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From Genetics to Psychosocial Functioning: Unraveling the Mediating Roles of Cognitive Reserve, Cognition, and Negative Symptoms in First-Episode Psychosis

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ABSTRACT

Background: Studies have shown associations between polygenic risk scores for educational attainment (PRS_{EA}), cognitive reserve (CR), cognition, negative symptoms (NS), and psychosocial functioning in first-episode psychosis (FEP). However, their specific interactions remain unclear. This study aimed to investigate the mediating roles of CR, cognition, and NS in the relationship between PRS_{EA} and psychosocial functioning one year after a FEP. Additionally, we sought to explore the impact of two NS subtypes on this relationship: diminished Expression (EXP-NS) and Motivation and Pleasure (MAP-NS).

Methods: A total of 138 FEP participants, predominantly male (70%), with a mean age of 24.77 years (SD = 5.29), underwent genetic, clinical, and cognitive assessments two months after study enrollment. Functioning evaluation followed at one-year

Members of PEPs Group are provided in Appendix A.

follow-up. To investigate the mediating role of CR, cognition, and NS in the relationship between PRS_{EA} and functioning, a serial mediation model was employed. Two further mediation models were tested to explore the differential impact of EXP-NS and MAP-NS. Mediation analysis was performed using the PROCESS macro version 4.1 within SPSS version 26.

Results: The serial mediation model revealed a causal chain for PRS_{EA} > CR > cognition > NS > Functioning ($\beta = -3.08$, 95%CI [−5.73, −0.43], $p = 0.023$). When differentiating by type of NS, only EXP-NS were significantly associated in the casual chain ($\beta = -0.17$, 95% CI [−0.39, −0.01], $p < 0.05$).

Conclusions: CR, cognition and NS -specifically EXP-NS- mediate the association between PRS_{EA} and psychosocial functioning at one-year follow-up in FEP patients. These results highlight the potential for personalized interventions based on genetic predisposition.

1 | Introduction

Functional impairment is a common feature of psychotic disorders that poses significant challenges to patients' wellbeing [1]. Difficulties include independent living activities, social and occupational impairment, even from the early stages, such as the first-episode psychosis (FEP). There is considerable variability in functional recovery after a FEP [2], with 60% of patients meeting remission criteria and only 40% achieving full recovery [3]. An extensive body of research has linked various factors to functioning including cognitive reserve (CR) [4], cognitive performance [5–8], negative symptoms (NS) [9–11], and recently, genetics [12].

The exploration of genetics as a factor influencing functioning has gained traction in recent years. Genetic variability-studied using polygenic risk scores (PRS)-is an important variable in FEP prognosis [13]. PRS aggregate the effects of numerous genetic variants across the human genome into a single score that predicts an individual's genetic predisposition to specific traits, phenotypes or even mental disorders [14], surpassing limitations of candidate-gene strategies [12]. Recent studies have demonstrated a clear association between PRSs for schizophrenia (SZ) and a higher risk of developing FEP [15]. Additionally, a positive correlation has been observed between PRS for SZ and severity of symptoms in individuals with FEP [16]. In this context, the PRS for educational attainment (PRS_{EA}) has garnered interest due to its associations with cognition and psychopathology. PRS_{EA} demonstrates an inverse correlation with psychotic symptomatology and a positive correlation with cognitive function within the FEP population. Additionally, is associated with a lower risk and later onset of relapse in early stages of SZ [17]. These findings suggest that PRS_{EA} may possess protective properties and could partly explain the genetic basis underlying CR.

A growing body of research emphasizes the protective role of CR, reflecting the brain's ability to resist neuropathological changes, minimize clinical manifestations, and compensate for cognitive deficits [18]. Individuals with higher CR present a later age of onset, better illness insight [19–22], reduced psychotic symptoms, better functioning and cognitive performance [22–25]. This is important since FEP patients exhibit impairments in verbal memory, attention, processing speed, working memory, executive functioning, and social cognition [26]. These impairments impact everyday functioning [27, 28], underscoring the critical role of cognition in predicting functioning [29, 30].

Closely linked to cognitive impairments are NS, which also play a crucial role in functioning. Greater NS severity is associated with a poorer quality of life, hindered functional recovery, and difficulties adhering to treatment [31]. Traditionally conceptualized as a unitary construct, NS are currently delineated into five domains: alogia, avolition, anhedonia, blunted affect, and asociality. Furthermore, a two-factor structure for NS has been proposed, with alogia and blunted affect forming a "Diminished Expression" factor (NS-EXP), while the remaining constitute a "Motivation and Pleasure" (NS-MAP) domain [32, 33]. Different pathophysiological mechanisms have subtended these two areas [34], leading to different functional outcomes and cognitive profiles [35–38].

While a recent study has highlighted a relationship among the aforementioned factors, with CR and NS mediating the connection between PRS_{EA} and functioning [39], the role of cognition in this relationship remains unanswered. Addressing this gap is crucial given its impact on the disorder [40].

1.1 | Aims of the study

The aim of the present study was to explore the mediating role of CR, cognition, and NS in the relationship between PRS_{EA} and psychosocial functioning in FEP at one-year follow-up. Additionally, we investigated the role of EXP-NS and MAP-NS in this relationship. We hypothesized that PRS_{EA} may be linked to higher CR, which in turn enhances cognitive performance, reduces NS, and therefore increases functioning.

2 | Material and Methods

2.1 | Sample

The sample comes from the "Phenotype-Genotype Interaction: Application of a Predictive Model in First Psychotic Episodes (PEPs study)" [41, 42], a multicenter, naturalistic, and longitudinal study, performed through the Biomedical Research Network Center for Mental Health (CIBERSAM) [43].

The inclusion criteria for the PEPs study were: (1) Aged 7–35 years at baseline evaluation; (2) < 12 months history of psychotic symptoms; (3) fluent Spanish, and (4) provide written informed consent. Exclusion criteria were: (1) Intellectual disability; (2) history of head trauma with loss of consciousness, and (3) organic disease with mental repercussions.

Summary

- Summations
  - Higher PRS_{EA} is linked to increased CR, which enhances cognitive performance and reduces negative symptoms, improving functioning one year after a first episode of psychosis.
  - EXP-NS significantly impacts the pathway from PRS_{EA} to functioning through cognition, suggesting potential avenues for targeted interventions.
  - PRS_{EA} may have protective properties and could partially explain the genetic basis underlying CR.
- Limitations
  - The use of less specialized scales, such as the PANSS for negative symptoms, and the absence of a cognitive reserve scale may limit both the interpretation and generalization of the results.
  - The lack of focus on specific cognitive domains prevents a detailed understanding of the relationships between single cognitive functions and negative symptoms.
  - The follow-up period was relatively brief, which limits its understanding of long-term interactions.

Specifically, 138 patients were included in this study, those who passed genetic quality control (described in Section 2.2.5: blood sampling and genotyping), completed assessments at one-year follow-up, were aged at least 16 years old (considering the age range typically assessed by most evaluation tools), self-reported European ancestry, and diagnosed with non-affective psychotic disorder at one year follow-up. Figure S1 contains the flowchart of the selection process.

For this study, a longitudinal design was employed with data collection at multiple time points. Genetics were collected at study entry. Cognitive, clinical, and cognitive reserve assessments were conducted two months after study enrollment to ensure clinical stability. Functioning was assessed at one-year follow-up.

The Clinical Research Ethics Committee of all participating centers approved the PEPs Project which was conducted following the ethical principles of the Declaration of Helsinki and Good Clinical Practice.

2.2 | Evaluation

2.2.1 | Clinical and Sociodemographics

Sociodemographic, clinical, and pharmacological data were collected. International consensus was used as a guideline for pharmacological treatment [44] and measured using chlorpromazine equivalents (CPZ).

Diagnoses were established using the Structured Clinical Interview for DSM (SCID-I-II) [45, 46] following DSM-IV-TR criteria. To ensure the reliability of diagnostic categories, all diagnostic assessments were finalized at the 1-year follow-up visit. As a result, the study sample was restricted to patients who met the criteria for non-affective psychosis. The Positive and Negative Syndrome Scale (PANSS) [47] was used to assess psychopathology. Higher scores indicate greater symptom severity. The PANSS is one of the most frequently used scales to measure NS severity, but it was not designed to exclusively evaluate them [48]. To account for this limitation, we applied the PANSS-Marder Factor Scores [49]. The total scores of the following items of the PANSS were used to calculate the NS Factor: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity and conversation flow (N6), motor retardation (G7) and active social avoidance (G16). Following previous studies using the PANSS, EXP factor was calculated as the sum of the following items: N1, N3, N6, and G7, and MAP with N2, N4 and G16 [50–52].

2.2.2 | Functional Assessment

The Functioning Assessment Short Test (FAST) [53] was used to evaluate overall functioning. Administered through an interview with both the patient and a caregiver or close associate, the FAST evaluates difficulties experienced. Higher scores indicate greater impairment.

2.2.3 | Cognitive Assessment

An extensive assessment was carried out by neuropsychologists. To assess verbal memory, the Verbal Learning Test Spain Complutense for Adults (TAVEC) [54] was used. Working memory was assessed by the Digit Span Subtest and the Letter-Number Sequencing Subtest of the Wechsler Adult Intelligence Scale-III (WAIS) [55]. Attention was tested with the Continuous Performance Test–II (CPT-II) [56]. Processing speed was assessed with the Trail Making Test- A (TMT-A) [57]. Executive functions were evaluated using the Wisconsin Card Sorting Test (WCST) [58]. Verbal fluency was evaluated using semantic (Animal Naming) [59] and phonemic fluency (F-A-S) tests [60]. Emotional intelligence was evaluated using Managing Emotion's branch from the Mayer-Salovey-Caruso Intelligence Test (MSCEIT) [61]. All cognitive measures were transformed into standardized t-scores using published norms. Principal component analysis (PCA) was used to reduce redundant cognitive measures to different cognitive domains, and to calculate a Global Cognitive Index.

2.2.4 | Cognitive Reserve Assessment

CR was quantified using a proxy, drawing on the findings of a previous study [23]. Based on existing literature highlighting the most used indicators in FEP [20, 22, 23], premorbid intelligence quotient (IQ), educational attainment level, and lifetime participation in leisure, social, and physical activities were used. Estimated premorbid IQ was evaluated with the Vocabulary subtest of the WAIS-III as a measure reflecting crystallized intelligence. Education was assessed considering the number of years of obligatory education completed as well

as parents' educational level, and lifetime school performance, assessed by the Premorbid Adjustment Scale (PAS) scholastic performance subdomain [62]. Finally, participation in leisure, social and physical activities was assessed by the FAST. This instrument allows us to assess specific life-domains such as interpersonal relationships and leisure time. For each participant, a CR Score was created via a PCA. Higher scores indicate better performance.

2.2.5 | Blood Samples and Genotyping

For blood sample collection, K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey) were used. They were subsequently stored at −20°C prior for shipment to the central laboratory for further analysis. The MagNA Pure LC DNA isolation kit—large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany) supported DNA extraction and DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware). 2.5 μg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

2.2.6 | PRS Calculation

Genotyping data were submitted to the Michigan Imputation Server [63], following the standard pipeline for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.12016 and Eagle v2.4 phasing.

GWAS summary results from the Social Science Genetic Association Consortium were obtained for the PRS calculation. Based on a previous study that we conducted [15] we selected the PRS_{EA} (1,131,881 individuals) [64], which considers the total number of completed years of schooling. Higher scores reflect a genetic liability for higher educational attainment. Duplicated and unknown strand GWAS summary single-nucleotide polymorphisms (SNPs) were excluded.

Quality control was performed with PLINK v1.07 [65]. Inclusion criteria for SNPs were minor allele frequency > 0.01, Hardy–Weinberg equilibrium $p > 10^{-6}$, marker missingness < 0.01 and imputation INFO > 0.8. Pruning was done using a window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate of < 0.01, matching chromosomal and database-labeled sex and relatedness π-hat < 0.125.

The PRS were constructed using PRS-CS, a method that implements a high-dimensional Bayesian regression to perform a continuous shrinkage of SNP effect sizes using GWAS summary statistics and an external linkage disequilibrium (LD) reference panel [66]. The LD reference panel was constructed using a European subsample of the UK Biobank [67]. For the remaining parameters, the default options as implemented in PRS-CS were adopted.

2.3 | Statistical Analysis

To circumvent redundant information of separate testing of cognitive variables and decrease measures to principal domains, a PCA was carried out. The neurocognitive assessment was represented by five factor scores (executive functions, sustained attention, verbal memory, working memory and verbal fluency) (Table S1) as well as processing speed, and emotional intelligence. Subsequently, another PCA was performed on the aforementioned cognitive domains to extract a Global Cognitive Index, resulting in a singular overall cognitive score.

The normality of continuous variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Before testing the mediation hypothesis, we tested the relationship between mediators and the outcome variable using Pearson's correlation coefficient. Mediation analysis was performed to test whether the effect of the causal variable (PRS_{EA}) on an outcome variable (FAST) is affected at one-year follow-up by one or more mediator variables (CR, cognitive performance and NS, MAP-NS, and EXP-NS)—assessed at two months after study enrollment. The relationship between variables is described by 3 possible effects: [1] Total effect (c), the association between causal variable and outcome variable; [2] Direct effect (c'), the effect of the causal variable on the outcome variable, when controlling for the mediator variables; and [3] Indirect effect, the effect of the causal variable on the outcome variable via the mediator variable. A serial mediation model was explored. This model tested a causal chain of the three mediators: CR, cognition and NS. Based on clinical evidence, we propose that PRS_{EA} may be linked to higher CR, which enhances cognitive performance, reduces NS and therefore increases functioning (PRSEA > CR > cognition > NS > Functioning) [17, 39, 68, 69]. For each model, we obtained total effect, direct effect, and total indirect effect of all mediator variables, as well as the indirect effect of each individual mediator or serial path.

The statistical significance of the indirect effect was tested with a nonparametric bootstrapping approach (5000 iterations) to obtain 95% confidence intervals. In these analyses, mediation is considered significant if the 95% bias corrected for the indirect effect does not include 0.

Analysis was performed using the PROCESS function V.4.1 in SPSS V.26. Model 6 was used. Model fit statistics were also reported using the following: a Comparative Fit Index (CFI) (satisfactory > 0.90), a Root Mean Square Error of Approximation (RMSEA) (satisfactory < 0.05), and a Standardized Root Mean Square Residual (SRMR) (satisfactory < 0.08) [70]. The fit indices were derived using the R package lavaan [71].

3 | Results

3.1 | Description of the Sample

Table 1 shows the characteristics of the sample, 70% male, with a mean age of 24.77 years (SD = 5.29). The mean score on the FAST scale was 19.37 and SD = 15.28. This score indicates some difficulty in social, occupational, or school functioning.

TABLE 1 | Main sociodemographic, functional and clinical features of the FEP sample ($N = 138$).

Sociodemographic variables (Mean ± SD or *n* (%)) [min-max]	
Sex (male/female)	96 (69.6)/42 (30.4)
Age (years)	24.77 ± 5.29[17–36]
Age at onset (years)	24.88 ± 5.25 [16–36]
Educational level	
No education	1 (0.7)
Primary education	25 (18.1)
Lower secondary education	52 (37.7)
Upper secondary and non-tertiary education	34 (24.6)
University	25 (18.1)
Others	1 (0.7)
Sociodemographic variables at 2 months (Mean ± SD or *n* (%)) [min-max]	
Chlorpromazine equivalents	421.48 ± 346.12 [0–2100]
No current antipsychotic treatment	17 (12)
Cannabis (yes)	30 (21)
Tobacco (yes)	99 (72)
Clinical and functional variables at 2 months (Mean ± SD)	
Cognitive reserve	75.76 ± 11.63 [52–112]
Global cognitive index	252.00 ± 84.31 [33–412]
Negative Marder PANSS Factor	16.52 ± 7.12 [7–35]
Clinical and functional variables at one-year follow-up (Mean ± SD)	
Negative Marder PANSS Factor	14.46 ± 6.60 [7–36]
Functioning (FAST)	19.37 ± 15.28 [0–72]
Diagnoses at one-year follow up (*n* (%))	
Schizophrenia	60 (43.5)
Psychotic disorder not specified	35 (25.4)
Brief psychotic disorder	19 (13.8)
Substance-induced psychosis	9 (6.5)
Schizoaffective disorder	9 (6.5)
Schizophreniform disorder	6 (4.3)

Abbreviations: FAST = Functioning Assessment Short Test; PANSS = Positive and Negative Syndrome Scale.

3.2 | Mediation Analyses

Before testing the mediation hypothesis, we tested the relationship between mediators and the outcome variable using Pearson's correlation coefficient. Functioning was negatively correlated with PRS_{EA} ($r = -0.20$, $p = 0.011$), CR ($r = -0.22$, $p = 0.004$), and cognition ($r = -0.28$, $p = 0.001$), and positively correlated with NS ($r = 0.56$, $p < 0.001$). Additionally, when analyzing EXP-NS and MAP-NS, their association with functioning were also significant: EXP-NS ($r = 0.48$, $p < 0.001$) and MAP-NS ($r = 0.52$, $p < 0.001$). As these correlations were significant, the conditions required to perform mediation analysis were fulfilled.

The serial mediation model hypothesizes a causal chain linking the three mediators in a specified order and direction flow. We proposed that PRS_{EA} may be linked to higher CR, which is associated with higher cognitive performance, reduces NS and, therefore, increases functioning (Figure 1). The total effect of PRS_{EA} on functioning was significant ($\beta = -3.08$, 95%CI [−5.73, −0.43], $p = 0.023$), whereas the direct effect and the total indirect effect were not (Table 2). Among the seven paths that could be inferred from the model, only the one including CR, cognition and NS was significant according to 5000 bootstrapped samples. Fitting indices indicated that the model fits the data satisfactorily (CFI = 1.00; RMSEA = 0.00; SRMR = 5.85×10^{-17}).

As shown in Table 3, by differentiating NS, we found that only the pathway involving CR, cognition, and EXP-NS as mediators showed significance. Specifically, the indirect effect of PRS_{EA} > CR > cognition > EXP-NS > Functioning was significant ($\beta = -0.17$, 95% CI [−0.39, −0.01], $p < 0.05$), suggesting that the influence of PRS_{EA} on functioning operates through this sequence of mediators (Figure 2). Specifically, PRS_{EA} showed a significant direct effect on CR ($\beta = 0.22$, $p = 0.018$). Additionally, CR predicted cognition ($\beta = 0.42$, $p < 0.001$), which in turn influenced EXP-NS factor with a negative coefficient ($\beta = -0.27$, $p = 0.014$). Ultimately, EXP-NS had a strong direct effect on functional impairment ($\beta = 0.46$, $p < 0.001$). Fitting indices indicated that the model fits the data satisfactorily (CFI = 1.00; RMSEA = 0.00; SRMR = 3.09 × 10 − 17). When exploring MAP-NS, none of the specific paths tested for mediation demonstrated significant indirect effects, indicating that the influence of PRS_{EA} on functioning via these pathways was not supported. The MAP-NS model, while also indicating some significant associations, did not demonstrate predictive power for cognition. In this model, PRS_{EA} was significantly associated with CR ($\beta = 0.22$, $p = 0.018$), and CR with cognition ($\beta = 0.42$, $p < 0.001$). However, neither PRS_{EA}, CR, nor cognition significantly predicted MAP-NS. The direct effect of MAP-NS on FAST was significant ($\beta = 0.59$, $p < 0.001$), but the pathway involving cognition did not reach significance (Table 4). Thus, while the total effect of PRS_{EA} on functioning was significant in both cases and the results demonstrate that both EXP-NS and MAP-NS impact functional outcomes, the specific indirect pathways varied in their significance, underscoring the nuanced role of different NS types in this relationship.

4 | Discussion

Our study provides important insights into the complex relationships between PRS_{EA}, CR, cognition, NS and its factors MAP-NS and EXP-NS, and functioning after one year of presenting a FEP.

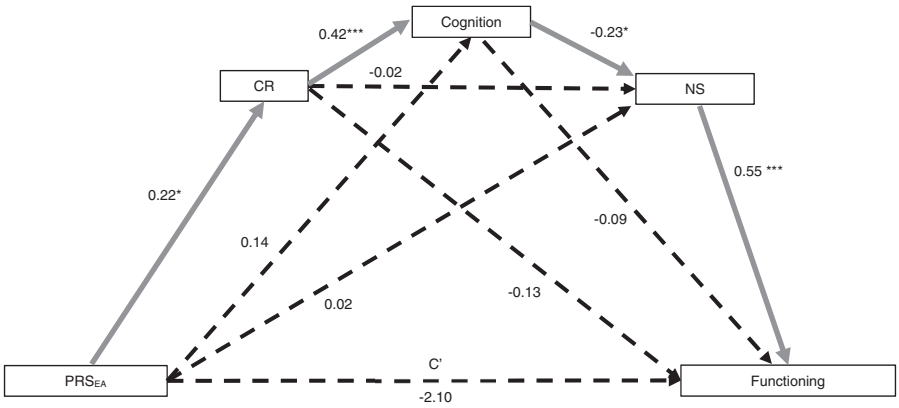

FIGURE 1 | The serial mediating effect of cognitive reserve, cognition and negative symptoms in the relationship between PRS_{EA} and functioning. All presented effects are standardized. C′ is the unstandardized direct effect coefficient of PRS_{EA} on functionality. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Grey lines represent path with significant indirect effect. Continuous lines denoted significant regression. Abbreviations: CR = Cognitive Reserve; NS=Negative Symptoms; PRS_{EA} = Polygenic risk score for educational attainment.

TABLE 2 | Non-standardized total, direct and indirect effects (total and of each individual mediator or path) of the mediation model using Marder PANSS negative factor score.

	β	[95% CI]	*p*
Total effect	−3.08	[−5.73, −0.43]	**0.023**
Direct effect	−2.10	[−4.29, 0.08]	0.059
Total indirect effect	−0.98	[−2.78, 0.90]	> 0.05
PRS_{EA} > CR > Functioning	−0.41	[−1.12, 0.06]	> 0.05
PRS_{EA} > GCog > Functioning	−0.18	[−0.73, 0.15]	> 0.05
PRS_{EA} > NS > Functioning	0.18	[−1.42, 1.84]	> 0.05
PRS_{EA} > CR > GCog > Functioning	−0.12	[−0.41, 0.10]	> 0.05
PRS_{EA} > CR > NS > Functioning	−0.03	[−0.50, 0.34]	> 0.05
PRS_{EA} > GCog > NS > Functioning	−0.26	[−0.70, 0.07]	> 0.05
PRS_{EA} > CR > GCog > NS > Functioning	−0.17	[−0.41, −0.004]	**< 0.05**

Note: Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CI = Confidence interval; CR = Cognitive Reserve; GCog = Global Cognitive Index; NS = Negative Symptoms; PRS_{EA} = polygenic risk score for educational attainment.

Two notable findings were observed. First, a significant mediation path through PRS_{EA} > CR > cognition > NS > functioning was found. This indicates that higher PRS_{EA} is associated with increased CR, which is associated with higher cognitive performance, leading to a reduction in NS, ultimately resulting in better functioning one year after a FEP. Second, our study underscores the importance of considering different NS. Notably, EXP-NS significantly influences the PRS_{EA} > CR > cognition > EXP-NS > functioning chain, while MAP-NS did not. This sheds light on several key processes that will be discussed in detail step-by-step. It traces the path from PRS_{EA}, to CR, then to cognition, followed by NS, and ultimately impacting functioning.

Firstly, PRS_{EA} has emerged as a promising avenue for investigating the genetic basis of CR [39], supported by the well-established association between education and CR. The concept of CR has long been recognized as involving a complex interplay of genetic and socio environmental factors [18]. Among these, IQ, education, occupation, leisure activities, and social interaction have received the most attention, probably due to the ease of quantifying them through socio-behavioral proxies [4, 72]. However, recent research has broadened the scope of inquiry by incorporating the role of PRS in understanding the genetic underpinnings of CR. In this context, a recent study identified CR and NS as mediators of the relationship between PRS_{EA} and functioning, indicating CR's potential genetic component [39]. Nonetheless, the specific role of cognition within this interplay remained to be elucidated.

Secondly, a substantial body of research has investigated the role of CR in cognition, focusing on early and chronic phases of psychosis. Studies involving FEP have consistently shown that individuals with higher CR exhibit superior performance across most cognitive domains compared to those with lower CR [22–25]. In the context of SZ, higher levels of CR are associated with a lower risk of developing the illness, a delayed disease onset, and better cognitive performance [73, 74]. Furthermore, the impact of cognition extends beyond cognitive performance, influencing relapse rates, hospitalization duration, social and

TABLE 3 | Non-standardized total, direct and indirect effects (total and of each individual mediator or path) of the mediation model using Expressivity/Diminished expression factor.

	β	[95% CI]	*p*
Total effect	−3.08	[−5.73, −0.43]	**0.023**
Direct effect	−2.22	[−4.56, 0.12]	0.062
Total indirect effect	−0.86	[−2.48, 0.77]	> 0.05
PRS_{EA} > CR > Functioning	−0.46	[−1.24, 0.05]	> 0.05
PRS_{EA} > GCog > Functioning	−0.19	[−0.88, 0.18]	> 0.05
PRS_{EA} > EXP > Functioning	0.30	[−1.02, 1.67]	> 0.05
PRS_{EA} > CR > GCog > Functioning	−0.13	[−0.46, 0.13]	> 0.05
PRS_{EA} > CR > EXP > Functioning	0.02	[−0.35, 0.36]	> 0.05
PRS_{EA} > GCog > EXP > Functioning	−0.25	[−0.65, 0.08]	> 0.05
PRS_{EA} > CR > GCog > EXP > Functioning	−0.17	[−0.39, −0.01]	**< 0.05**

Note: Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CI = Confidence interval; CR = Cognitive Reserve; GCog = Global Cognitive Index; EXP = Expressivity/Diminished expression; PRS_{EA} = polygenic risk score for educational attainment.

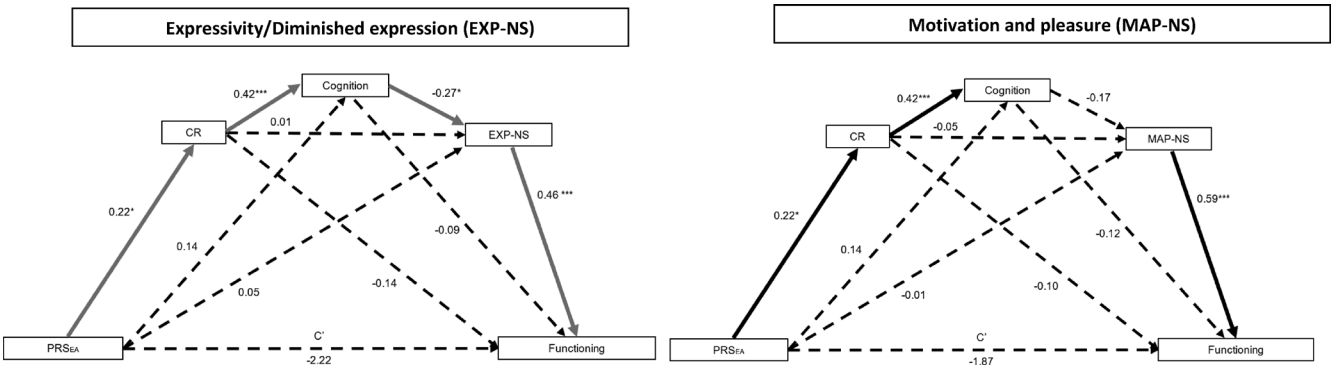

FIGURE 2 | The serial mediating effect of cognitive reserve, cognition and negative symptoms (EXP-NS and MAP-NS) in the relationship between PRS_{EA} and functioning. All presented effects are standardized. C′ is the unstandardized direct effect coefficient of PRS_{EA} on functionality. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Grey lines represent path with significant indirect effect. Continuous lines denoted significant regression. Abbreviations: CR = Cognitive Reserve; PRS_{EA} = Polygenic risk score for educational attainment.

TABLE 4 | Non-standardized total, direct and indirect effects (total and of each individual mediator or path) of the mediation model using Motivation and pleasure factor.

	β	[95% CI]	*p*
Total effect	−3.08	[−5.73, −0.43]	**0.023**
Direct effect	−1.87	[−3.97, 0.23]	0.081
Total indirect effect	−1.22	[−3.02, 0.77]	> 0.05
PRS_{EA} > CR > Functioning	−0.34	[−0.95, 0.13]	> 0.05
PRS_{EA} > GCog > Functioning	−0.24	[−0.79, 0.11]	> 0.05
PRS_{EA} > MAP > Functioning	−0.06	[−1.79, 1.78]	> 0.05
PRS_{EA} > CR > GCog > Functioning	−0.16	[−0.48, 0.04]	> 0.05
PRS_{EA} > CR > MAP > Functioning	−0.10	[−0.68, 0.31]	> 0.05
PRS_{EA} > GCog > MAP > Functioning	−0.19	[−0.68, 0.08]	> 0.05
PRS_{EA} > CR > GCog > MAP > Functioning	−0.13	[−0.36, 0.05]	> 0.05

Note: Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CI = Confidence interval; CR = Cognitive Reserve; GCog = Global Cognitive Index; MAP = Motivation and pleasure; PRS_{EA} = polygenic risk score for educational attainment.

vocational functioning, treatment resistance, and symptom severity [31].

Thirdly, although cognition and NS are clearly interrelated [75–77], disentangling the precise relationship between them remains a challenge. A recent systematic review demonstrates that NS are differentially associated with various cognitive domains in FEP [31]. Considering that existing research suggests clinically significant distinctions in the presentation of NS dimensions [78], we consider both EXP-NS and MAP-NS. Our results indicate that these two components differentially relate to cognition, where EXP shows a significant association, but MAP does not. This finding aligns with existing literature, which demonstrates that MAP-NS is strongly correlated with deficits in different aspects of motivation, goal-directed actions, and executive functioning, while EXP-NS is associated with general social and non-social cognitive impairments [79–81].

Fourth, our model shows robust associations between NS and daily functioning, consistent with research in high-risk populations [82], FEP [69, 83] and SZ [84]. This association extends to both overall NS and EXP-NS and MAP-NS domains. Interestingly, our findings and existing literature converge to suggest that MAP-NS domain is associated with more pronounced impairment in functioning than the EXP-NS domain [38, 85, 86].

Our findings hold significant implications for clinical practice. Firstly, they contribute to the development of a clinical framework for precision psychiatry. Our findings suggest that current treatments aimed at enhancing CR and cognitive performance may mitigate NS and improve functional outcomes. Considering the two proposed models can further refine intervention strategies: the EXP-NS model highlights the importance of cognitive function in NS related to expressivity, so interventions that improve cognitive function could potentially reduce them and improve overall outcomes. Conversely, the MAP-NS model suggests that NS related to motivation and pleasure directly impact functional outcomes, with less influence from cognitive factors. This implies that these symptoms might require alternative therapeutic approaches that directly target motivation and engagement, rather than focusing solely on cognitive improvement.

Although this study offers valuable data, some limitations should be mentioned. Firstly, the PANSS scale is considered outdated for assessing NS compared to scales like the Brief Negative Symptom Scale (BNSS) [87, 88]. However, we addressed this limitation by employing the Marder Factor Scores, which provided a more nuanced evaluation of NS [48]. Similarly, at the time of data collection, no validated tool to assess CR in people with serious mental illness existed. Fortunately, the field has seen the development of the Cognitive Reserve Assessment Scale in Health (CRASH) (73)for adults and the Cognitive Reserve Questionnaire for Adolescents (CoRe-A) [89]. Another limitation is the use of a Global Cognitive Index. While this index incorporates different measures, it doesn't allow for a deeper exploration of how each specific domain relates to NS. While valuable as a starting point, future research should address this limitation by focusing on specific cognitive domains. An aspect worth to mention is that, although a minority of patients in our sample received high doses of antipsychotics, a previous pharmacovigilance study conducted within this same FEP cohort demonstrated that 87.2% of patients were prescribed antipsychotic doses within guideline-recommended ranges [90]. Given the naturalistic design of our study and the characteristics of the cohort, some prescriptions exceeded standard dosing recommendations. Nevertheless, these data provide a representative view of real-world clinical prescription practices for FEP patients in a national context. While the follow-up period was relatively brief, limiting the depth of our understanding of long-term interactions, this shorter timeframe was intentionally chosen to minimize participant attrition. Finally, future research should explore the interplay between genetics, CR, cognition, NS, and functioning with other factors such as duration of untreated psychosis (DUP) [91], cannabis use [92], age of onset [93], and antipsychotic choice [94], among others, because of their impact on cognitive performance and functional outcomes in patients experiencing a FEP. These variables may offer valuable insights into the heterogeneity of the disorder and inform personalized treatment strategies. Despite these limitations, the study presents some noteworthy strengths. Firstly, it investigated one of the largest and well-defined samples of FEP patients in Spain, resulting in reliable data that can be applied to a wider population. Additionally, the PRS calculations leveraged the most comprehensive GWAS datasets. This enhanced the capture of genetic variants relevant to the investigated phenotypes. Furthermore, the use of PRS-CS method for PRS calculation overcomes the limitation of arbitrary SNP p-value thresholding by refining the estimated effect of each loci.

5 | Conclusion

The mediation path $PRS_{EA} > CR > cognition > NS > functioning$ delineates a clear sequence through which genetic predisposition for educational attainment can enhance CR, thereby improving cognitive performance, reducing NS, and ultimately leading to better functional outcomes. By differentiating between NS, targeting EXP-NS through interventions aimed at improving cognitive function may be a valuable approach for early intervention to improve functioning in FEP patients.

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Ethics Statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflicts of Interest

E. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda. M. Garriga has received support from Ferrer, Janssen and Lundbeck. G. Mezquida has received support from Boehringer Ingelheim. Dr. Gonzalez-Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Alter, Angelini, Novartis, Rovi, Takeda, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, and the European Framework Program of Research. Dr. R. Rodriguez-Jimenez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de InvestigaciónBiomédicaen Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/BMD-2422 AGES; S2017/BMD-3740; S2022/BMD-7216), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini, Rovi. MPGP has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. FDS has received grants from the Spanish Foundation of Psychiatry and Mental Health and the European Psychiatric Association. C. Diaz-Caneja has received funding from Instituto de Salud Carlos III (PI17/00481, PI20/00721, PI23/00625) and the European Union (Grant No. 101057182, project Youth-GEMs) and honoraria or travel support to attend conferences from Angelini, Janssen, and Viatris. R. Rodriguez-Jimenez has received funding from Madrid Regional Government (S2022/BMD-7216). A. Roldán has served as advisor or speaker for the companies Otsuka, Rovi, Angelini and Casen Recordati (unrelated to the present work). A. Mané has received financial support to attend meetings, travel support, and served as a speaker/advisory board from Otsuka, Lundbeck, Angelini, Neuraxpharm and Janssen Cilag. The rest of the authors report no biomedical financial interests or potential conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13779.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix A

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