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

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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.

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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. (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 χ^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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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 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 Total errors –T score 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* 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 Number of recalled words (delayed) – z score Number of recognised words – z score
Visual memory	Wechsler Memory Scale (Wechsler, 1998), Visual reproduction subtest	Immediate recall score – scale score 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 **Schizophrenia** **Schizophreniform disorder**	33 (62%) 20 (38%)		28 (61%) 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] 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] Follow-up: 3.28 (p=0.07) [a]

a ANOVA (F value)

b Mann-Whitney U (Z value)

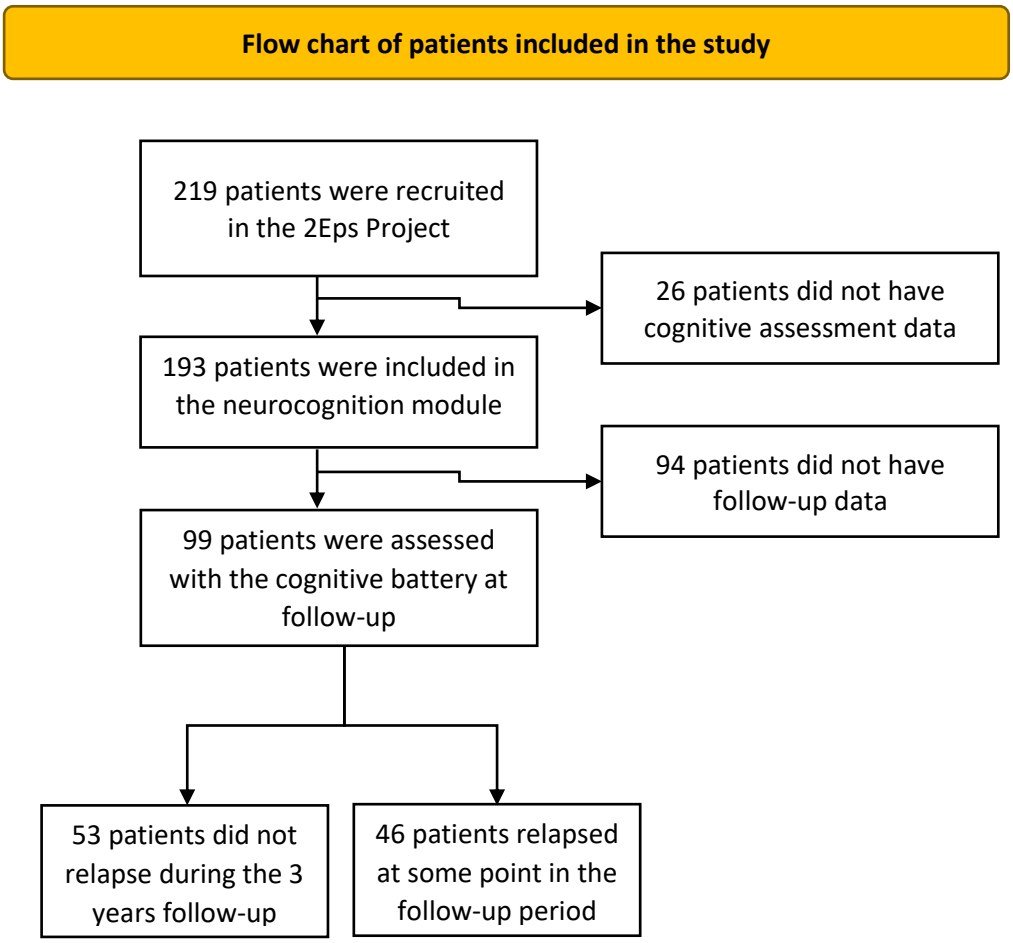
Abbreviations: IQ= Intelligence Quotient; PAS= Premorbid Adjustment Scale; CR= Cognitive Reserve; GAF= Global Assessment of Functioning; FAST=Functioning Assessment Short Test; CPZ= Chlorpromazine equivalents; YMRS= Young Mania Rating Scale; MADRS= Montgomery Åsberg Depression Rating; PANSS= Positive 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)
Click here to access/download;Figure(s);Figure1_ Flow chart.pdf



Figure(s)

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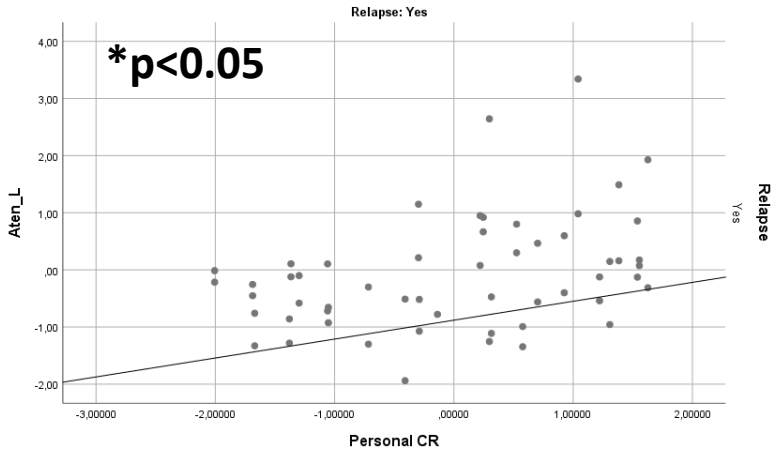
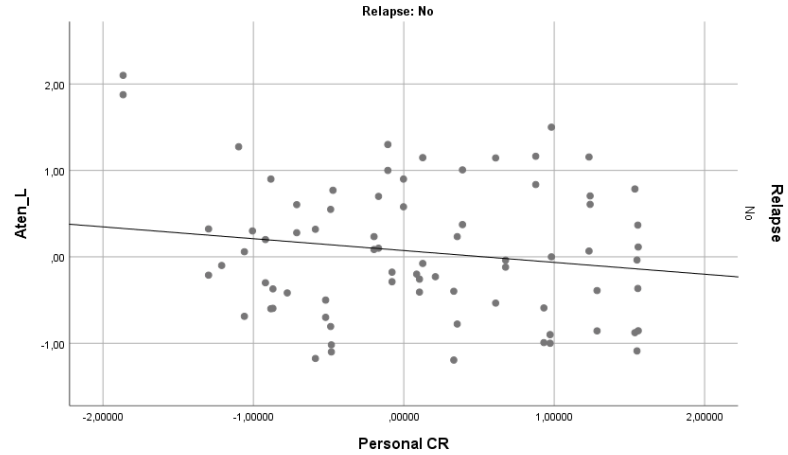
Figure 2

2a

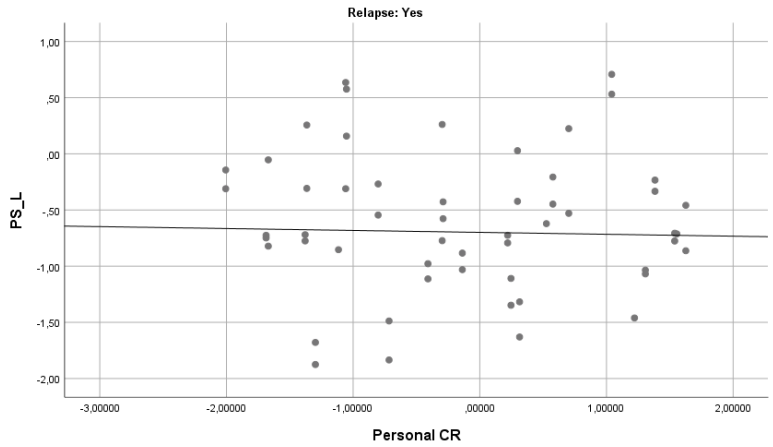
ATTENTION

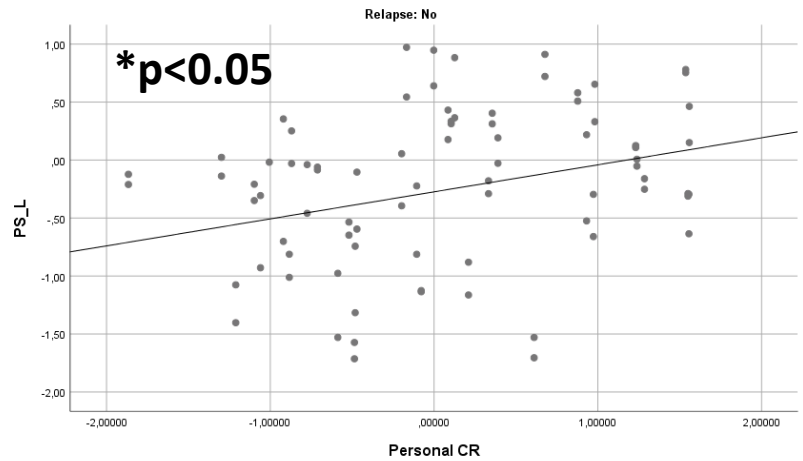




2b

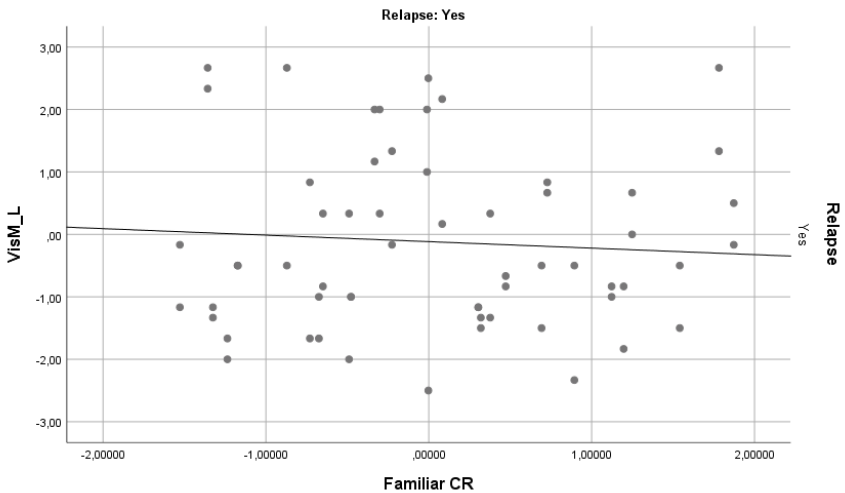
PROCESSING SPEED

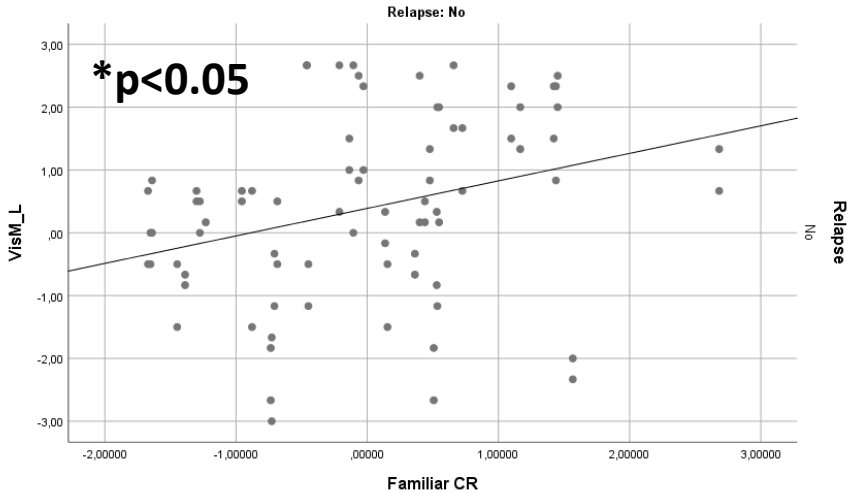




2c

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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