a similar learning effect from time 1 to time 2. Hence, the main effect of Verbal Memory in Table 3 even though there were no differences between groups at time 1 or time 2. This, in my opinion, is potentially an important result. Presumably, men with FES tend to show more left temporal lobe involvement than women, and the samples here tend to have a relatively high percentage of female participants (relative to other studies). The premorbid intellect estimates from WAIS-III vocabulary are also higher than expected, though here too this could reflect a group effect of combining quite a few women. I won't belabor this more aside from suggesting that VM alone may be a better indicator of risk for relapse than is suggested here.

Certainly, what you suggest is very interesting. Here, we aimed to explore the potential toxic effects, if any, of relapse on cognition. As you point out, a significant effect of relapse over verbal memory was found, but we did not find significant differences in any of the cognitive functions studied between relapsing and non-relapsing patients at baseline. We discussed about the relationship between relapse and cognition (page 12): “It was discussed in the discussion section “There is evidence that relapse is related to worse cognitive functioning (Hori et al., 2020). It is possible that relapse has a negative effect on cognitive functioning but also that patients with worse cognitive functioning are more prone to relapse. Here, we did not find significant differences in cognitive performance between patients who relapsed and those who did not, either before or after relapse."

Also, the use non-parametrics in the baseline comparison of VM scores is somewhat puzzling to me. I wonder if the non-normal distribution resulted from including the TAVEC recognition score - we have decades of data to suggest no significant recognition deficits in this sample; that may have undermined their analysis (or at least their normal distribution).
Given that their approach was a priori I would not suggest redoing the analysis except out of interest for the authors.

Following your suggestion, we have recalculated VM without including recognition, but both variables (baseline and final) had again a non-normal distribution. We have not made changes to the manuscript in this respect.

Also, it would be useful for the authors to mention if they used alternate forms of the TAVEC or if they repeated the same form (and mention learning effects). The significant insight effect on WCST might also be worth mentioning (both groups showed substantial gains on EXE - unsure if this was due entirely to WCST or if the T of L contributed.

We did not consider applying alternative forms of the TAVEC. The study established a minimum time of 6 months between cognitive evaluations (in case patients relapsed shortly after entering the study), to minimize practice effects. Of the 46 patients who relapsed, 10 did so before 6 months. In these cases, we waited until at least 6 months had passed since the initial evaluation to perform the final cognitive evaluation. More than half of the sample of patients who relapsed were evaluated a second time after one year from the first evaluation. And for patients who did not relapse, time between assessments was of 36 months.
Regarding WCST, although an improvement over time was observed in both groups, this improvement was not significant. To clarify it, we have added this sentence in the methods section "All participants were assessed on clinical, functional and cognitive variables again at follow-up or relapse visits. The study established a minimum time of 6 months between cognitive evaluations (in case patients relapsed shortly after entering the study), to minimize practice effects."

In presenting Z scores in table 2 it is unclear whether they represent deviation from a normative sample (possibly corrected by sex, age, education) or from the group M and SD reported here. A footnote to table 1 might address this, or a footnote in table 2 (perhaps even better). When the authors report 1 SD (approximately) of impairment in their sample this might be true based on a normative comparison but if they used the current sample to calculate this Z then they would need to take account of this as it would significantly underestimate the amount of impairment. This may not be particularly relevant as they mention that the used relatively few non-normative calculations but they do not indicate which ones. That would be helpful. Also, given that they are using well established tests here I'm unsure of why they could not find adequate normative data on which to base their z score calculations (though I am unfamiliar with what norms are available for all of these
tests in Spanish). I think they have made their point here (aside from the 1 SD inference) and it would take much effort to go back and 're-standardize', though I think that would have been stronger, particularly if they used uncorrected (i.e. by age, sex, educ) Standard Scores (rather than T-scores, or within sample group scores).

In table 1 (third column), we describe the scores used to calculate the cognitive functions composite scores. T-scores, scale scores and z-scores are standardized scores based on normative data provided by the test's manuals. Raw scores are those obtained directly by our assessment. Raw scores were standardized using the FES patients means and s.d. As you can see in table 1, we did so only with verbal fluency (animals), TMT-A and digit span test (forward and backwards, since the WAIS only provide normative data for total digit span scores).
We have added a footnote in the table to clarify this point.

I find it interesting that the authors include the Premorbid Adjustment Scale in their calculation of 'personal' CR. The PAS has both an adaptability subscale and a performance subscale. Typically this is obtained by interview with the patient but there is an interesting literature on differences based on interview with family members. It would be helpful if the authors could clarify 'how' they obtained the data for these ratings. I'm also interested in the separation of 'adaptability' and 'performance'. Perhaps the authors only used the 'performance' numbers in their CR calculation. A brief sentence on the interview process and on the scoring approach would help future replications.

As you suggest, we have added a sentence explaining the sources of information used to complete the PAS. Some authors such as Allen et al. (2001) and Norman et al. (2005) provided evidence for the existence of at least two domains of premorbid adjustment, distinguishing between academic premorbid adjustment (school performance and school adaptation) and social premorbid adjustment (sociability, peer relations, and social-sexual). Thus, it appears that adaptability and performance might be related. However, to assess CR we have used the most commonly proposed proxy indicators of CR, which do not include school adaptation. Also, we aimed to be consistent with our previous research and taking into account that is a subanalysis of a multicenter, naturalistic and longitudinal project (Amoretti et al., 2016; 2018; Bernardo et al., 2013) we used the available common tools.

There were a few odd grammatical errors but I'm sure they will catch these on review.

This work underwent a professional proofreading, but now we have also asked a native speaker colleague to revise the text. We have incorporated his suggestions and hope that the manuscript will now be better.

In summary, this is a well written piece that introduces a potentially important distinction between premorbid estimates based on traditional psychometrics (WAIS VOC) versus familial estimates. Facsinating to me that they produce different interactions when it comes to cognitive deficits that arise (or play a causal role) in relapse.

Might want to search for Z of -55 (I think the authors intended -0.55). I believe I also came across a Z of .0004

We have corrected those z values.

Reviewer 2: The authors aim to study the relationship among cognition, relapse, and cognitive reserve (CR). Specifically, the study aims to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. This is an understudied area of research, and could be clinically relevant. However, I have questions regarding the rationale, method, and interpretation of the study results, and these are enumerated below.

Thank you for your comments. We have addressed them as follows:

In the abstract, please briefly define the term "cognitive reserve".

We have included a brief explanation of the term in the abstract.

Introduction

1. The authors suggest that there are other important factors that are associated with relapse in schizophrenia such as longer duration of untreated psychosis, premorbid adjustments, and psychosocial factors. As a reader, I expected the authors to address these factors in their analysis. If they are indeed as important as the authors remark, I suggest that authors also include them in the analysis as well/ explain why only premorbid adjustment (i.e., a component of CR) was examined for associations with relapse.

In the present work we aimed to investigate the effects of relapse over cognition, and the role of cognitive reserve as potentially able to attenuate those effects. The relationship between

relapse and demographic, clinical and treatment variables has been addressed in a previous work of our group with these sample (Bioque et al 2022 Clinical and treatment predictors of relapse during a three-year follow-up of a cohort of first episodes of schizophrenia. Schizophr Res. 2022 May;243:32-42. doi: 10.1016/j.schres.2022.02.026).

2. The introduction should describe how cognitive reserve is usually measured.

We have now included a paragraph in the introduction including more information about how cognitive reserve is measured (page 5, first paragraph).

3. The aim of the study was to "determine whether relapse was associated with cognitive impairment, controlling for the effects of CR". The introduction, however, states very briefly that there may be an indirect role of cognition on the factors (such as non-adherence to treatment) that are associated with relapse. It is not clear from the introduction that there exists a strong association between cognition and relapse in FEP, and that it needs to be studied?
A paragraph exposing some evidence of the association of cognitive impairment and relapse has been included in the introduction (page 4, 3rd paragraph).

4. Did the authors mean 'familial' CR?
As you point out, we meant “familial”. We have corrected it in the text.

5. Did the authors hypothesize that the type of CR (i..e personal vs. familial) would differentially influence association between cognition and relapse? This is not clear from the introduction

Since the differentiation of personal and familial CR resulted from the PCA, we had not formulated a previous hypothesis about the role of each component of CR over cognition and relapse. In fact, it is the first study to assess the influence of the type of CR on the association between cognition and relapse.

Methods
1. The methods section should describe the clinical importance of choosing a 3-year window to study relapse.

A description of the reasons to choose a 3-year window to study relapse has been included in the methods section.

2. How was relapse determined at the end of 3 years?

Ninety-nine (51.3%) patients continued in the study until the final assessments, either because of a relapse (*n* = 46) or because they finished the 3-year follow-up (*n* = 53). Those patients who relapsed, did so at any time between inclusion and 3 years. And the ones who made the final assessment 3 years after inclusion, were those who did not relapse.
Patients were evaluated every 3 months during that 3-year period. At each evaluation it was assessed whether they were still in remission according to Andreasen's criteria. If not, they underwent the final assessment. Then, when clinically stable, they underwent neuropsychological assessment.

3. Was there a difference in medication status (were all individuals medicated) and comorbid illnesses between those who relapsed vs. those who did not, which may have affected the results? It would be important to take these variables into consideration.

Table 1 shows CPZ equivalents mean doses in both groups, showing no baseline differences. At follow-up, there were differences between both groups. This was an expected result, since the episode treatment requires higher doses of medication. Our work's aim was to explore the differential influence, if any, of cognitive reserve in a baseline similar sample, over the course of illness, regarding cognition. So we did not consider to include CPZ as a covariate because both groups did not differ in CPZ doses at study entry. The relapse condition is itself intrinsically associated with higher antipsychotic doses. Therefore, we consider that including antipsychotic doses in addition would be like over-correcting the data.

4. The authors would need to correct for the seven mixed-models that they tested

Thank you for your comment. We have considered your suggestion and we have performed the Benjamini-Hochberg method for controlling the false discovery rate in our regression analysis as a sensitivity analysis.

| **Outcome** | **Explanatory** | **Coefficient (IC95%, p_value)** | p_value_adj |
|---|---|---|---|
| Attention | Relapse | -0.18 (-0.46,0.10, p=0.213) | 0,282 |
| | Personal CR (PCR) | -0.16 (-0.35,0.04, p=0.117) | 0,186 |
| | Familial CR (FCR) | 0.06 (-0.07,0.20, p=0.360) | 0,423 |
| | TimePost | 0.21 (-0.08,0.50, p=0.153) | 0,230 |
| | Relapse:Personal CR (PCR) | **0.48 (0.20,0.75, p=0.001)** | **0,007** |
| Processing speed | Relapse | **-0.40 (-0.62,-0.18, p<0.001)** | **0,007** |
| | Personal CR (PCR) | **0.24 (0.08,0.39, p=0.002)** | **0,009** |
| | Familial CR (FCR) | **0.13 (0.02,0.24, p=0.016)** | **0,046** |
| | TimePost | 0.13 (-0.08,0.34, p=0.219) | 0,282 |
| | Relapse:Personal CR (PCR) | **-0.27 (-0.48,-0.49, p=0.017)** | **0,046** |
| Working memory | Relapse | -0.15 (-0.39,0.08, p=0.196) | 0,279 |
| | Personal CR (PCR) | **0.25 (0.14,0.37, p<0.001)** | **0,007** |
| | Familial CR (FCR) | **0.14 (0.02,0.25, p=0.022)** | **0,050** |
| | TimePost | 0.06 (-0.17,0.29, p=0.593) | 0,640 |
| Verbal memory | Relapse | **-0.49 (-0.86,-0.12, p=0.009)** | **0,035** |
| | Personal CR (PCR) | 0.15 (-0.03,0.33, p=0.098) | 0,165 |
| | Familial CR (FCR) | **0.21 (-0.03,0.39, p=0.020)** | **0,049** |
| | TimePost | 0.19 (-0.17,0.55, p=0.306) | 0,376 |
| Visual memory | Relapse | **-0.50 (-0.95,-0.06, p=0.027)** | **0,052** |
| | Familial CR (PCR) | **0.48 (0.25,0.70, p<0.001)** | **0,007** |
| | Personal CR (FCR) | **0.45 (0.17,0.73, p=0.002)** | **0,009** |
| | TimePost | 0.05 (-0.39,0.49, p=0.828) | 0,860 |
| | Relapse:Familial CR (FCR) | **-0.51 (-0.97,-0.06, p=0.027)** | **0,052** |
| Social cognition | Relapse | -0.13 (-0.53,0.27, p=0.518) | 0,583 |
| | Personal CR (PCR) | **0.24 (0.05,0.44, p=0.016)** | **0,046** |
| | Familial CR (FCR) | 0.16 (-0.18,0.21, p=0.869) | 0,869 |
| | TimePost | 0.39 (-0.01,0.79, p=0.054) | 0,097 |

Most of our findings remain significant after adjustment with the exception of the interaction Relapse:Familial CR (FCR) for “Visual memory”, that is in the limit of significance (p=0.052). Apart from focusing only upon statistical significance (adjusted or not), we considered important to focus on the magnitude of effects, which is this particular case is 0.5, which is a considerable effect for psychological studies.

As the reviewer surely know, the adjustment of p_values is a matter of great controversy. Some authors that claim that paying a penalty for having more information and perform several contrast with your data should be unacceptable.

- Feise, R.J. Do multiple outcome measures require p-value adjustment?. *BMC Med Res Methodol* **2**, 8 (2002).
- Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990 Jan;1(1):43-6.

p-value adjustments reduce the chance of making type I errors, but increase the chance of making type II errors and might shield some potentially clinically important observed associations from more intense investigation in future studies. Since this is an exploratory study and the analysis of the seven outcomes was based on our research questions (were not post hoc comparisons) and after assessing that the main results do not change particularly after adjustment, we prefer to maintain the non-adjusted statistical findings in order to further research experiments can confirm these associations or deny them.

Results

1. Also, the interaction between personal CR and relapse was significant. "and relapse" is missing

This omission has been corrected in the text.

Discussion

The differential influence of CR (whether personal or familiar) on the association between cognition and relapse should be commented on. Eg., why might familiar CR be more associated with visual memory, while personal CR is associated more with processing speed?

We have added a paragraph discussing the differential influence of CR over processing speed and visual memory (page 13, 2nd paragraph)

“In addition to direct significant association of personal and familial CR with most cognitive functions, we also found differential effects of personal and familial CR over processing speed and working memory in non-relapsing patients, respectively. These differences may be due to the differential weight of illness-related factors in each cognitive function. Processing speed may be more prone to be affected by illness since the early phases of illness (Cuesta et al., 2015; González-Blanch et al., 2010), so higher premorbid abilities could represent a higher threshold against impairment. In general

terms, there is evidence that cognitive functions are heritable (Blokland et al., 2017), and specifically moderate to high heritability has been reported regarding visual memory (Darst et al., 2015; Goldberg Hermo et al., 2014). The interaction between illness effects and heritability of visual memory may explain the differential positive effect of familial CR in non-relapsing patients. “

2. The clinical importance of this study, if any, should be discussed.

A paragraph at the end of the discussion has been added to further discuss the clinical importance of the study.

**TITLE: Relapse, cognitive reserve, and their relationship with cognition in first episode schizophrenia: a 3-year follow-up study.**

**RUNNING TITLE: Relapse, cognitive reserve and cognition in FES**

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Abstract: 249

**ABSTRACT**

Schizophrenia is frequently characterized by the presence of multiple relapses. Cognitive impairments are core features of schizophrenia. Cognitive reserve (CR) is the ability of the brain to compensate for damage caused by pathologies such as psychotic illness. As cognition is related to CR, the study of the relationship between relapse, cognition and CR may broaden our understanding of the course of the disease. We aimed to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. Ninety-nine patients with a remitted first episode of schizophrenia or schizophreniform disorder were administered a set of neuropsychological tests to assess premorbid IQ, attention, processing speed, working memory, verbal and visual memory, executive functions and social cognition. They were followed up for 3 years (*n*=53) or until they relapsed (*n*=46). Personal and familial CR was estimated from a principal component analysis of the premorbid information gathered. Linear mixed-effects models were applied to analyse the effect of time and relapse on cognitive function, with CR as covariate. Patients who relapsed and had higher personal CR showed less deterioration in attention, whereas those with higher CR (personal and familial CR) who did not relapse showed better performance in processing speed and visual memory. Taken together, CR seems to ameliorate the negative effects of relapse on attention performance and shows a positive effect on processing speed and visual memory in those patients who did not relapse. Our results add evidence for the protective effect of CR over the course of the illness.

**Keywords:** schizophrenia; cognition; cognitive reserve; relapse.

## 1. INTRODUCTION

Schizophrenia is a chronic and disabling disorder with a course frequently characterized by the presence of multiple relapses. Around 40–63% of patients may have a relapse in the first 3 years after a first episode of psychosis (FEP) (Alvarez-Jimenez et al., 2012). Prevention of relapses represents a challenge in clinical practice, considering the negative consequences that relapsing may have for patients, such as neurotoxic effects (Andreasen et al., 2013), harming themselves or others and a negative impact in interpersonal relationships, education or employment (Emsley et al., 2013).

The most studied predictors of relapse after the FEP are non-adherence to pharmacological treatment and substance abuse (Alvarez-Jimenez et al., 2012; Bergé et al., 2016; Bowtell et al., 2018a). There are, however, other factors that have been associated with relapse, such as longer duration of untreated psychosis (Altamura et al., 2001), premorbid adjustment (Alvarez-Jimenez et al., 2012; Bowtell et al., 2018b; Robinson et al., 1999) and psychosocial factors (Alvarez-Jimenez et al., 2012; Bowtell et al., 2018b; Kam et al., 2015).

Cognitive impairment is closely related to outcome (Cuesta et al., 2020; Mucci et al., 2021) because it is a core feature of schizophrenia (Green and Harvey, 2014; Green et al., 2019; Kraus and Keefe, 2007) but it may also have a role in non-adherence ((Velligan et al., 2017). There may be an indirect role of cognition in the factors that are associated with relapse (Kadakia et al., 2022) but relapse also may have an effect on cognition (Hori et al., 2020; Pukrop et al., 2006; Rund et al., 2007). The results of comparative and longitudinal studies including first episode patients and multi-episode patients suggest a negative effect of relapse on cognition. For example, Rund et al. (2007), found a worsening in verbal memory tasks in patients with two or more relapses at two years after the first episode of psychosis. Also, Barder et al. (2013) found that early relapse was a strong predictor of impairment in verbal fluency and verbal memory. Hori et al (2020), in a comparative study, reported an association between an increased number of hospitalizations and a worsening in verbal memory, working memory, verbal fluency, and executive functions.

The cognitive reserve (CR) hypothesis postulates that patients with higher premorbid intellectual functions will be more able to compensate for the damage caused by

psychotic illness (Amoretti and Ramos-Quiroga, 2021; Barnett et al., 2006). CR is determined by several factors, such as genetic and environmental factors. Genes are responsible, among other things, of brain size and weight, and synaptic density, as well as of congenital intellectual ability. Environmental factors include modifiable aspects such as education and mental and physical activity (Bora, 2015). Thus, CR results of the interaction of cognitive experiences and genes (Amoretti and Ramos-Quiroga, 2021). In the field of mental disorders the concept of CR has not been accurately defined and has been characterized by different variables. Traditionally in scientific research, CR was estimated using the premorbid intelligence quotient (IQ). However, the role of environmental factors on CR development is now also relevant. The most common proposed proxies of CR include estimated premorbid IQ, educational level an occupational attainment (Amoretti et al., 2016; Amoretti et al., 2018; Barnett et al., 2006; Buonocore et al., 2018; de la Serna et al., 2013; Nucci et al., 2012; Pettigrew and Soldan, 2019).

The components of the CR, such as premorbid adjustment, have been associated with the potential benefit of cognitive remediation in patients with schizophrenia (Buonocore et al., 2019), and poor premorbid adjustment has been associated with higher rates of relapse (Robinson et al., 1999). Furthermore, low education and premorbid IQ were among the best predictors of relapse and follow-up withdrawal in a 2-year follow-up study (Fond et al., 2019). Considering that the presence of relapse is associated with a worse prognosis (Birchwood et al., 1998; Emsley et al., 2013; Kadakia et al., 2022), it would be interesting to study the factors that may attenuate the harmful effects of relapse.

### 1.1. Aims of the study

Our aim was to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. In particular, we hypothesized that CR would play an attenuating role in the effects of relapse on cognitive functioning at final assessment.

## 2. METHODS

This study is part of the "Clinical and neurobiological determinants of second episodes of schizophrenia. Longitudinal study of first episode of psychosis" (2EPs Project), which is a naturalistic, multicentre, coordinated, longitudinal follow-up study of first-episode schizophrenia (FES) patients with an illness course of less than 5 years and a 3-year longitudinal-prospective follow-up design. A 3-year-follow up window was considered taking into account that 80% of relapses occur in the first 5 years after the FES (Alvarez-Jiménez et al., 2011; Robinson et al., 1999; Robinson et al., 2005), and the inclusion criteria established less than 5 years since the FES (finally the mean was of 1.56 ±1.37 years). Also, longer follow-up period may have resulted in higher attrition rates. All participants were assessed on clinical, functional and cognitive variables again at follow-up or relapse visits. The study established a minimum time of 6 months between cognitive evaluations (in case patients relapsed shortly after entering the study), to minimize practice effects.

The project involves six modules: general and basic; neuroimaging; adherence; neurocognition; physical health; and biological. The present study was framed within the general and neurocognition modules. The background, rationale and study design are fully described elsewhere (Bernardo et al., 2021).

**2.1. Subjects**

The patients included in the 2EPs Project met the following inclusion criteria: age 16–40 years at the time of first assessment (baseline); a diagnosis of schizophrenia or schizophreniform disorder according to DSM-IV criteria (APA, 1994); being in remission from the first psychotic episode (for up to 5 years) according to Andreasen's criteria (Andreasen et al., 2005); not having relapsed after the first psychotic episode; fluent in Spanish; and providing the signed informed consent. The exclusion criteria were: having experienced a traumatic brain injury with loss of consciousness; presenting intellectual disability understood not only as IQ <70 but also presenting malfunctioning and problems with adaptative processes; and/or presenting organic disease with mental repercussion.

A total of 219 patients were recruited in the 2EPs Project. The patients had baseline clinical data and 193 of these patients were included in the neurocognition module. Finally, 99 patients were assessed with the cognitive battery at follow-up: 53 patients

did not relapse during the 3-year follow-up period and 46 patients relapsed at some point in the follow-up (Fig. 1).

The study was approved by the research ethics committees of all participating clinical centres and was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice.

### 2.2. Procedures

#### 2.2.1. Sociodemographic and clinical assessments

We collected demographic and clinical data for all participants, including age, education, parents' education, functioning at the moment of the assessments, antipsychotic treatment and psychopathological status.

Functioning was assessed with the Global Assessment of Functioning (GAF) scale (APA, 1994) and the Functioning Assessment Short Test (FAST) (Amoretti et al., 2021a; Rosa et al., 2007). The GAF is a scale designed to assess the severity of symptoms related to the level of functioning, on a scale from 1 to 100, where higher scores indicate better functioning. The FAST assesses six domains of functioning (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time) and comprises 24 items, each item rated from 0 (no difficulty) to 3 (severe difficulty); higher scores represent higher disability.

Antipsychotic treatment was converted to chlorpromazine equivalents (CPZ) according to the guidelines provided by Leucht et al. (2016).

The psychopathological status was assessed by means of the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987; Peralta and Cuesta, 1994), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

#### 2.2.2. Cognitive assessments

Neuropsychological assessment included a comprehensive battery of 15 standardized cognitive tests, designed to encompass the seven cognitive domains included in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative (Marder and Fenton, 2004; Nuechterlein et al., 2004;

Nuechterlein et al., 2008). The neuropsychological tests employed and the measures selected for this work are detailed in Table 1.

Experienced psychologists administered the tests, in two sessions of 1–1.5 hours to facilitate cooperation. Previously, an inter-rater reliability study was conducted to ensure that all psychologists reached intraclass correlation coefficients of 0.80 in two of the tests of the battery: the Wechsler Adult Intelligence Scale (WAIS-III) vocabulary subtest and the Wisconsin Card Sorting Test (WCST). In these tests, the final score may partially depend on the judgement of the rater administering and correcting the test.

### 2.2.3. Cognitive reserve assessments

We assessed CR using the most common proxy indicators: premorbid IQ assessed using the vocabulary subtest of the WAIS-III (Wechsler, 1999); patients' and parents' education (as a categorical variable with seven categories, from unfinished elementary studies to university studies or higher); and scholastic performance at childhood and adolescence, measured with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). The PAS was completed with all the available sources of information (patient, parents and/or medical charts). When patients were assessed they had already experienced a FES, so the premorbid variables could only be estimated. We applied a principal component analysis (PCA) to obtain a combined score for CR. We obtained two factor scores (eigenvalues >1), the first one with high loadings on scholastic performance of the PAS and patients' education, combined with premorbid IQ ('personal CR'), and the second one with high loading in parents' education ('familial CR').

## 2.3. Statistical analyses

We examined the distribution of the sociodemographic and cognitive variables to adjust the analyses in each case. We compared the sociodemographic and clinical characteristics of patients relapsing and not relapsing with one-way ANOVA and Mann-Whitney U tests. Gender distribution between groups was compared using $\chi^2$ tests.

Regarding the cognitive variables, we transformed the selected measures for each of the neuropsychological tests to *z*-scores. We used the group means and standard deviations in those tests where no normative data were available and converted standard scores if the tests provided these normative scores. From the tests' *z*-scores,

we computed the scores of the cognitive functions (see Table 1). Cognitive scores were reversed when necessary to ensure that higher scores indicate better performance.

To assess the effects of relapse on the cognitive functions over time, with personal and familiar CR as covariates, a linear mixed-effects model was fitted to each of the cognitive functions. We selected this model because of its advantage in dealing with missing values. Each model included the time at assessment (baseline and 3 years/relapse), the relapse/non-relapse condition, the PCR, the FCR and the interactions between PCR or FCR with the relapse/non-relapse condition, in order to assess if there was a differential evolution of cognitive performance or a differential mean global cognitive performance associated with CR in those patients relapsing/not relapsing. Non-significant interactions were excluded from the models. Results from the mixed models were presented as the coefficients with their 95% confidence interval. The significance level was set at $p = 0.05$ and the statistical analyses were carried out using SPSS (Version 25) (IBM Corp., 2017).

**3. RESULTS**

From the 193 patients who were assessed at baseline, 99 (51.3%) continued in the study until the final assessments, either because of a relapse ($n = 46$) or because they finished the 3-year follow-up ($n = 53$). No significant differences were found in age ($z = -1.05$, $p = 0.30$), years of education ($z = -0.55$, $p = 0.585$), PANSS positive syndrome scale ($z = -0.18$, $p = 0.86$), PANSS negative syndrome scale ($z = -1.28$, $p = 0.20$), PANSS general ($z = -0.75$, $p = 0.46$), PANSS total scores ($z = -1.09$, $p = 0.28$) or the YMRS total score ($z = -1.17$, $p = 0.25$) between those who dropped out of the study and those who completed the follow-up. The patients who dropped out of the study showed more depressive symptoms assessed with the MADRS ($z = -2.26$, $p = 0.024$). Regarding cognitive assessments, patients who dropped out of the study showed significantly lower scores in attention ($t = 2.89$, $p = 0.004$) and executive function ($t = -2.2$, $p = 0.03$) compared to those who continued.

Only years of education, premorbid IQ and PAS late adolescence had a normal distribution. Relapsing and non-relapsing patients did not differ in sociodemographic and premorbid variables (Table 2). Regarding clinical and functioning variables, both groups were similar at baseline but patients who relapsed showed higher scores at

follow-up in the PANSS, YMRS and MADRS, were taking higher doses of antipsychotics and had worse functioning measured by the GAF and the FAST compared with those patients who did not relapse. This was an expected result because clinical assessments in relapsing patients were obtained during the relapsing episode. Regarding cognitive scores, all the variables had normal distributions except for verbal memory and social cognition baseline scores, which were compared with non-parametric tests. Relapsing and non-relapsing patients did not show significant differences in cognitive performance at baseline or at follow-up (Table 2).

Seven mixed-effects models were tested, one per cognitive function. First we performed the models by including time of assessment (baseline or final assessment), relapse, both CR variables and the interactions between relapse and CR and between relapse and time. Secondly, we tested the models again by eliminating those variables/interactions that were not significant. Table 3 shows the final models obtained, except for executive functions, which did not show significant associations with time of assessment, relapse or CR variables.

A significant interaction between relapse and personal CR was found in attention performance. In those patients who relapsed, for each unit increase in personal CR the attention scores increased by 0.32 units (*z*-scores). This value results from subtracting the personal CR coefficients from the interaction coefficients. Higher scores in attention mean better performance. There was no significant association in those patients who did not relapse (Fig. 2a).

Patients who relapsed showed worse mean global performance in processing speed than patients who did not relapse (Table 3, Supplementary Fig. 1b). A positive significant association was found between personal/familial CR and processing speed. Also, the interaction between personal CR and relapse was significant, showing a coefficient of −0.03 in the relapse group and 0.24 for the non-relapsing group. In other words, higher scores of personal CR have minor effects (a decrease of 0.03 units per unit of increased personal CR) in the relapse group, whereas in the non-relapsing group a positive association (an increase of 0.24 units) was found between both variables. Thus, personal CR had a positive effect in those patients who did not relapse but no effect in the relapsing patients (Fig. 2b).

Personal and familial CR showed a significant positive association with working memory for both relapsing and non-relapsing patients (Table 3).

Regarding verbal memory, patients who relapsed showed a worse mean global performance compared with those who did not relapse. Furthermore, a positive association with familial CR was found (Table 3, Supplementary Fig. 1d).

Patients who relapsed showed worse mean global performance in visual memory than patients who did not relapse (Table 2, Supplementary Fig. 1e). Personal and familial CR was positively associated with visual memory performance. There was also a significant interaction between familial CR and relapse. Patients who relapsed showed a coefficient of −0.06, which reflects an almost null association between visual memory and familial CR. In contrast, patients who did not relapse showed a coefficient of 0.45, which means that for each unit increase in familial CR the visual memory score increases by 0.45 units (Fig. 2c).

Regarding social cognition, a positive association with personal CR was found. Furthermore, a trend towards significance was found in time, showing a trend to improve over time in the whole group of patients (as relapse was not significant in the mixed-effects model, considering the effect of the CR covariates) (Supplementary Fig. 1h).

## 4. DISCUSSION

In this study, we aimed to ascertain whether relapse was related to cognitive impairment by considering CR (i.e. personal and familial CR) in a sample of FES remitted patients. Three main results were found. First, we found that personal CR, in combination with relapse, was associated with attention and processing speed performance, and that the interaction of familial CR and relapse was associated with visual memory performance. Specifically, patients who relapsed showed a positive association between personal CR and attention scores. This significant association was not found in patients who did not relapse. In contrast, patients who did not relapse showed a positive association between higher personal CR and better performance in processing speed, whereas no association was found in patients who relapsed. Regarding familial CR, those patients who did not relapse showed a positive association between higher familial CR and better performance in visual memory. Second, the main

effects of CR were found to be related to cognitive functioning: higher personal CR was related to higher scores in processing speed, working memory, verbal memory and social cognition; and higher familial CR was associated with better performance in processing speed, working memory, verbal and visual memory and social cognition. Third, patients who relapsed and did not have similar sociodemographic characteristics had similar baseline clinical, CR and cognitive functioning profiles.

There is evidence that relapse is related to worse cognitive functioning (Hori et al., 2020). It is possible that relapse has a negative effect on cognitive functioning but also that patients with worse cognitive functioning are more prone to relapse. Here, we did not find significant differences in cognitive performance between patients who relapsed and those who did not, either before or after relapse. Our patients had only experienced one psychotic episode in the previous 5 years, so those who relapsed were having their second episode. Thus, the lack of differences between patients relapsing and not relapsing could be due to the reduced number of relapses experienced and the limited illness duration.

We found different results regarding relapse and CR depending on the cognitive function. On the one hand, we found a differential effect of personal CR (as a combined CR score of premorbid adjustment and premorbid IQ) on attention in relapsing and non-relapsing patients. The positive association between personal CR and attention in relapsing patients may indicate that higher personal CR represents a protection from the negative effects of relapse on attention, as this effect was not observed in non-relapsing patients. In other words, considering that relapsing and non-relapsing patients did not show significant differences in the final assessments, those patients who relapsed and had better personal CR showed higher scores in attention. Attention has been described as vulnerable to the effects of relapse, being stable even months after the episode remission (Addington and Addington, 1997). According to these findings, attention may be more sensitive to relapse and also more influenced by CR. This could explain why no effect was observed in patients who did not relapse.

On the other hand, we found positive associations in non-relapsing patients regarding personal CR and processing speed and also familial CR and visual memory. These associations were not found in relapsing patients. In those cases, patients who did not relapse showed a beneficial effect of CR on processing speed and visual memory,

whereas in relapsing patients the 'toxic' effects of relapse may have outweighed the positive effects of the CR. These toxic effects of relapse may be similar to the effects of cannabis use in FEP patients; in a previous study, a higher protective effect over clinical and functional outcomes was found in those patients who did not use cannabis (Amoretti et al., 2022).

Our results regarding the association of higher CR with better cognitive functioning are in agreement with previous research (Amoretti et al., 2016; Amoretti et al., 2021b; Amoretti et al., 2020; de la Serna et al., 2013). Higher CR in FEP patients has been related to better outcomes in cognitive functioning in longitudinal studies. Specifically, two studies have reported better performance in adolescent patients with schizophrenia and schizoaffective disorders (de la Serna et al., 2013) and FEP patients (Camprodon-Boadas et al., 2021) for memory, working memory and attention at 2 and 5 years' follow-up, respectively. Premorbid adjustment, which also represents a marker of CR, has also been associated with better verbal fluency and memory scores (Addington and Addington, 2005). In a previous study with FEP patients, we reported an association of better premorbid adjustment with cognitive functioning in processing speed, working and verbal memory, executive functions and social cognition (Cuesta et al., 2015).

In addition to direct significant association of personal and familial CR with most cognitive functions, we also found differential effects of personal and familial CR over processing speed and working memory in non-relapsing patients, respectively. These differences may be due to the differential weight of illness-related factors in each cognitive function. Processing speed may be more prone to be affected by illness since the early phases of illness (Cuesta et al., 2015; González-Blanch et al., 2010), so higher premorbid abilities could represent a higher threshold against impairment. In general terms, there is evidence that cognitive functions are heritable (Blokland et al., 2017), and specifically moderate to high heritability has been reported regarding visual memory (Darst et al., 2015; Goldberg Hermo et al., 2014). The interaction between illness effects and heritability of visual memory may explain the differential positive effect of familial CR in non-relapsing patients.

At group level, baseline clinical, premorbid and cognitive characteristics did not differentiate those patients who were going to relapse from those who were not. However, the observed relationship between CR and cognition suggests that a better CR

may attenuate the negative effects of relapse. Relapse, as supported by studies comparing multi-episode samples of patients (Braw et al., 2008; Hori et al., 2020; Pukrop et al., 2006; Sponheim et al., 2010), seems to have a toxic effect over cognition, with those patients who have a higher number of relapses showing a more impaired cognitive profile than those who have never relapsed or have relapsed fewer times. Therefore, identifying factors that can prevent the negative effects of relapses on cognition, and taking into account that cognition is a central feature and closely related to functioning in schizophrenia, should be a priority in the study of the course of this disorder.

The differential results concerning the relationship of CR and the different cognitive functions may be due to the characteristics of the sample: they were young patients, with a short duration of illness and only one previous psychotic episode; their mean cognitive scores were around one standard deviation below the mean, which means collectively that they showed mild cognitive impairment, as reported by other authors (Sheffield et al., 2018). Thus, the positive effects of CR in these patients may not be as visible as in other patients with a longer disease course and a higher number of relapses.

The inclusion of parental schooling as a measure for the calculation of CR could be arguable. However, parents are responsible for providing stimulating environments during childhood and these environments have an influence over children's neurodevelopment (Langa et al., 2008). Thus, parental education may enhance children's CR either by means of genes or the childhood environment (e.g. by providing more stimulating activities) (Aartsen et al., 2019). Also, higher levels of school attainment are associated with highly educated parents (Chen et al., 2020).

Our results should be interpreted while considering some limitations. About 50% of patients included in the study decided not to continue in the study until the end. This is a frequent problem in follow-up studies. However, patients who continued in the study and those who dropped out only showed significant differences in depressive symptoms and executive functions, with worse results for those patients who dropped out.

We did not include a control group to compare the longitudinal cognitive performance. However, most of the tests disposed of normative data to make the comparisons.

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. Notwithstanding, to solve this limitation, in 2019, our group developed the Cognitive Reserve Assessment Scale in Health (CRASH) (Amoretti et al., 2019). This scale is the first measure designed specifically for patients with severe mental illness.

What can be concluded from our results is that CR interacts with relapse and that both have a role on cognition. Those patients who relapsed and had higher personal CR showed less deterioration in attention after relapse; furthermore, those patients with higher personal and familial. CR who did not relapse showed better performance in processing speed and visual memory. Our results add evidence for the protective effect of CR over the course of the illness. Thus, it may be useful to evaluate CR as it may considerably improve our understanding of individual differences in the impact of relapses on cognition in patients with a FES. Moreover, assessing CR enables the identification of patients who could benefit from interventions centered on CR stimulation and engaging lifestyle (de la Serna et al., 2021).

**Figure 1.** Flow chart of patients included in the study

**Figure 2.** Scatterplots of the mixed-effects models interactions between CR and cognitive functions, in relapsing and non-relapsing patients.

**Supplementary Fig 1.** Error bar graphs of cognitive scores at baseline and final assessment (endpoint), in relapsing and non-relapsing patients

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**TITLE: Relapse, cognitive reserve, and their relationship with cognition in first episode schizophrenia: a 3-year follow-up study.**

**RUNNING TITLE: Relapse, cognitive reserve and cognition in FES**

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**ABSTRACT**

Schizophrenia is frequently characterized by the presence of multiple relapses. Cognitive impairments are core features of schizophrenia. Cognitive reserve (CR) is the ability of the brain to compensate for damage caused by pathologies such as psychotic illness. As cognition is related to CR, the study of the relationship between relapse, cognition and CR may broaden our understanding of the course of the disease. We aimed to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. Ninety-nine patients with a remitted first episode of schizophrenia or schizophreniform disorder were administered a set of neuropsychological tests to assess premorbid IQ, attention, processing speed, working memory, verbal and visual memory, executive functions and social cognition. They were followed up for 3 years (*n*=53) or until they relapsed (*n*=46). Personal and familial CR was estimated from a principal component analysis of the premorbid information gathered. Linear mixed-effects models were applied to analyse the effect of time and relapse on cognitive function, with CR as covariate. Patients who relapsed and had higher personal CR showed less deterioration in attention, whereas those with higher CR (personal and familial CR) who did not relapse showed better performance in processing speed and visual memory. Taken together, CR seems to ameliorate the negative effects of relapse on attention performance and shows a positive effect on processing speed and visual memory in those patients who did not relapse. Our results add evidence for the protective effect of CR over the course of the illness.

**Keywords:** schizophrenia; cognition; cognitive reserve; relapse.

## 1. INTRODUCTION

Schizophrenia is a chronic and disabling disorder with a course frequently characterized by the presence of multiple relapses. Around 40–63% of patients may have a relapse in the first 3 years after a first episode of psychosis (FEP) (Alvarez-Jimenez et al., 2012). Prevention of relapses represents a challenge in clinical practice, considering the negative consequences that relapsing may have for patients, such as neurotoxic effects (Andreasen et al., 2013), harming themselves or others and a negative impact in interpersonal relationships, education or employment (Emsley et al., 2013).

The most studied predictors of relapse after the FEP are non-adherence to pharmacological treatment and substance abuse (Alvarez-Jimenez et al., 2012; Bergé et al., 2016; Bowtell et al., 2018a). There are, however, other factors that have been associated with relapse, such as longer duration of untreated psychosis (Altamura et al., 2001), premorbid adjustment (Alvarez-Jimenez et al., 2012; Bowtell et al., 2018b; Robinson et al., 1999) and psychosocial factors (Alvarez-Jimenez et al., 2012; Bowtell et al., 2018b; Kam et al., 2015).

Cognitive impairment is closely related to outcome (Cuesta et al., 2020; Mucci et al., 2021) because it is a core feature of schizophrenia (Green and Harvey, 2014; Green et al., 2019; Kraus and Keefe, 2007) but it may also have a role in non-adherence (Velligan et al., 2017). There may be an indirect role of cognition in the factors that are associated with relapse (Kadakia et al., 2022) but relapse also may have an effect on cognition (Hori et al., 2020; Pukrop et al., 2006; Rund et al., 2007). The results of comparative and longitudinal studies including first episode patients and multi-episode patients suggest a negative effect of relapse on cognition. For example, Rund et al. (2007), found a worsening in verbal memory tasks in patients with two or more relapses at two years after the first episode of psychosis. Also, Barder et al. (Barder et al., 2013) found that early relapse was a strong predictor of impairment in verbal fluency and verbal memory. Hori et al (2020), in a comparative study, reported an association between an increased number of hospitalizations and a worsening in verbal memory, working memory, verbal fluency, and executive functions.

The cognitive reserve (CR) hypothesis postulates that patients with higher premorbid intellectual functions will be more able to compensate for the damage caused by

psychotic illness (Amoretti and Ramos-Quiroga, 2021; Barnett et al., 2006). CR is determined by several factors, such as genetic and environmental factors. Genes are responsible, among other things, of brain size and weight, and synaptic density, as well as of congenital intellectual ability. Environmental factors include modifiable aspects such as education and mental and physical activity (Bora, 2015). Thus, CR results of the interaction of cognitive experiences and genes (Amoretti and Ramos-Quiroga, 2021). In the field of mental disorders the concept of CR has not been accurately defined and has been characterized by different variables. Traditionally in scientific research, CR was estimated using the premorbid intelligence quotient (IQ). However, the role of environmental factors on CR development is now also relevant. The most common proposed proxies of CR include estimated premorbid IQ, educational level and occupational attainment (Amoretti et al., 2016; Amoretti et al., 2018; Barnett et al., 2006; Buonocore et al., 2018; de la Serna et al., 2013; Nucci et al., 2012; Pettigrew and Soldan, 2019).

The components of the CR, such as premorbid adjustment, have been associated with the potential benefit of cognitive remediation in patients with schizophrenia (Buonocore et al., 2019), and poor premorbid adjustment has been associated with higher rates of relapse (Robinson et al., 1999). Furthermore, low education and premorbid IQ were among the best predictors of relapse and follow-up withdrawal in a 2-year follow-up study (Fond et al., 2019). Considering that the presence of relapse is associated with a worse prognosis (Birchwood et al., 1998; Emsley et al., 2013; Kadakia et al., 2022), it would be interesting to study the factors that may attenuate the harmful effects of relapse.

### 1.1. Aims of the study

Our aim was to determine whether relapse was associated with cognitive impairment, controlling for the effects of CR. In particular, we hypothesized that CR would play an attenuating role in the effects of relapse on cognitive functioning at final assessment.

## 2. METHODS

This study is part of the "Clinical and neurobiological determinants of second episodes of schizophrenia. Longitudinal study of first episode of psychosis" (2EPs Project), which is a naturalistic, multicentre, coordinated, longitudinal follow-up study of first-episode schizophrenia (FES) patients with an illness course of less than 5 years and a 3-year longitudinal-prospective follow-up design. A 3-year-follow up window was considered taking into account that 80% of relapses occur in the first 5 years after the FES (Alvarez-Jiménez et al., 2011; Robinson et al., 1999; Robinson et al., 2005), and the inclusion criteria established less than 5 years since the FES (finally the mean was of 1.56 ±1.37 years). Also, longer follow-up period may have resulted in higher attrition rates. All participants were assessed on clinical, functional and cognitive variables again at follow-up or relapse visits. The study established a minimum time of 6 months between cognitive evaluations (in case patients relapsed shortly after entering the study), to minimize practice effects.

The project involves six modules: general and basic; neuroimaging; adherence; neurocognition; physical health; and biological. The present study was framed within the general and neurocognition modules. The background, rationale and study design are fully described elsewhere (Bernardo et al., 2021).

### 2.1. Subjects

The patients included in the 2EPs Project met the following inclusion criteria: age 16–40 years at the time of first assessment (baseline); a diagnosis of schizophrenia or schizophreniform disorder according to DSM-IV criteria (APA, 1994); being in remission from the first psychotic episode (for up to 5 years) according to Andreasen's criteria (Andreasen et al., 2005); not having relapsed after the first psychotic episode; fluent in Spanish; and providing the signed informed consent. The exclusion criteria were: having experienced a traumatic brain injury with loss of consciousness; presenting intellectual disability understood not only as IQ <70 but also presenting malfunctioning and problems with adaptative processes; and/or presenting organic disease with mental repercussion.

A total of 219 patients were recruited in the 2EPs Project. The patients had baseline clinical data and 193 of these patients were included in the neurocognition module. Finally, 99 patients were assessed with the cognitive battery at follow-up: 53 patients

did not relapse during the 3-year follow-up period and 46 patients relapsed at some point in the follow-up (Fig. 1).

The study was approved by the research ethics committees of all participating clinical centres and was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice.

### 2.2. Procedures

#### 2.2.1. Sociodemographic and clinical assessments

We collected demographic and clinical data for all participants, including age, education, parents' education, functioning at the moment of the assessments, antipsychotic treatment and psychopathological status.

Functioning was assessed with the Global Assessment of Functioning (GAF) scale (APA, 1994) and the Functioning Assessment Short Test (FAST) (Amoretti et al., 2021a; Rosa et al., 2007). The GAF is a scale designed to assess the severity of symptoms related to the level of functioning, on a scale from 1 to 100, where higher scores indicate better functioning. The FAST assesses six domains of functioning (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time) and comprises 24 items, each item rated from 0 (no difficulty) to 3 (severe difficulty); higher scores represent higher disability.

Antipsychotic treatment was converted to chlorpromazine equivalents (CPZ) according to the guidelines provided by Leucht et al. (Leucht et al., 2016).

The psychopathological status was assessed by means of the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987; Peralta and Cuesta, 1994), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

#### 2.2.2. Cognitive assessments

Neuropsychological assessment included a comprehensive battery of 15 standardized cognitive tests, designed to encompass the seven cognitive domains included in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative (Marder and Fenton, 2004; Nuechterlein et al., 2004;

Nuechterlein et al., 2008). The neuropsychological tests employed and the measures selected for this work are detailed in Table 1.

Experienced psychologists administered the tests, in two sessions of 1–1.5 hours to facilitate cooperation. Previously, an inter-rater reliability study was conducted to ensure that all psychologists reached intraclass correlation coefficients of 0.80 in two of the tests of the battery: the Wechsler Adult Intelligence Scale (WAIS-III) vocabulary subtest and the Wisconsin Card Sorting Test (WCST). In these tests, the final score may partially depend on the judgement of the rater administering and correcting the test.

### 2.2.3. Cognitive reserve assessments

We assessed CR using the most common proxy indicators: premorbid IQ assessed using the vocabulary subtest of the WAIS-III (Wechsler, 1999); patients' and parents' education (as a categorical variable with seven categories, from unfinished elementary studies to university studies or higher); and scholastic performance at childhood and adolescence, measured with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). The PAS was completed with all the available sources of information (patient, parents and/or medical charts). When patients were assessed they had already experienced a FES, so the premorbid variables could only be estimated. We applied a principal component analysis (PCA) to obtain a combined score for CR. We obtained two factor scores (eigenvalues >1), the first one with high loadings on scholastic performance of the PAS and patients' education, combined with premorbid IQ ('personal CR'), and the second one with high loading in parents' education ('familial CR').

## 2.3. Statistical analyses

We examined the distribution of the sociodemographic and cognitive variables to adjust the analyses in each case. We compared the sociodemographic and clinical characteristics of patients relapsing and not relapsing with one-way ANOVA and Mann-Whitney U tests. Gender distribution between groups was compared using $|^2$ tests.

Regarding the cognitive variables, we transformed the selected measures for each of the neuropsychological tests to *z*-scores. We used the group means and standard deviations in those tests where no normative data were available and converted standard scores if the tests provided these normative scores. From the tests' *z*-scores,

we computed the scores of the cognitive functions (see Table 1). Cognitive scores were reversed when necessary to ensure that higher scores indicate better performance.

To assess the effects of relapse on the cognitive functions over time, with personal and familiar CR as covariates, a linear mixed-effects model was fitted to each of the cognitive functions. We selected this model because of its advantage in dealing with missing values. Each model included the time at assessment (baseline and 3 years/relapse), the relapse/non-relapse condition, the PCR, the FCR and the interactions between PCR or FCR with the relapse/non-relapse condition, in order to assess if there was a differential evolution of cognitive performance or a differential mean global cognitive performance associated with CR in those patients relapsing/not relapsing. Non-significant interactions where excluded from the models. Results from the mixed models were presented as the coefficients with their 95% confidence interval. The significance level was set at $p = 0.05$ and the statistical analyses were carried out using SPSS (Version 25) (Corp., 2017).

**3. RESULTS**

From the 193 patients who were assessed at baseline, 99 (51.3%) continued in the study until the final assessments, either because of a relapse ($n = 46$) or because they finished the 3-year follow-up ($n = 53$). No significant differences were found in age ($z = -1.05$, $p = 0.30$), years of education ($z = -0.55$, $p = 0.585$), PANSS positive syndrome scale ($z = -0.18$, $p = 0.86$), PANSS negative syndrome scale ($z = -1.28$, $p = 0.20$), PANSS general ($z = -0.75$, $p = 0.46$), PANSS total scores ($z = -1.09$, $p = 0.28$) or the YMRS total score ($z = -1.17$, $p = 0.25$) between those who dropped out of the study and those who completed the follow-up. The patients who dropped out of the study showed more depressive symptoms assessed with the MADRS ($z = -2.26$, $p = 0.024$). Regarding cognitive assessments, patients who dropped out of the study showed significantly lower scores in attention ($t = 2.89$, $p = 0.004$) and executive function ($t = -2.2$, $p = 0.03$) compared to those who continued.

Only years of education, premorbid IQ and PAS late adolescence had a normal distribution. Relapsing and non-relapsing patients did not differ in sociodemographic and premorbid variables (Table 2). Regarding clinical and functioning variables, both groups were similar at baseline but patients who relapsed showed higher scores at

follow-up in the PANSS, YMRS and MADRS, were taking higher doses of antipsychotics and had worse functioning measured by the GAF and the FAST compared with those patients who did not relapse. This was an expected result because clinical assessments in relapsing patients were obtained during the relapsing episode. Regarding cognitive scores, all the variables had normal distributions except for verbal memory and social cognition baseline scores, which were compared with non-parametric tests. Relapsing and non-relapsing patients did not show significant differences in cognitive performance at baseline or at follow-up (Table 2).

Seven mixed-effects models were tested, one per cognitive function. First we performed the models by including time of assessment (baseline or final assessment), relapse, both CR variables and the interactions between relapse and CR and between relapse and time. Secondly, we tested the models again by eliminating those variables/interactions that were not significant. Table 3 shows the final models obtained, except for executive functions, which did not show significant associations with time of assessment, relapse or CR variables.

A significant interaction between relapse and personal CR was found in attention performance. In those patients who relapsed, for each unit increase in personal CR the attention scores increased by 0.32 units (*z*-scores). This value results from subtracting the personal CR coefficients from the interaction coefficients. Higher scores in attention mean better performance. There was no significant association in those patients who did not relapse (Fig. 2a).

Patients who relapsed showed worse mean global performance in processing speed than patients who did not relapse (Table 3, Supplementary Fig. 1b). A positive significant association was found between personal/familial CR and processing speed. Also, the interaction between personal CR and relapse was significant, showing a coefficient of −0.03 in the relapse group and 0.24 for the non-relapsing group. In other words, higher scores of personal CR have minor effects (a decrease of 0.03 units per unit of increased personal CR) in the relapse group, whereas in the non-relapsing group a positive association (an increase of 0.24 units) was found between both variables. Thus, personal CR had a positive effect in those patients who did not relapse but no effect in the relapsing patients (Fig. 2b).

Personal and familial CR showed a significant positive association with working memory for both relapsing and non-relapsing patients (Table 3).

Regarding verbal memory, patients who relapsed showed a worse mean global performance compared with those who did not relapse. Furthermore, a positive association with familial CR was found (Table 3, Supplementary Fig. 1d).

Patients who relapsed showed worse mean global performance in visual memory than patients who did not relapse (Table 2, Supplementary Fig. 1e). Personal and familial CR was positively associated with visual memory performance. There was also a significant interaction between familial CR and relapse. Patients who relapsed showed a coefficient of −0.06, which reflects an almost null association between visual memory and familial CR. In contrast, patients who did not relapse showed a coefficient of 0.45, which means that for each unit increase in familial CR the visual memory score increases by 0.45 units (Fig. 2c).

Regarding social cognition, a positive association with personal CR was found. Furthermore, a trend towards significance was found in time, showing a trend to improve over time in the whole group of patients (as relapse was not significant in the mixed-effects model, considering the effect of the CR covariates) (Supplementary Fig. 1h).

## 4. DISCUSSION

In this study, we aimed to ascertain whether relapse was related to cognitive impairment by considering CR (i.e. personal and familial CR) in a sample of FES remitted patients. Three main results were found. First, we found that personal CR, in combination with relapse, was associated with attention and processing speed performance, and that the interaction of familial CR and relapse was associated with visual memory performance. Specifically, patients who relapsed showed a positive association between personal CR and attention scores. This significant association was not found in patients who did not relapse. In contrast, patients who did not relapse showed a positive association between higher personal CR and better performance in processing speed, whereas no association was found in patients who relapsed. Regarding familial CR, those patients who did not relapse showed a positive association between higher familial CR and better performance in visual memory. Second, the main

effects of CR were found to be related to cognitive functioning: higher personal CR was related to higher scores in processing speed, working memory, verbal memory and social cognition; and higher familial CR was associated with better performance in processing speed, working memory, verbal and visual memory and social cognition. Third, patients who relapsed and did not have similar sociodemographic characteristics had similar baseline clinical, CR and cognitive functioning profiles.

There is evidence that relapse is related to worse cognitive functioning (Hori et al., 2020). It is possible that relapse has a negative effect on cognitive functioning but also that patients with worse cognitive functioning are more prone to relapse. Here, we did not find significant differences in cognitive performance between patients who relapsed and those who did not, either before or after relapse. Our patients had only experienced one psychotic episode in the previous 5 years, so those who relapsed were having their second episode. Thus, the lack of differences between patients relapsing and not relapsing could be due to the reduced number of relapses experienced and the limited illness duration.

We found different results regarding relapse and CR depending on the cognitive function. On the one hand, we found a differential effect of personal CR (as a combined CR score of premorbid adjustment and premorbid IQ) on attention in relapsing and non-relapsing patients. The positive association between personal CR and attention in relapsing patients may indicate that higher personal CR represents a protection from the negative effects of relapse on attention, as this effect was not observed in non-relapsing patients. In other words, considering that relapsing and non-relapsing patients did not show significant differences in the final assessments, those patients who relapsed and had better personal CR showed higher scores in attention. Attention has been described as vulnerable to the effects of relapse, being stable even months after the episode remission (Addington and Addington, 1997). According to these findings, attention may be more sensitive to relapse and also more influenced by CR. This could explain why no effect was observed in patients who did not relapse.

On the other hand, we found positive associations in non-relapsing patients regarding personal CR and processing speed and also familial CR and visual memory. These associations were not found in relapsing patients. In those cases, patients who did not relapse showed a beneficial effect of CR on processing speed and visual memory,

whereas in relapsing patients the 'toxic' effects of relapse may have outweighed the positive effects of the CR. These toxic effects of relapse may be similar to the effects of cannabis use in FEP patients; in a previous study, a higher protective effect over clinical and functional outcomes was found in those patients who did not use cannabis (Amoretti et al., 2022).

Our results regarding the association of higher CR with better cognitive functioning are in agreement with previous research (Amoretti et al., 2016; Amoretti et al., 2021b; Amoretti et al., 2020; de la Serna et al., 2013). Higher CR in FEP patients has been related to better outcomes in cognitive functioning in longitudinal studies. Specifically, two studies have reported better performance in adolescent patients with schizophrenia and schizoaffective disorders (de la Serna et al., 2013) and FEP patients (Camprodon-Boadas et al., 2021) for memory, working memory and attention at 2 and 5 years' follow-up, respectively. Premorbid adjustment, which also represents a marker of CR, has also been associated with better verbal fluency and memory scores (Addington and Addington, 2005). In a previous study with FEP patients, we reported an association of better premorbid adjustment with cognitive functioning in processing speed, working and verbal memory, executive functions and social cognition (Cuesta et al., 2015).

In addition to direct significant association of personal and familial CR with most cognitive functions, we also found differential effects of personal and familial CR over processing speed and working memory in non-relapsing patients, respectively. These differences may be due to the differential weight of illness-related factors in each cognitive function. Processing speed may be more prone to be affected by illness since the early phases of illness (Cuesta et al., 2015; González-Blanch et al., 2010), so higher premorbid abilities could represent a higher threshold against impairment. In general terms, there is evidence that cognitive functions are heritable (Blokland et al., 2017), and specifically moderate to high heritability has been reported regarding visual memory (Darst et al., 2015; Goldberg Hermo et al., 2014). The interaction between illness effects and heritability of visual memory may explain the differential positive effect of familial CR in non-relapsing patients.

At group level, baseline clinical, premorbid and cognitive characteristics did not differentiate those patients who were going to relapse from those who were not.

However, the observed relationship between CR and cognition suggests that a better CR may attenuate the negative effects of relapse. Relapse, as supported by studies comparing multi-episode samples of patients (Braw et al., 2008; Hori et al., 2020; Pukrop et al., 2006; Sponheim et al., 2010), seems to have a toxic effect over cognition, with those patients who have a higher number of relapses showing a more impaired cognitive profile than those who have never relapsed or have relapsed fewer times. Therefore, identifying factors that can prevent the negative effects of relapses on cognition, and taking into account that cognition is a central feature and closely related to functioning in schizophrenia, should be a priority in the study of the course of this disorder.

The differential results concerning the relationship of CR and the different cognitive functions may be due to the characteristics of the sample: they were young patients, with a short duration of illness and only one previous psychotic episode; their mean cognitive scores were around one standard deviation below the mean, which means collectively that they showed mild cognitive impairment, as reported by other authors (Sheffield et al., 2018). Thus, the positive effects of CR in these patients may not be as visible as in other patients with a longer disease course and a higher number of relapses.

The inclusion of parental schooling as a measure for the calculation of CR could be arguable. However, parents are responsible for providing stimulating environments during childhood and these environments have an influence over children's neurodevelopment (Langa et al., 2008). Thus, parental education may enhance children's CR either by means of genes or the childhood environment (e.g. by providing more stimulating activities) (Aartsen et al., 2019). Also, higher levels of school attainment are associated with highly educated parents (Chen et al., 2020).

Our results should be interpreted while considering some limitations. About 50% of patients included in the study decided not to continue in the study until the end. This is a frequent problem in follow-up studies. However, patients who continued in the study and those who dropped out only showed significant differences in depressive symptoms and executive functions, with worse results for those patients who dropped out.

We did not include a control group to compare the longitudinal cognitive performance. However, most of the tests disposed of normative data to make the comparisons.

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. Notwithstanding, to solve this limitation, in 2019, our group developed the Cognitive Reserve Assessment Scale in Health (CRASH) (Amoretti et al., 2019). This scale is the first measure designed specifically for patients with severe mental illness.

What can be concluded from our results is that CR interacts with relapse and that both have a role on cognition. Those patients who relapsed and had higher personal CR showed less deterioration in attention after relapse; furthermore, those patients with higher personal and familial. CR who did not relapse showed better performance in processing speed and visual memory. Our results add evidence for the protective effect of CR over the course of the illness. Thus, it may be useful to evaluate CR as it may considerably improve our understanding of individual differences in the impact of relapses on cognition in patients with a FES. Moreover, assessing CR enables the identification of patients who could benefit from interventions centered on CR stimulation and engaging lifestyle (de la Serna et al., 2021).

**Figure 1.** Flow chart of patients included in the study

**Figure 2.** Scatterplots of the mixed-effects models interactions between CR and cognitive functions, in relapsing and non-relapsing patients.

**Supplementary Fig 1.** Error bar graphs of cognitive scores at baseline and final assessment (endpoint), in relapsing and non-relapsing patients

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Table 1. Neuropsychological assessment. Tests and measures included for each cognitive domain

| | Type of test | Measures included in the analyses |
|---|---|---|
| **Premorbid IQ** | Wechsler Adult Intelligence Scale-III, Vocabulary subtest (WAIS-III)(Wechsler, 1999) | IQ: (Total scale score x 5)+50 |
| **Attention** | Continuous Performance Test-II (CPT-II) (Conners, 2000) | D' prime -T score |
| **Processing Speed** | Trail Making Test (Form A) (Reitan and Wolfson, 1993) | Time in seconds* |
| | Stroop Test, Word-Colour (Golden, 1978) | Number of words read –T score<br>Number of correct colours identified – T score |
| | Wechsler Adult Intelligence Scale-III, Digit symbol coding subtest(Wechsler, 1999) | Total scale score |
| | Test Barcelona, Animal Words (Peña-Casanova, 1990) | Number of correct responses* |
| **Executive Function** | Wisconsin Card Sorting Test, (WCST-128) (Heaton et al., 1993) | Perseverative errors –T score<br>Total errors –T score<br>Conceptual level responses – T score |
| | Tower of London | Total correct scores – T score |
| **Working Memory** | Wechsler Adult Intelligence Scale-III, Digit Span Test (Wechsler, 1999) | Number of correct responses backwards –raw score*<br>Number of correct responses forward –raw score* |
| | Wechsler Adult Intelligence Scale-III, Letter-Number Sequencing (Wechsler, 1999) | Number of correct responses - scale score |
| **Verbal Memory** | California Verbal Learning Test, Spanish version (TAVEC) (Benedet and Alejandre, 1998) | Number of recalled words (short term) - z score<br>Number of recalled words (delayed) – z score<br>Number of recognised words – z score |
| **Visual memory** | Wechsler Memory Scale (Wechsler, 1998), Visual reproduction subtest | Immediate recall score – scale score<br>Delayed recall score – scale score |
| **Social cognition** | Mayer-Salovey-Caruso Emotional Intelligence Test, Managing emotions branch (MSCEIT) (Mayer et al., 2009) | Total score – IQ score |

* z-scores calculated from the mean and standard deviation of the FES patient sample itself.

Table 2. Sociodemographic, clinical and cognitive characteristics of the sample.

| | **No relapse (3 years follow-up) N=53** | | **Relapse N=46** | | **Between groups differences ANOVA /Mann-Whitney U (F/Z) or $X^2$ (p-value)** |
|---|---|---|---|---|---|
| **Age (years)** | 26.9 (5.9) | | 25.5 (5.6) | | 1.49 (p=0.23)[a] |
| **Education (years)** | 11.4 (2.9) | | 11.7 (2.9) | | -0.47 (p=0.64)[b] |
| **Gender (male/female)** | 40/13 | | 31/15 | | 0.79 (p=0.37) |
| **Mother education (years)** | 10.2 (2.9) | | 10.5 (3) | | -0.76 (p=0.45) [b] |
| **Father education** | 10.6 (2.9) | | 11.1 (3.3) | | -0.66 (p=0.51) [b] |
| **Premorbid IQ** | 99.1 (16.9) | | 96.2 (12.6) | | 0.91 (p=0.34) [a] |
| **PAS childhood** | 5.7 (3.6) | | 4.9 (4.0) | | -0.09 (p=0.93) [b] |
| **PAS early adolescence** | 8.2 (4.7) | | 7.8 (5.6) | | -0.44 (p=0.66) [b] |
| **PAS late adolescence** | 8.9 (5.1) | | 8.6 (5.3) | | 0.08 (p=0.78) [a] |
| **Personal CR** | 0.04 (0.9) | | -0.06 (1.1) | | 0.19 (P=0.67) [a] |
| **Familiar CR** | -0.03 (1.0) | | 0.04 (1.0) | | 0.09 (p=0.77) [a] |
| **Diagnosis**<br>**Schizophrenia**<br>**Schizophreniform disorder** | 33 (62%)<br>20 (38%) | | 28 (61%)<br>18 (39%) | | 5.9 (p=0.32) |
| | **Baseline** | **Follow-up** | **Baseline** | **Follow-up** | |
| **GAF** | 71.4 (16.0) | 79.9 (12.2) | 72.4 (13.9) | 46.1 (12.6) | Baseline: -0.20 (p=0.84) [b]<br>Follow-up: -7.55 (p<0.001) [b] |
| **FAST** | 24.4 (18.5) | 16.5 (17.5) | 21.4 (17.8) | 27.9 (16.3) | Baseline: -0.69 (p=0.49) [b]<br>Follow-up: -3.58 (p<0.001) [b] |
| **CPZ** | 265.7 (225.0) | 225.2 (203.83) | 323.0 (303.0) | 371.1 (306.1) | Baseline: -0.51 (p=0.61) [b]<br>Follow-up: -2.48 (p=0.01) [b] |
| **YMRS** | 0.9 (2.0) | 0.7 (1.8) | 0.96 (1.7) | 8.9 (8.8) | Baseline: -0.69 (p<0.49) [b]<br>Follow-up: -6.12 (p<0.001) [b] |
| **MADRS** | 6.2 (7.0) | 3.9 (5.6) | 5.07 (5) | 11.2 (6.8) | Baseline: -0.17 (p=0.87) [b]<br>Follow-up: 35.29 (p<0.001) [b] |

| | | | | | |
|---|---|---|---|---|---|
| **PANSS positive score** | 9.3 (2.8) | 8.8 (2.8) | 9.3 (2.9) | 19.0 (7.4) | Baseline: -0.03 (p=0.980) [b]<br>Follow-up: -7.16 (p<0.001) [b] |
| **PANSS negative score** | 13.5 (4.8) | 12.0 (4.7) | 13.0 (5.5) | 18.0 (7.7) | Baseline: -0.72 (p=0.474) [b]<br>Follow-up: -4.03 (p<0.001) [b] |
| **PANSS general score** | 23.9 (6.8) | 22.4 (7.1) | 23.9 (6.5) | 36.6 (12.4) | Baseline:-0.16 (p=0.877) [b]<br>Follow-up: -6.17 (p<0.001) [b] |
| **PANSS total score** | 46.7 (13.0) | 43.0 (13.4) | 46.1 (12.6) | 73.6 (24.6) | Baseline: -0.11 (p<0.92) [b]<br>Follow-up: -5.76 (p<0.001) [b] |
| **Cognitive functions** | | | | | |
| **Working memory** | -0.04 (0.9) | -0.004 (0.8) | -0.15 (0.8) | -0.17 (0.8) | Baseline: 0.45 (p=0.51) [a]<br>Follow-up: 1.02 (p=0.32) [a] |
| **Verbal memory** | -0.38 (1.3) | -0.21 (1.1) | -0.71 (1.2) | -0.55 (1.2) | Baseline: -1.43 (p=0.15) [b]<br>Follow-up: 2.12 (p=0.15) [a] |
| **Processing speed** | -0.42 (0.8) | -0.32 (0.8) | -0.64 (0.6) | -0.55 (0.7) | Baseline: 2.11 (p=0.15) [a]<br>Follow-up: 2.24 (p=0.14) [a] |
| **Visual memory** | 0.06 (1.6) | 0.31 (1.3) | -0.29 (1.4) | -0.19 (1.4) | Baseline: 1.29 (p=0.26) [a]<br>Follow-up: 3.04 (p=0.08) [a] |
| **Attention** | -0.02 (0.6) | 0.24 (0.9) | -0.16 (0.7) | -0.03 (1.0) | Baseline: 0.95 (p=0.33) [a]<br>Follow-up: 1.67 (p=0.20) [a] |
| **Executive functions** | 0.12 (1.1) | 0.42 (1.0) | -0.20 (0.1) | 0.04 (0.9) | Baseline: 2.88 (p=0.09) [a]<br>Follow-up: 1.52 (p=0.22) [a] |
| **Social cognition** | 0.003 (0.9) | 0.62 (1.2) | 0.1 (1.0) | 0.14 (1.2) | Baseline: -0.53 (p=0.60) [b]<br>Follow-up: 3.28 (p=0.07) [a] |

a ANOVA (F value)

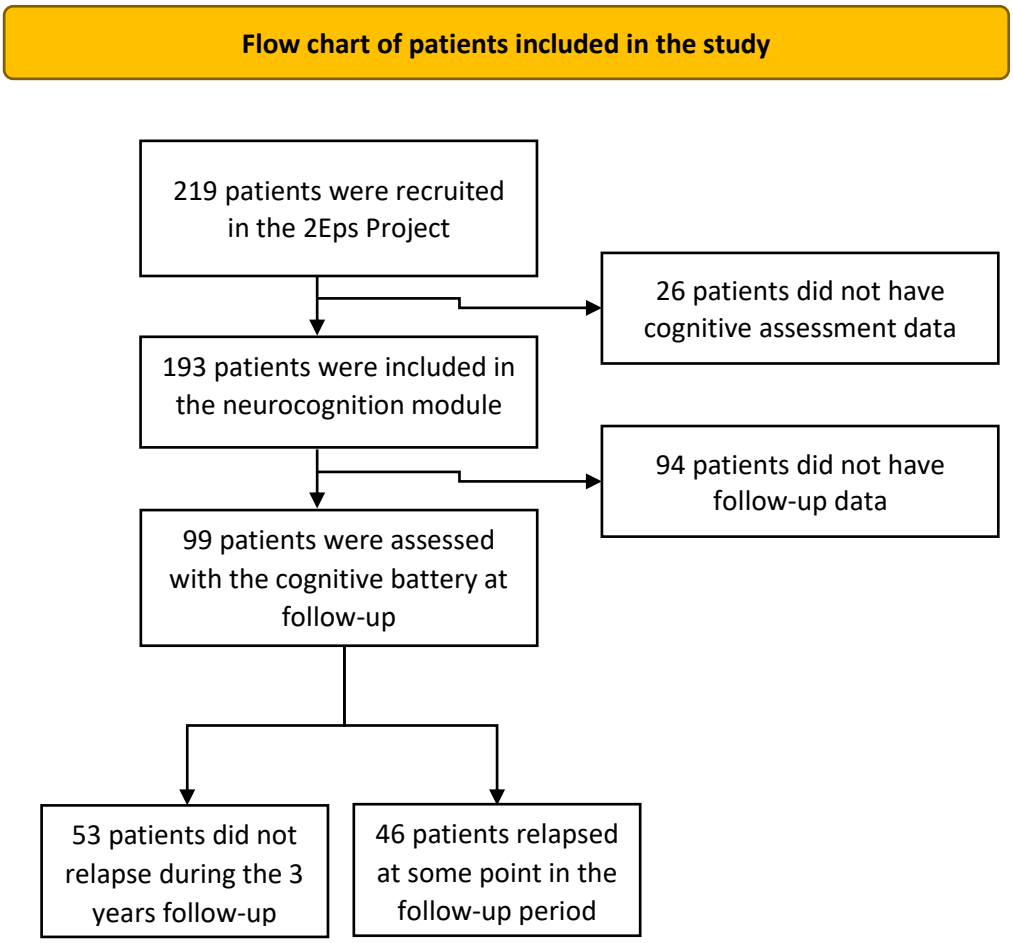
b Mann-Whitney U (Z value)

Abbreviations: IQ= Intelligence Quotient; PAS= Premorbid Adjustment Scale; CR= Cognitive Reserve; GAF= Global Assessment of Functioning; FAST=Functioning Assessment Short Test; CPZ= Chlorpromazine equivalents; YMRS= Young Mania Rating Scale; MADRS= Montgomery Åsberg Depression Rating; PANSS= Positive and Negative Symptoms Scale.

Table 3. Mixed-effects models results, testing the effects of time at assessment (baseline and 3 years/relapse), relapse/not relapse condition, personal and familial CR, and the interactions between time, relapse condition and CR (time x relapse and personal/familial CR x relapse) over cognitive functions.

| Outcome | Explanatory | Coefficient (CI95%, p_value) |
|---|---|---|
| Attention | Relapse | -0.18 (-0.46,0.10, p=0.213) |
| | Personal CR (PCR) | -0.16 (-0.35,0.04, p=0.117) |
| | Familial CR (FCR) | 0.06 (-0.07,0.20, p=0.360) |
| | Time | 0.21 (-0.08,0.50, p=0.153) |
| | Relapse x Personal CR (PCR) | **0.48 (0.20,0.75, p=0.001)** |
| Processing speed | Relapse | **-0.40 (-0.62,-0.18, p<0.001)** |
| | Personal CR (PCR) | **0.24 (0.08,0.39, p=0.002)** |
| | Familial CR (FCR) | **0.13 (0.02,0.24, p=0.016)** |
| | Time | 0.13 (-0.08,0.34, p=0.219) |
| | Relapse x Personal CR (PCR) | **-0.27 (-0.48,-0.49, p=0.017)** |
| Working memory | Relapse | -0.15 (-0.39,0.08, p=0.196) |
| | Personal CR (PCR) | **0.25 (0.14,0.37, p<0.001)** |
| | Familial CR (FCR) | **0.14 (0.02,0.25, p=0.022)** |
| | Time | 0.06 (-0.17,0.29, p=0.593) |
| Verbal memory | Relapse | **-0.49 (-0.86,-0.12, p=0.009)** |
| | Personal CR (PCR) | 0.15 (-0.03,0.33, p=0.098) |
| | Familial CR (FCR) | **0.21 (-0.03,0.39, p=0.020)** |
| | Time | 0.19 (-0.17,0.55, p=0.306) |
| Visual memory | Relapse | **-0.50 (-0.95,-0.06, p=0.027)** |
| | Personal CR (PCR) | **0.48 (0.25,0.70, p<0.001)** |
| | Familial CR (FCR) | **0.45 (0.17,0.73, p=0.002)** |
| | Time | 0.05 (-0.39,0.49, p=0.828) |
| | Relapse x Familial CR (FCR) | **-0.51 (-0.97,-0.06, p=0.027)** |
| Social cognition | Relapse | -0.13 (-0.53,0.27, p=0.518) |
| | Personal CR (PCR) | **0.24 (0.05,0.44, p=0.016)** |
| | Familial CR (FCR) | 0.16 (-0.18,0.21, p=0.869) |
| | Time | 0.39 (-0.01,0.79, p=0.054) |

Abbreviations: CR= Cognitive Reserve; PCR= Personal Cognitive Reserve; FCR= Familial Cognitive Reserve.



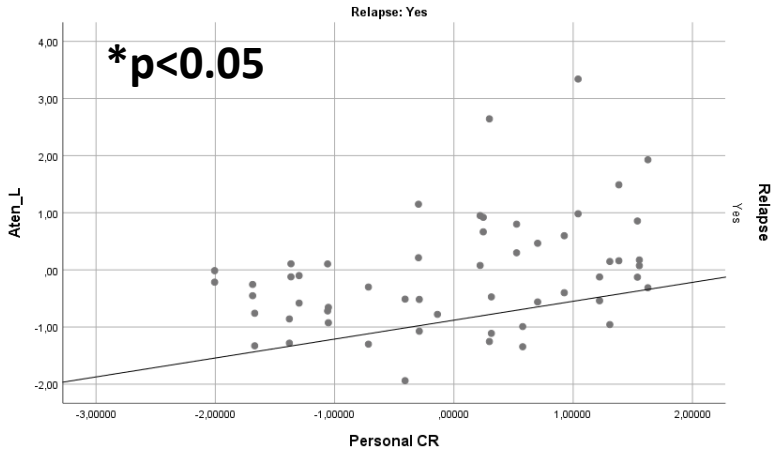
Figure(s)

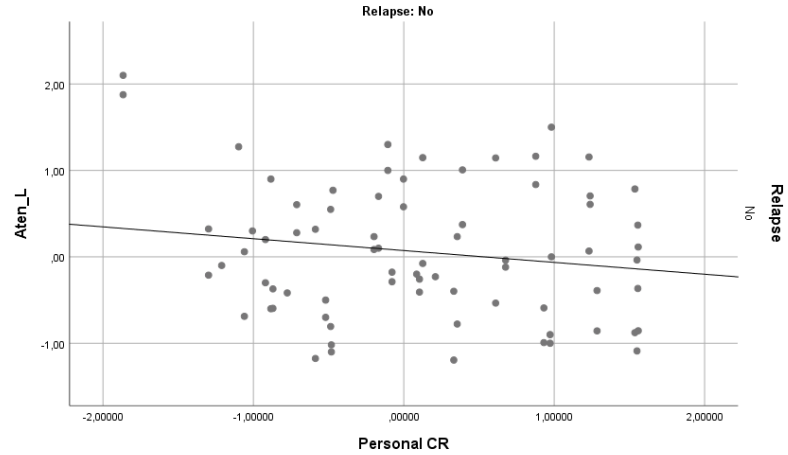


# Figure 2

## 2a

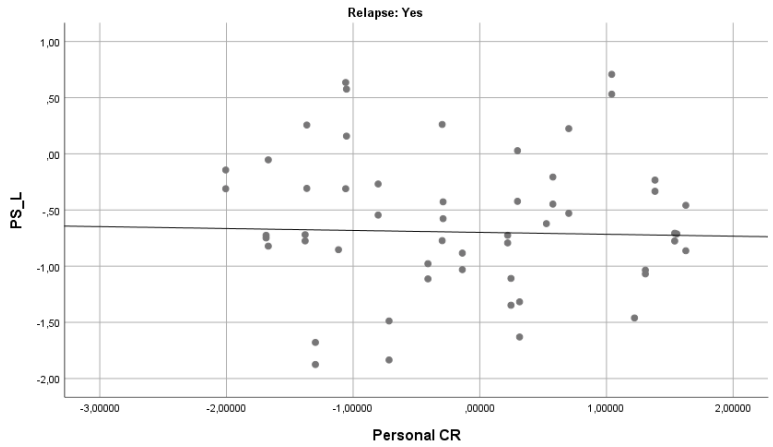
## ATTENTION

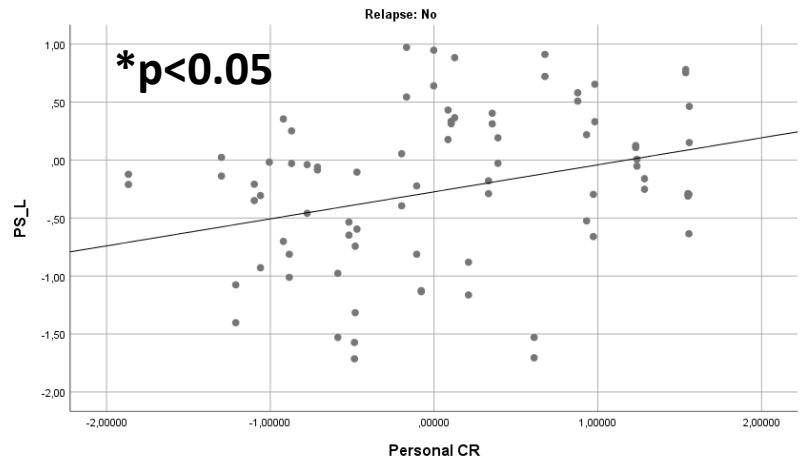



## 2b

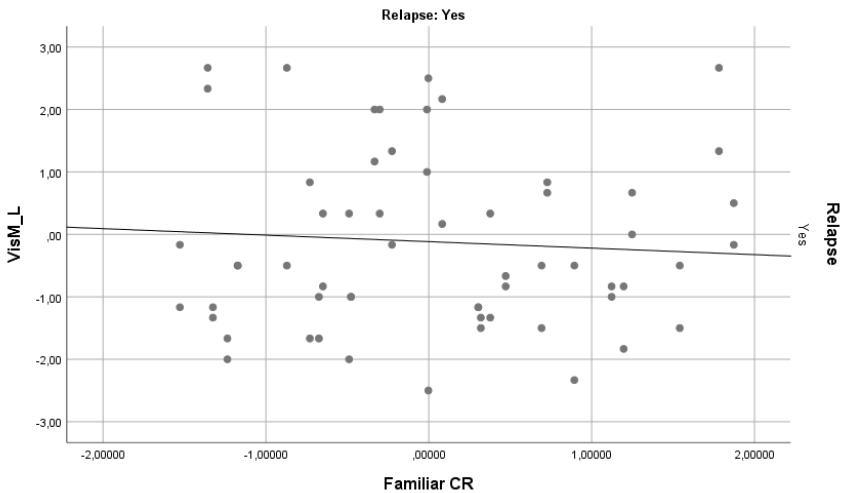
## PROCESSING SPEED

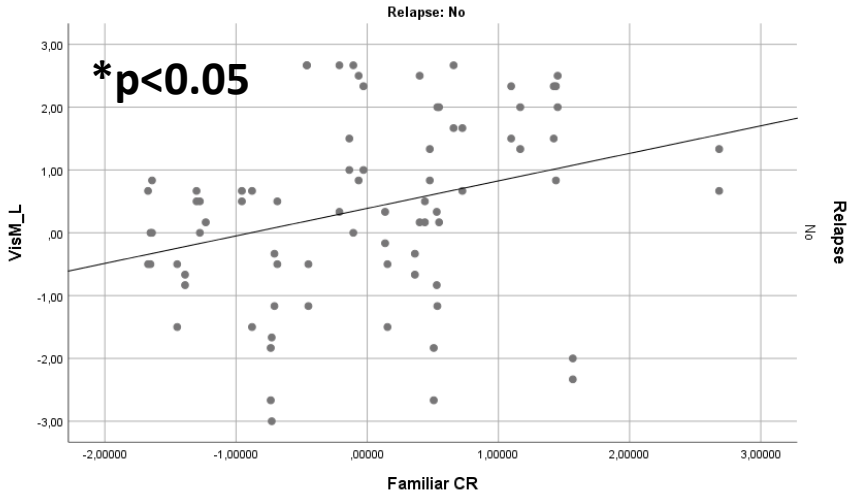


**2c**

# VISUAL MEMORY



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**Contributors**

All authors contributed to data collection. AMST and SA managed and analyzed the clinical data and wrote the first version of the paper; MEG and GM contributed to data analysis and literature searches. MBe coordinated the 2EPs study, and MC coordinated the neurocognition module of the study. All the authors contributed to the final version of the paper.

**Conflicts of interest**

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