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ORIGINAL ARTICLE

A family study on first episode of psychosis patients: Exploring neuropsychological performance as an endophenotype

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Abstract

Introduction: Family studies provide a suitable approach to analyzing candidate endophenotypes of schizophrenia, including cognitive features.

Objective: To characterize different neurocognitive functions in a group of patients with first episode of psychosis (FEP), their first-degree relatives (parents and siblings), and healthy controls (HC), in order to identify potential endophenotypes for schizophrenia spectrum disorders (SSD).

Methods: Participants were assessed in the context of a national project in Spain called PAFIP-FAMILIAS. They completed the same neuropsychological battery, which included tests of verbal memory, visual memory, processing speed, working memory, executive functions, motor dexterity, attention, and theory of mind. Group comparisons were performed using one-way ANOVA, followed by tests of multiple comparisons when appropriate.

Results: One hundred thirty-three FEP patients were included, as well as 244 of their first-degree relatives (146 parents and 98 siblings) and 202 HC. In general, relatives showed an intermediate performance between the HC and the FEP patients in all neurocognitive domains. However, the domains of executive functions and attention stood out, as relatives (especially parents) showed similar performance to FEP patients. This was replicated when selecting patients subsequently diagnosed with schizophrenia and their relatives.

Conclusion: These findings suggest that executive and attention dysfunctions might have a family aggregation and could be relevant cognitive endophenotypes for psychotic disorders. The study shows the potential of exploring intra-family neuropsychological performance supporting neurobiological and genetic research in SSD.

Nancy Murillo-García and Alexandre Díaz-Pons first-shared authorship.

KEYWORDS
cognition, endophenotypes, psychotic disorders, relatives, schizophrenia spectrum disorders

1 | INTRODUCTION

Schizophrenia is a highly heritable disorder[1] with a lifetime morbidity rate of 0.5–1.0%.[2] Its etiology remains unknown, but it is suspected that interactions between genetic features and environmental stressors might cause onset variability between patients.[3] Family studies are a convenient approach in disentangling the heterogeneity among schizophrenia spectrum disorders (SSD) since they provide the opportunity to investigate the genetic and environmental factors potentially related to the disease.[4] Furthermore, designs including unaffected relatives allow for the investigation of possible endophenotypes, and as such, are a powerful neurobiological platform to better understand the underlying neurobiological mechanisms of the disorder.

It is widely demonstrated that patients present neurocognitive impairments following a first episode of psychosis (FEP), performing on average one standard deviation below the general population in neuropsychological tests.[5] This dysfunction is global and affects different functions including attention, working memory, verbal learning, visual learning, processing speed, reasoning, and social cognition.[6] Evidence has shown that these cognitive deficits influence the individual's functionality.[7] Likewise, cognitive functioning in patients with SSD is associated with different long-term outcomes, including the severity and remission of symptoms, and independence in activities of daily living.[8,9] Previous family studies have shown that healthy first-degree relatives of FEP patients present slight cognitive deficits halfway between the proband and healthy controls (HC)[10-14]; and this phenotypic similarity among family members may be explained in part by a hereditary component. It has been estimated that genetic factors account for between 33% and 64% for working memory,[15,16] 42% for intelligence quotient (IQ),[17] and 56% for sustained attention.[16] Hence, through the neuropsychological assessment of unaffected relatives of patients with psychosis, we could identify the cognitive domains with higher familial aggregation and propose them as potential endophenotypes for the disorder.[18] Intermediate phenotypes or endophenotypes are observable and quantifiable traits considered manifestations of a disorder that must meet the following criteria: (a) be associated with illness in the population, (b) be heritable, (c) be primarily state-independent, (d) be co-segregated within families along with the disease, (e) be found in affected family members and unaffected family members at a higher rate than in the general population.[19]

Significant outcomes

- FEP patients performed the lowest of all groups in all cognitive domains.
- First-degree healthy relatives had an intermediate performance between FEP patients and healthy controls in almost all neuropsychological measures.
- The subgroup of relatives showed deficits in executive functions and attention, similar to those of affected individuals. Executive function and attention appear to be the best suitable candidates from the assessed variables to establish cognitive endophenotypes for schizophrenia.

Limitations

- Due to its lack of diversity, the present study may be affected by its sample selection, limiting the generalizability of its findings to other racial and/or ethnic groups.
- Cross-sectional designs, as the one in the present study, do not provide information on the longitudinal cognitive course of the participants.
- The possible influence of aging on cognitive outcomes, despite age covariation, cannot be completely ruled out.

Diverse neurocognitive functions are being explored as candidate endophenotypes for psychosis using family designs. Among the most promising candidates are IQ,[20,21] executive functions,[22,23] attention,[24,25] working memory,[10] and processing speed.[11,26] On the contrary, recent studies found that social cognition was impaired only in patients with SSD, but not in their relatives, suggesting that this deficit is more related to pathophysiological processes of the disease than family aggregation.[12,27] Consequently, more research focused on specific cognitive functions associated with the risk for psychosis is needed. Zhang et al.[13] found that the degree of cognitive impairment among family members differs depending on the genetic risk for schizophrenia, wherein families with greater genetic liability showed more severe neuropsychological deficits. Thus, relatives of FEP patients that subsequently developed schizophrenia may have worse neurocognitive performance than individuals at risk for other psychotic disorder, as shown in tasks of executive function and processing speed.[28]

1.1 | Aims of the study

The present study aimed to characterize different neurocognitive functions in a group of FEP patients, their first-degree unaffected relatives (parents and siblings), and a group of HC, in order to identify potential endophenotypes for SSD. Based on previous evidence, we hypothesized that the group of relatives would show an intermediate cognitive performance between FEP patients and HC in several domains, therefore providing evidence for their value as observable markers of the disease. Unlike some previous family studies, this project aimed to compare the suitability of different cognitive functions, for what eight specific cognitive domains were assessed among participants. Furthermore, to explore the possible effect of diagnosis, a secondary analysis was carried out with patients subsequently diagnosed with schizophrenia and their relatives. Finally, we hoped to offer more statistical power to previous findings by studying a large sample of families at risk of psychosis.

2 | METHODS

2.1 | Setting

This study includes three groups of participants: FEP patients, their first-degree relatives, and a subset of HC. The individuals with FEP were recruited from a large epidemiological program for initial phases of psychosis, named PAFIP, at the University Hospital Marqués de Valdecilla (Cantabria, Spain), from 2001 to 2018.[29,30] In addition to being an epidemiological project, this was an intervention program for both inpatients and outpatients with FEP, who received multidisciplinary treatment from psychiatric nursing, psychiatry, psychology, and social work during a 3-year follow-up period. FEP patients were referred from the inpatient unit, outreach mental health services, and healthcare centers in the region of Cantabria. Since PAFIP was the only mental healthcare service specialized in FEP at that time in Cantabria, its participants could be considered an epidemiological representation of the population in this community. Out of the 668 FEP patients that were enrolled in PAFIP, 387 had completed the baseline cognitive evaluation. Therefore, their first-degree relatives were eligible for participating in a family-based study called PAFIP-FAMILIAS (FIS PI17/00221). In the context of this second project, between January 2018 and March 2021, the parents and siblings of the aforementioned patients (see Figure 1) were contacted by phone and invited to complete the same neuropsychological assessment as the probands. A total of 244 relatives, members of 133 families, participated in the study. Finally,

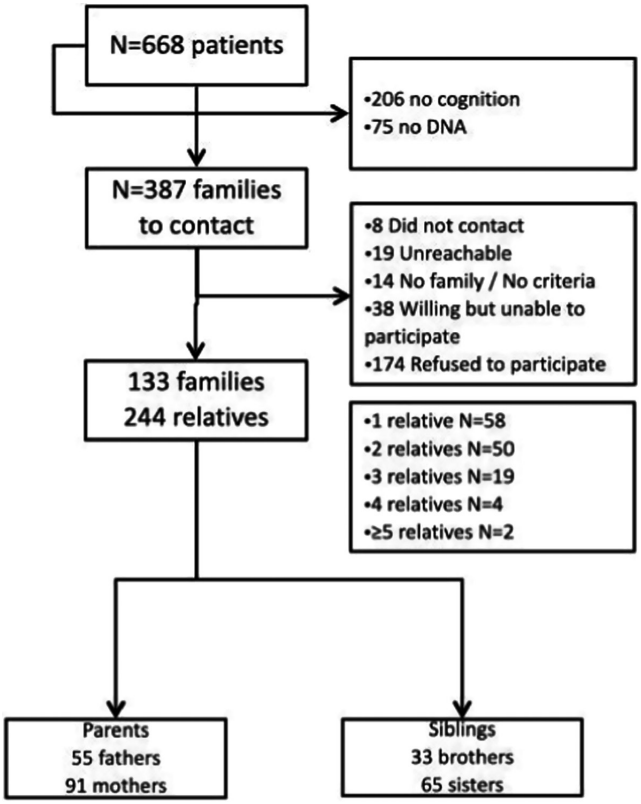

FIGURE 1 Flow diagram for patients and their first-degree relatives enrolled in the PAFIP-FAMILIAS project

data obtained on a group of 202 HC from the PAFIP project, who were recruited through advertisements from the local community between 2001 and 2018, were used for comparison.

2.2 | Ethics

Both the PAFIP and PAFIP-FAMILIAS projects were approved by the local institutional review committee (CEIm Cantabria) in accordance with international research ethics standards (approval numbers NCT0235832 and 2017.247). All participants were informed about the objectives of the study and gave their written consent. The PAFIP-FAMILIAS project allocated an economic compensation of 50€ to the relatives for covering expenses derived from the trip and the time in our neuropsychology laboratory.

2.3 | Inclusion criteria

First episode of psychosis patients enrolled in the PAFIP study met the following inclusion criteria: (1) 15–60 years of age; (2) lived within the catchment area; (3) experiencing a FEP; (4) no prior treatment with antipsychotic

medication or, if previously treated, a total lifetime of antipsychotic treatment of <6 weeks; and (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or not otherwise specified (NOS) psychosis.[31] Exclusion criteria included meeting the DSM-IV criteria for drug or alcohol dependence, having an intellectual disability, having a history of neurological disease, or head injury. The diagnoses were confirmed through the use of the Structured Clinical Interview for DSM-IV (SCID-I) conducted by an experienced psychiatrist within 6 months of the baseline visit.

For the groups of relatives and HC, the inclusion criteria were as follows: (1) age over 15 years, (2) good domain of the Spanish language, and (3) ability to give informed consent in writing. Exclusion criteria included an absence of history of psychiatric diagnosis related to psychotic illness spectrum, absence of organic brain pathology, and an absence of intellectual disability or substance use disorders according to DSM-V criteria.

2.4 | Sociodemographic and clinical assessment

For all the participants, sociodemographic information regarding sex, age, and educational attainment (estimated by years of education completed) was recorded through interviews. Additional premorbid information for FEP patients was obtained via medical records and interviews at baseline, including the age at psychosis onset (defined as the age when the emergence of the first continuous psychotic symptom occurred); duration of untreated illness (DUI, defined as the time from the first nonspecific symptom related to psychosis); and duration of untreated psychosis (DUP, defined as the time from the first continuous psychotic symptom to initiation of adequate antipsychotic drug treatment). Positive symptoms were assessed by the Scale for the Assessment of Positive Symptoms (SAPS)[32] and negative symptoms by the Scale for the Assessment of Negative Symptoms (SANS).[33] The patients' premorbid adjustment was assessed with the premorbid adjustment scale (PAS).[34] Functional assessment was conducted with The Disability Assessment Scale (DAS) Spanish version.[35] General psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS).[36]

As for the relatives and HC, they completed a single evaluation session of approximately one hour. Their psychiatric history was screened by the abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH),[37] a semi-structured psychiatric interview that enquires about the presence of clinical symptoms for mania, depression, and positive, disorganized, and negative dimensions of psychosis.

2.5 | Neurocognitive assessment

Expert neuropsychologists carried out a neurocognitive battery to estimate the participants' premorbid IQ and their performance on eight domains that have been shown to be impaired in SSD.[38] The subsample of FEP patients completed the neuropsychological assessment at baseline once they were stable, after being included in the PAFIP program, on average 10.5 weeks after their inclusion. The relatives and HC were evaluated at the time of inclusion in the study.

The WAIS-III vocabulary subtest[39] was used to estimate premorbid IQ, as it has been demonstrated to offer a valid proxy measure of crystallized intelligence.[40] Different tests were used to assess: (1) verbal memory (Rey Auditory Verbal Learning Test, RAVT[41]); (2) visual memory (Rey Complex Figure, RFC[42]); (3) processing speed (WAIS-III Digit Symbol subtest[39]); (4) working memory (WAIS-III Digits Backward subtest[39]); (5) executive function (Trail Making Test part B, TMTB[43]); (6) motor dexterity (The Grooved Pegboard Test[43]); (7) attention (Continuous Performance Test, CPT[44]); and (8) theory of mind (The Reading the Mind in the Eyes Task, RMET[45]). In order to make direct comparisons between the performance of the subjects, the T-scores derived from the WAIS-III subtests (Vocabulary, Digit Symbol, and Digits Backward), and the raw scores of the other tests were transformed into *Z* scores. Prior to standardization, raw cognitive scores were reversed when appropriate so they were all in a positive direction.[31]

An indicator of global deficit score (GDS) was estimated from individual performance on all neuropsychological tests. Following the method of Reichenberg et al.,[5] raw scores of each test were first converted into *T*-scores (derived from the comparisons with a healthy subsample) and then into deficit scores ranging from 0 (indicating no impairment) to 5 (denoting severe impairment). Subsequently, the GDS was obtained by estimating the average of the deficit scores of each test. Previous studies have established that GDS scores greater than or equal to 1 indicate overall impairment.[46]

2.6 | Data analysis

Statistical analyses were performed using the Statistical Package for Social Science version 19.0.[47] Descriptive statistics were estimated on sociodemographic, clinical, and neurocognitive data. Univariate analyses (ANCOVA) were run to compare continuous variables between groups, while chi-square was used for categorical variables. Comparisons of neurocognitive data were covariated with sex, age, and years of education. When ANCOVA yielded significant differences, pairwise comparisons were

conducted with Bonferroni correction. All statistical tests were two-tailed, and significance was determined at the 0.05 level. The main analysis was carried out comparing all FEP patients, their relatives, and HC. Later, only patients subsequently diagnosed with schizophrenia, their relatives and HC were compared to contrast the main results.

3 | RESULTS

3.1 | Sample and family description

After contacting the eligible families of the 387 FEP patients who completed the baseline evaluation of the PAFIP program, 579 individuals composed the final sample of the present study. From these, 133 were FEP patients, 244 were their relatives (146 parents, 98 siblings), and 202 were HC (see Figure 1). All 133 families consisted of at least one first-degree relative, either a parent or a sibling, of a patient.

3.2 | Sociodemographic and clinical findings

Comparisons are shown in Table 1. FEP patients and HC were more frequently male (61.65% and 60.89%, respectively; $p < 0.001$) than parents and siblings. FEP patients were younger ($M = 26.70$ years of age, SD = 8.4) than their relatives ($p < 0.001$) and HC ($p = 0.021$). As expected, parents were older ($M = 61.53$ years of age, SD = 7.73) than siblings and HC ($p < 0.001$), and siblings were older ($M = 40.66$ years of age, SD = 13.16) than HC ($p < 0.001$). FEP patients had completed fewer years of education ($M = 10.40$, SD = 3.38) than their siblings ($p < 0.001$), who at the same time outranked parents ($M = 12.47$, SD = 3.62; $p = 0.005$). Regarding the history of psychopathology, HC reported significantly lower percentage of symptoms throughout life (9.42%) than the rest of the participants ($p < 0.001$), followed by siblings (32.65%, $p < 0.001$) and parents (31.03%, $p < 0.001$).

3.3 | Neurocognitive findings

Several significant differences were found between groups, with FEP patients performing the lowest in all the neurocognitive domains (see Table 1). In processing speed, FEP patients ($Z = -1.12$, SD = 1.13) were significantly outperformed by the rest of participants ($p < 0.001$); while parents ($Z = -0.19$, SD = 0.96) showed a statistical tendency to perform worse than HC ($p = 0.063$). In verbal memory, the group of patients ($Z = -0.66$, SD = 1.01) obtained lower scores than HC ($p < 0.001$) and siblings ($p = 0.049$). On the task of visual memory, FEP patients ($Z = -0.71$, SD = 1.00) underperformed their siblings and HC ($p < 0.001$). In working memory, FEP patients ($Z = -0.55$, SD = 0.81) were significantly worse than HC ($p < 0.001$) and siblings ($p = 0.003$). In executive functions, both FEP patients ($Z = -1.15$, SD = 1.67) and their parents ($Z = -1.27$, SD = 2.69) underperformed HC ($p < 0.001$ and $p = 0.003$, respectively). In motor dexterity, the group of FEP patients ($Z = -1.51$, SD = 3.00) was worse than siblings and HC ($p < 0.001$). Regarding attention, FEP patients ($Z = -2.75$, SD = 4.11) demonstrated a deficit compared to siblings ($p = 0.003$) and HC ($p < 0.001$). Similarly, FEP patients obtained lower scores in ToM ($Z = -0.65$, SD = 0.94) than HC ($p < 0.001$) and siblings ($p = 0.002$). The cognitive profile of all groups is presented in Figure 2.

Significant differences were found in the measure of global cognitive deficit. FEP patients presented higher GDS values ($M = 1.10$, SD = 0.86) than HC and siblings ($p < 0.001$), indicating greater level of impairment. The group of parents also showed significantly higher GDS values ($M = 0.80$, SD = 0.87) in relation to HC ($p = 0.003$) and siblings ($p = 0.049$).

3.4 | Secondary analysis on patients with schizophrenia and their relatives

Six months after the psychosis onset, 46.61% of the patients were diagnosed with schizophrenia and the rest with other psychotic disorders. Schizophrenia patients had significantly longer DUI and DUP than patients with other diagnosis ($W = 3300.05$, $p < 0.001$; and $W = 3293.0$, $p < 0.001$, respectively).

To explore whether the diagnosis of patients could influence cognitive outcomes, we repeated the cognitive comparisons selecting only patients with schizophrenia ($n = 62$), their relatives (67 parents, 42 siblings), and HC (202). The findings in this subsample were similar to those obtained in the entire sample of FEP patients, as patients with schizophrenia had the worst performance of all groups in every cognitive domain (see Table 2). Parents of patients with schizophrenia performed worse than HC in executive functions ($p = 0.015$); and both parents and siblings underperformed HC in the attention task ($p = 0.005$ and $p = 0.011$, respectively). Also, compared to HC, both patients with schizophrenia ($p < 0.001$), their parents ($p = 0.002$) and siblings ($p = 0.028$) showed worse GDS scores.

4 | DISCUSSION

This family study of FEP patients aimed on exploring neurocognitive endophenotypes in SSD. The main finding is that deficits on executive functions and attention, shared

TABLE 1 Comparisons between FEP patients, their first-degree relatives, and HC

		Patients (FEP) (*N* = 133)		Parents (P) (*N* = 146)		Siblings (S) (*N* = 98)		Controls (HC) (*N* = 202)	Statistics		Paired comparisons
Sociodemographics	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	***X***	***p*-Value**	
Gender (male)	133	82 (61.65)	146	55 (37.67)	98	33 (33.67)	202	123 (60.89)	36.05	<0.001	FEP > P*; FEP > S*; P < HC*; S < HC*
	n	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***F***		
Age	132	26.70 (8.44)	145	61.53 (7.73)	98	40.66 (13.16)	201	29.70 (8.15)	421.98	<0.001	FEP < P*; FEP < S*; FEP < HC ($p = 0.021$); S < P*; HC < P*; HC < S*
Years of education	132	10.40 (3.38)	145	10.69 (3.54)	98	12.47 (3.62)	201	10.70 (2.72)	8.86	<0.001	FEP < S*; P < S ($p = 0.005$)
Premorbid information											
IQ	133	100.28 (13.14)	146	105.09 (11.66)	98	103.72 (11.47)	201	101.53 (10.78)	2.18	0.088	
Clinical variables	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	***X***		
CASH (yes)	133	133 (100)	145	45 (31.03)	98	32 (32.65)	191	18 (9.42)	280.46	<0.001	FEP > P*; FEP > S*; FEP > HC*; P > HC*; S > HC*
	n	**Mean (SD)**									
Schizophrenia diagnosis	62	46.61%									
DUI (months)	130	19.67 (31.60)									
DUP (months)	132	12.72 (28.42)									
PAS	96	3.06 (2.19)									
SAPS	132	14.63 (4.87)									
SANS	131	6.57 (6.25)									
BPRS	131	65.68 (15.10)									
Neuropsychological data	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***F***		
Processing speed	132	−1.12 (1.13)	145	−0.19 (0.96)	98	0.02 (0.99)	201	0.24 (1.00)	61.89	<0.001	FEP < P*; FEP < S*; FEP < HC*
Verbal memory	132	−0.66 (1.01)	145	−0.30 (1.00)	98	−0.30 (1.00)	201	−0.14 (1.00)	8.95	<0.001	FEP < S ($p = 0.049$); FEP < HC*
Visual memory	131	−0.71 (1.00)	143	−0.33 (1.25)	98	−0.08 (0.87)	200	−0.27 (1.00)	7.99	<0.001	FEP < S*; FEP < HC*
Working memory	132	−0.55 (0.81)	145	−0.10 (0.92)	98	−0.09 (0.91)	200	−0.16 (1.00)	6.20	<0.001	FEP < S ($p = 0.003$); FEP < HC ($p = 0.001$)
Executive function	130	−1.15 (1.67)	141	−1.27 (2.69)	97	−0.76 (1.37)	201	−0.21 (1.00)	11.11	<0.001	FEP < HC*; P < HC ($p = 0.003$)
Motor dexterity	131	−1.51 (3.00)	144	−1.17 (2.71)	98	−0.35 (1.33)	201	−0.24 (1.00)	12.74	<0.001	FEP < S ($p = 0.001$); FEP < HC*
Attention	128	−2.75 (4.11)	139	−1.26 (4.09)	98	−1.11 (2.93)	182	−0.40 (1.00)	14.46	<0.001	FEP < S ($p = 0.003$); FEP < HC*
ToM	105	−0.65 (0.94)	144	−0.25 (1.01)	98	0.11 (0.95)	179	0.07 (1.00)	8.69	<0.001	FEP < S ($p = 0.002$); FEP < HC*
GDS	124	1.10 (0.86)	135	0.80 (0.87)	97	0.51 (0.55)	181	0.38 (0.44)	35.19	<0.001	FEP > S*; FEP > HC*; P > S ($p = 0.049$); P > HC ($p = 0.003$)

Note: Neuropsychological comparisons are covariated by sex, age, and years of education.

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CASH, Comprehensive Assessment of Symptoms and History; DUI, duration of untreated illness; DUP, duration of untreated psychosis; FEP, First Episode Psychosis; GDS, Global Deficit Score; IQ, Intelligence Quotient; PAS, Premorbid Adjustment Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SD, Standard Deviation; ToM, Theory of Mind.

*$p<0.001$.

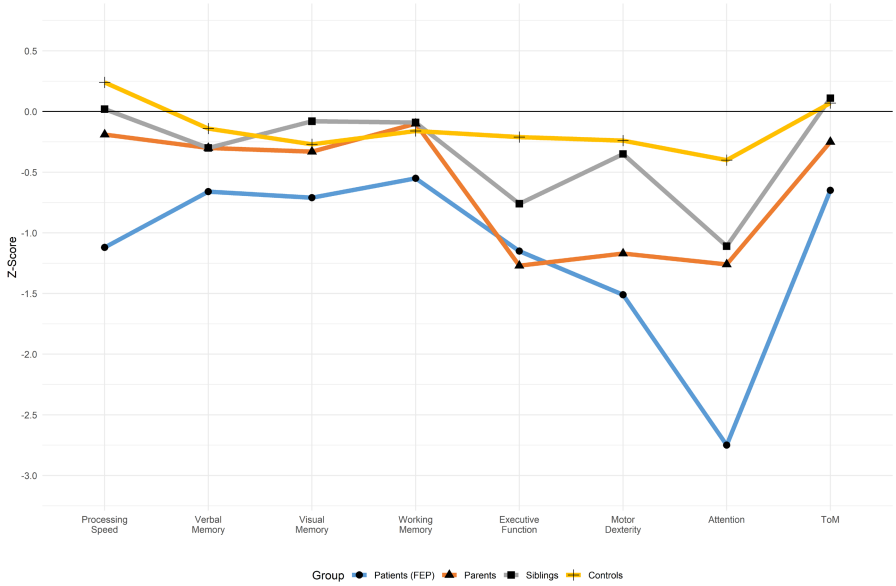

FIGURE 2 Neurocognitive profile of the participants in the PAFIP-FAMILIAS project (*Note*: Scores corrected by sex, age, and years of education)

by FEP patients, their parents, and their siblings, may be the best candidates. These findings could be explained by both environmental and genetic factors.

In terms of the sociodemographic characteristics of the participants, we found that the sex distribution differed significantly between groups. There were more males in the group of FEP patients than in the others, corresponding to evidence of a higher prevalence of psychosis among men.[48-50] On the contrary, there were significantly more females in the groups of relatives, which is interesting for further research focused on the roles of primary caregivers of FEP patients. The prevalence of females in the group of relatives might influence their cognitive outcomes. We have previously described that females have better cognitive performance after 3-year follow-up,[31] as well as a higher educational level compared to males.[8] However, it is unknown whether this pattern of results would be replicated in unaffected siblings and parents of these patients. Future studies focused on exploring the possible effect of sex on the cognitive endophenotypes of SSD will be of great interest.

Regarding years of education, we found that siblings had completed significantly more years of education than FEP patients and parents, which is similar to the findings of other family studies.[16,51,52] Since the contribution of years of education to cognitive reserve and good functional outcomes in FEP has been confirmed,[53,54] the educational attainment of their siblings could be suggested as a protective factor against the risk of developing psychosis. This effect is particularly important in this population as they share the genetic risk burden of the disorder with the affected individual. Alternatively, another possible explanation is that the lower educational attainment of FEP patients could be consequence of the prodromal symptoms of psychosis. Yet, recent findings of our research group observed impaired intellectual ability before the illness, suggesting abnormal neurodevelopment as a critical component in the pathogenesis of SSD.[8] Another relevant issue regarding educational attainment implies the participants' age, which could explain in part the differences in education, and given that FEP patients were evaluated at a younger age than their siblings, they had less time to accomplish higher educational levels. Also, it should be noted that younger generations are completing more years of formal education,[55,56] thus siblings younger than the proband might be able to achieve a higher educational level due to environmental factors. While it is likely that patients and their siblings shared a similar environment during childhood and adolescence, the differences between these two groups suggest variations that may have influenced their cognitive courses.[57] A relevant moderator of the cognitive course and the educational attainment among FEP patients might be their specific diagnosis, wherein schizophrenia is associated with worse neuropsychological outcomes than other psychosis.[28] Also, FEP patients with cognitive decline already present at the time illness onset have been previously described.[58] That make possible to suggest that a lower educational achievement could be related to those latent deficits.[8] Another possible moderator of cognition in FEP patients might be antipsychotic medication, although previous research from our group suggests that medication status might not be a confusing factor.[59,60]

As expected due to our exclusion criteria, statistical differences were confirmed in the history of psychopathology between HC and the rest of the groups. Although the relatives included in this study did not meet diagnostic criteria for any psychopathological disorder, they reported a higher prevalence of psychopathological symptoms throughout life compared to HC; who, in addition to

TABLE 2 Comparisons between FEP patients that subsequently were diagnosed with schizophrenia, their first-degree relatives, and HC

	Schizophrenia patients (SZ) ($n = 62$)		Parents (P) ($n = 67$)		Siblings (S) ($n = 42$)		Healthy controls (HC) ($n = 202$)		Statistics		Paired comparisons
Sociodemographics	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	***n***	***N* (%)**	**X**	***p*-Value**	
Gender (male)	62	41 (66.12)	67	24 (35.82)	42	16 (38.09)	202	123 (60.89)	20.70	<0.001	HC > S ($p = 0.007$); HC > P*; P < SZ ($p = 0.001$); S < SZ ($p = 0.005$)
	n	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***F***		
Age	62	26.26 (7.62)	67	61.54 (8.27)	42	37.12 (12.66)	202	29.71 (8.16)	252.77	<0.001	HC<S*; HC < P*; HC > SZ ($p = 0.040$); S < P; S > SZ*; P > SZ*
Years of education	62	10.18 (3.14)	66	10.05 (3.29)	42	12.52 (3.05)	201	10.84 (2.72)	7.19	<0.001	HC < S ($p = 0.005$); S > P*; S > SZ*
Premorbid Information											
IQ	62	97.94 (12.15)	66	102.94 (11.10)	42	100.79 (11.77)	200	100.63 (10.78)	1.49	0.217	
	n	**Mean (SD)**									
DUI (months)	60	33.0	40.3								
DUP (months)	61	22.6	38.4								
PAS	42	3.5	2.1								
SAPS	61	13.6	4.4								
SANS	61	8.2	6.5								
BPRS	60	65.4	15.2								
Neuropsychological data											
Processing Speed	62	−1.42 (1.05)	66	−0.12 (0.94)	42	−0.26 (1.05)	201	0.09 (1.00)	41.09	<0.001	HC > SZ*; S > SZ*; P > SZ*
Verbal Memory	62	−0.56 (1.10)	66	−0.31 (0.98)	42	−0.36 (1.02)	201	−0.15 (1.00)	3.78	0.011	HC > SZ ($p = 0.013$)
Visual Memory	61	−0.63 (1.05)	64	−0.06 (1.67)	42	0.04 (0.89)	200	−0.20 (1.00)	3.22	0.023	HC > FEP ($p = 0.046$); S > SZ ($p = 0.030$)
Working Memory	62	−0.49 (0.80)	66	0.06 (0.91)	42	−0.14 (1.01)	200	−0.15 (1.00)	2.56	0.055	
Executive Function	62	−1.16 (1.53)	64	−1.31 (2.96)	41	−0.85 (1.26)	201	−0.16 (1.00)	9.67	<0.001	HC > SZ*; P < HC ($p = 0.015$)
Motor Dexterity	62	−1.68 (4.01)	66	−1.40 (2.48)	42	−0.58 (1.49)	201	−0.14 (1.00)	10.54	<0.001	HC > SZ*
Attention	60	−2.30 (3.82)	63	−2.38 (4.61)	42	−1.70 (2.92)	182	−0.14 (1.00)	13.20	<0.001	HC > S ($p = 0.011$); HC > SZ*; HC > P ($p = 0.005$)
ToM	48	−0.47 (0.93)	65	−0.38 (1.10)	42	−0.15 (0.94)	179	−0.03 (1.00)	3.10	0.027	HC > SZ ($p = 0.041$)
GDS	59	1.11 (0.91)	61	0.88 (0.89)	41	0.66 (0.60)	181	0.35 (0.44)	27.03	<0.001	HC < S ($p = 0.028$); HC < P ($p = 0.002$); HC < SZ*; S < SZ ($p = 0.004$)

Note: Neuropsychological comparisons are covariated by sex, age, and years of education.

Abbreviations: BPRS: Brief Psychiatric Rating Scale; CASH: Comprehensive Assessment of Symptoms and History; DUI: duration of untreated illness; DUP: duration of untreated psychosis; GDS: Global Deficit Score; IQ: Intelligence Quotient; PAS: Premorbid Adjustment Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SD: Standard Deviation; SZ: Schizophrenia; ToM: Theory of Mind.

*$p < 0.001$.

reporting lower rates of symptoms, were mainly related to adjustment disorders, but not to psychotic-like experiences. These findings imply a higher epigenetic vulnerability to mental illness among families of individuals with FEP,[61] where genetic predisposition could be interacting with harmful triggers present in the common environment.[62,63] The siblings could be particularly affected by these risk factors, as they shared both genetic loading and parenting environment with the affected individual.[64] In turn, this risk of developing a psychiatric disorder could be associated with neurocognitive performance, thus, a future line of study in family designs is to explore psychiatric history as a mediating variable of cognitive outcomes.

In terms of neurocognitive findings, relevant statistical differences emerged among neurocognitive domains between FEP patients, siblings, parents, and HC. Generally, all relatives showed an intermediate performance between HC and FEP patients, except in executive functions, wherein parents showed significant deficits that were similar to that of the affected individuals. It is worth mentioning that this executive dysfunction was replicated in the subsample of patients diagnosed with schizophrenia and their parents, suggesting that deficits in this domain could be a cognitive marker in SSD. Previous studies with patients with SSD and their healthy parents have found cognitive deficits in both groups, especially in executive functioning.[22,23,65] In fact, it has been reported that executive impairments are particularly affected by genetic loading.[65,66] Therefore, the higher the genetic risk for schizophrenia, the greater the deficit would be among first-degree relatives in the aforementioned functions. Taken together, these findings suggest that executive dysfunction might have a greater family aggregation and could be a relevant cognitive endophenotype for psychosis.

Attention is another cognitive domain that has been proposed as a promising endophenotype of SSD due to its significant genetic component and its deficits in unaffected relatives of the patient.[24,25,67] Even though our results did not show significant differences in the attentional performance between first-degree relatives of FEP patients and HC, we observed a tendency for the former to perform below healthy people. Notably, when selecting only patients diagnosed with schizophrenia and their relatives, the attention deficits of parents and siblings reached statistical significance. These results suggest that attention deficits have a great family aggregation among families at risk of schizophrenia, although milder deficits are also observed in families vulnerable to other types of psychosis. This corresponds with previous evidence indicating that cognitive impairment along the SSD varies in severity (being more pronounced in schizophrenia) but not in kind.[28] The more severe attention deficit in patients with schizophrenia and their families could owe to an increased genetic risk. Lemvigh et al.[16] carried out a study with 214 twins, concordant or discordant for a SSD, to investigate genetic and environmental loadings associated with neurocognition, reporting that sustained attention was strongly related to schizophrenia liability. Overall, these findings indicate that attention may be a valid endophenotype in both schizophrenia and other types of psychosis. However, future studies must confirm whether attention deficits have diverse degrees of severity according to patients' diagnosis.

In accordance with previous studies of our group,[68] the present results showed a severe deficit in processing speed of FEP patients. Similar to several studies and meta-analyses,[12,69,70] the first-degree relatives in our sample had intermediate deficits between patients and HC. Previous research has identified slow processing speed as essential in the full clinical presentation of schizophrenia[71]; therefore, it might be a manifestation of the disease more than a familial feature.[72] Family aggregation of neurocognition has been widely supported.[13,67,73,74] Yet, our results indicate that the patients' processing speed deficit is more associated with psychosis onset. This in turn may be explained with the diathesis-stress model,[75] where the accumulation of stressful life events causing psychosocial stress could precipitate the FEP.[3,76] Another environmental factor potentially related to psychosis onset is cannabis consumption, which in combination with childhood trauma contributes to a double hit that might influence the pathogenesis of the disease.[77]

Lastly, we found that the relatives, especially siblings, performed similarly to healthy individuals in the domains of verbal memory, visual memory, working memory, motor dexterity, and ToM. As well, the IQ of parents and siblings did not differ significantly from HC. These results partially replicated previous findings[12,78] and suggest that the deficits of FEP patients in such cognitive functions are caused to a greater extent by the disease itself more than by family aggregation, thus not being the best suitable candidates as endophenotypes for SSD. For example, in the working memory domain, FEP patients underperformed all other participants, even their parents, indicating that the deficit might be explained by pathological processes associated with the illness. However, this contrasts with previous evidence about the value of working memory,[10] ToM,[79] and IQ[20,21] as cognitive markers of psychosis. The heterogeneity of findings between studies could be due to the specific diagnosis of the patients or the stage of the illness. Although our results were similar both with the entire sample of FEP patients and with the subsample of patients with schizophrenia, more studies are required to explore possible differences between cognitive endophenotypes for psychosis in general vs schizophrenia in specific. Our results confirm the findings by Valerio et al.,[28]

who described that cognitive differences between patients with schizophrenia and other psychoses consisted in the severity of the deficit but not in the type of impairment. According to these data, a common neurodevelopmental basis might underlie SSD, with schizophrenia being the most severe manifestation.

Overall, our study adds certainty on the existing literature aimed on disentangling the contribution of familiarity to neurocognition, helping to establish cognitive endophenotypes for SSD. The findings of shared features in executive functions and attention domains between patients and their first-degree relatives shed some light on the path to identify potential causes of psychosis, while simultaneously being potentially useful in the implementation of preventive and therapeutic interventions.

4.1 | Strengths and limitations

The main strength of this study is the inclusion of parents and siblings from a group of FEP patients. Their inclusion allowed us to analyze the profile of the relatives according to their relationship with the proband. Likewise, the inclusion of HC allowed us to compare the participants with a sample of the general population. Regarding the neuropsychological battery, the assessment of a wide range of neurocognitive domains was the same for all participants, which made it possible to directly compare scores between groups. Despite these strengths, the study had some limitations that must be taken into account when analyzing its results. First, all the participants were predominantly Caucasian and from the northern region of Spain, limiting the generalizability of findings to other racial and ethnic groups. Second, the cross-sectional design used here does not provide information on the longitudinal cognitive course of the participants. In addition, although age differences between the participants were statistically controlled by including it as a covariate, the possible effect of aging on their cognitive outcomes cannot be ruled out, especially in the case of parents. Evaluating siblings after reaching 30 years old is an advantage, as they are considered to have exceeded the peak age for psychosis risk[80,81]; however, their cognitive performance may have varied from younger ages. This could be controlled in prospective studies by following people at risk for psychosis from adolescence. It is also relevant to mention that we have not addressed the control of medication status in the group of FEP patients. However, previous studies by our group indicated that the use of different antipsychotics did not represent a confounding factor for cognitive function.[59,60] Finally, the contribution of genetic analyses has not been considered in the present study.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this article is available upon request from the corresponding author, RAA.

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