RESUMEN
Esta tesis investiga la relación entre el cociente intelectual (CI) y los trastornos del espectro de la esquizofrenia. Mediante cinco estudios se examina el CI y sus factores genéticos en individuos con primer episodio de psicosis (PEP) y sus familiares de primer grado, comparados con controles sanos. Se observa que el CI de los individuos con PEP se mantiene estable después de 10 años, e incluso aumenta en algunos casos. Los participantes con PEP se desvían del potencial cognitivo familiar, ya que tienden a puntuar menos que sus padres y hermanos en la prueba de CI. Los individuos con PEP tienen mayor riesgo genético de esquizofrenia que otros grupos. Esta predisposición se asocia a la desviación del CI respecto a sus familiares. El potencial cognitivo no alcanzado podría ser un factor de riesgo de psicosis, subrayando su importancia para la implementación de estrategias personalizadas de prevención, diagnóstico y tratamiento temprano.

ABSTRACT
This thesis investigates the relationship between intelligence quotient (IQ) and schizophrenia spectrum disorders. Five studies examine IQ and its genetic factors in people with first-episode psychosis (FEP) and their first-degree relatives, compared with healthy controls. The IQ of FEP individuals is found to remain stable after 10 years, and in some cases even improve. FEP participants deviate from familial cognitive potential, as they tend to score lower on the IQ test than their parents and siblings. The FEP group has a higher genetic risk for schizophrenia than their relatives and controls. This genetic predisposition is significantly associated with their IQ deviation from their relatives. The unrealized cognitive potential may be a risk factor for psychosis and underline its importance for the implementation of personalized prevention, diagnosis and early treatment strategies.

UC | Escuela de **Doctorado**

Tesis Doctoral

2024

INTELIGENCIA Y ESQUIZOFRENIA: HALLAZGOS FENOTÍPICOS Y GENÉTICOS DE UN ESTUDIO DE DISEÑO FAMILIAR
INTELLIGENCE AND SCHIZOPHRENIA: PHENOTYPIC AND GENETIC INSIGHTS FROM A FAMILY DESIGN STUDY

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Universidad de **Cantabria**

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Programa de Doctorado en Biología Molecular y Biomedicina

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INTELLIGENCE AND SCHIZOPHRENIA: PHENOTYPIC AND GENETIC INSIGHTS FROM A FAMILY DESIGN STUDY

Doctoral thesis presented by

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ABSTRACT

Background: Low intelligence quotient (IQ) has been linked to schizophrenia spectrum disorders (SSDs), potentially serving as an endophenotype. Lower IQs are consistently found in affected individuals from the first episode of psychosis (FEP), suggesting that neurocognitive deficits are premorbid. The FEP patients' lower IQ may be partly explained by a combined influence of genetic factors linked to both intelligence and schizophrenia. Furthermore, FEP patients may show a significant deviation in IQ from their siblings and parents, potentially increasing their risk for developing psychosis.

Aim: This dissertation aimed to study the association between IQ and SSD by exploring phenotypic and genetic factors in a sample of FEP patients, their first-degree relatives, and healthy controls.

Methods: This research included participants from the PAFIP (Programa de Atención a Fases Iniciales de Psicosis) and PAFIP-FAMILIAS projects in Santander, Cantabria (Spain). The initial sample included 133 patients, 244 first-degree relatives, and 202 healthy controls. The specific hypotheses were tested through five different studies. A longitudinal case-control design examined neuropsychological performance in FEP patients and controls at 10-year follow-up. Two family cross-sectional designs investigated neuropsychological performance and familial aggregation of IQ. A systematic review identified genetic variants underlying the shared genetic architecture of IQ and SSDs. Finally, polygenic scores estimated genetic risk for schizophrenia and its influence on IQ.

Results: FEP patients displayed lower IQs than controls, with some individuals exhibiting stable or improved IQ over 10 years, but no evidence of decline. Familial analyses revealed a tendency for IQ similarity within families. Deviation from familial IQ emerged as a potential risk factor for SSDs, with FEP patients demonstrating the greatest deviation also showing premorbid childhood difficulties. The systematic review identified thousands of potentially pleiotropic genetic variants with small effects on both IQ and schizophrenia. Polygenic risk scores successfully differentiated genetic risk for schizophrenia, with FEP patients showing the highest scores. Interestingly, this risk score was significantly associated with deviation from familial IQ in FEP patients.

Conclusions: The relationship between IQ and SSDs is complex and likely influenced by multiple factors. By analysing deviations from expected familial cognitive profiles, researchers may be able to identify a subgroup of individuals at high risk of developing psychosis. Personalized prevention plans,

early diagnosis and treatment approaches should integrate both phenotypic and genetic perspectives to account for individual variation.

RESUMEN

Antecedentes: El bajo cociente intelectual (CI) se ha asociado con los trastornos del espectro de la esquizofrenia (TEE), lo que lo convierte en un potencial endofenotipo útil para la investigación y la detección temprana. Diversos estudios han demostrado que los individuos con TEE presentan un CI significativamente inferior al de la población general, incluso desde el primer episodio de psicosis (PEP). Este hallazgo sugiere que los déficits neurocognitivos podrían ser preexistentes a la aparición de la sintomatología psicótica. El bajo CI en pacientes con PEP podría estar influenciado por factores genéticos compartidos con la enfermedad. Se ha observado que estos individuos a menudo presentan una desviación significativa en el CI con respecto a sus hermanos y padres, lo que podría ser un factor de riesgo para el desarrollo de psicosis.

Objetivo: Esta tesis tuvo como objetivo estudiar la asociación entre el CI y los TEE mediante la exploración de factores fenotípicos y genéticos en una muestra de pacientes con PEP, sus familiares de primer grado y controles sanos.

Métodos: Esta investigación incluyó participantes de los proyectos PAFIP (Programa de Atención a Fases Iniciales de Psicosis) y PAFIP-FAMILIAS en Santander, Cantabria (España). La muestra inicial incluyó 133 pacientes, 244 familiares de primer grado y 202 controles sanos. Las hipótesis específicas se probaron a través de cinco estudios diferentes. Un diseño longitudinal de casos y controles examinó el desempeño neuropsicológico en pacientes con PEP y controles sanos en un seguimiento de 10 años. Dos diseños familiares transversales investigaron el desempeño neuropsicológico y la agregación familiar del CI. Una revisión sistemática identificó polimorfismos subyacentes a la arquitectura genética compartida del CI y los TEE. Finalmente, se estimaron puntuaciones poligénicas para estudiar el riesgo genético de esquizofrenia y su influencia sobre el CI.

Resultados: Los pacientes con PEP mostraron un CI inferior al de los controles. Este déficit se mantuvo estable o incluso aumentó ligeramente a lo largo de 10 años, sin mostrar un deterioro significativo. Los análisis familiares revelaron una tendencia a la similitud del CI dentro de las familias. Los pacientes con PEP no alcanzaron su potencial cognitivo familiar, lo que se observó como una

desviación del CI familiar. Esta desviación emergió como un factor de riesgo potencial para los TEE, ya que se asoció con dificultades premórbidas en la infancia. La revisión sistemática identificó miles de polimorfismos potencialmente pleiotrópicos con pequeños efectos sobre el CI y sobre la esquizofrenia. Las puntuaciones de riesgo poligénico diferenciaron satisfactoriamente el riesgo genético de esquizofrenia, ya que los pacientes con PEP mostraron las puntuaciones más altas. Esta puntuación de riesgo genético al trastorno se asoció significativamente con la desviación del CI familiar en pacientes con PEP.

Conclusiones: La relación entre el CI y los TEE es compleja y multifactorial. El análisis de las desviaciones individuales en los perfiles cognitivos, en comparación con lo esperado para sus familias, podría permitir la identificación de un subgrupo de personas con alto riesgo de desarrollar psicosis. El estudio de estos perfiles, considerando factores fenotípicos y genéticos diferenciales, abre la puerta a la creación de planes de prevención personalizados, al diagnóstico temprano y a enfoques de tratamiento individualizados.

GLOSSARY AND ABBREVIATIONS

Crystallised intelligence: The knowledge, skills, and abilities you acquire through education and experience. It reflects the accumulated factual knowledge, vocabulary, and understanding of the world.

CVN (Copy Number Variant): A deletion or duplication of a DNA segment, affecting a larger region of genetic material.

DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition): Reference book published by the American Psychiatric Association (APA) that outlines criteria for diagnosing mental disorders. It's a widely used tool by mental health professionals for diagnosis, treatment planning, and insurance purposes.

Familiality: Also called familial aggregation or familial transmission. Refers to phenotypic similarity for a certain trait observed between family members, likely due to a combination of shared genetic and environmental influences.

FEP (First Episode Psychosis): Initial presentation of symptoms associated with schizophrenia spectrum disorders (SSDs). It describes the first time an individual experiences these significant disruptions in their thoughts and perceptions.

GWAS (Genome-Wide Association Study): A large-scale study that identifies genetic variations (SNPs) associated with specific traits or diseases.

Intelligence: A person's overall mental ability to learn, reason, problem-solve, adapt to new situations, and understand complex concepts. It encompasses various cognitive skills like memory, attention, processing speed, and critical thinking.

IQ (Intelligence Quotient): A standardized score that aims to assess a person's intellectual abilities compared to their age group.

Neurocognition: Mental processes involving the brain, such as learning, memory, attention, and problem-solving.

Neuropsychological tests: Standardized assessments used to evaluate an individual's neurocognitive functioning in various domains.

PAFIP (Programa de Atención a Fases Iniciales de Psicosis): Clinical and research program on first-episode psychosis carried out in Santander, Cantabria (Spain), from 2001 to 2018. This project recruited a cohort of FEP patients and a group of healthy controls.

PAFIP-FAMILIAS: A nationally funded research project recruiting a group of unaffected relatives of FEP patients previously enrolled in the PAFIP program that was carried out between 2018 and 2022.

PGS (Polygenic Scores): A numerical value that summarizes the effects of many genetic variations (often SNPs) across the entire genome. This score is used to estimate an individual's genetic predisposition for a particular trait or disease.

PGS-IQ (Polygenic Scores for Intelligence Quotient): A quantitative measure of an individual's genetic predisposition to intelligence. It is calculated by analysing thousands of genetic variations associated with the disorder according to the latest GWAS on general cognitive ability. Higher PGS-IQ scores indicate the potential for higher intelligence.

PGS-SCZ (Polygenic Scores for Schizophrenia): A quantitative score that estimates an individual's genetic risk of developing schizophrenia. It is calculated by analysing thousands of genetic variations associated with the disorder according to the latest GWAS on schizophrenia. Higher PGS-SCZ scores indicate a greater genetic risk for developing schizophrenia.

Pleiotropy: A single gene that influences multiple traits.

SNP (Single Nucleotide Polymorphism): A variation in a single DNA nucleotide that occurs in a population.

SSD (Schizophrenia Spectrum Disorder): A group of mental disorders characterized by impaired thought processes, hallucinations, and delusions.

WAIS (Wechsler Adults Intelligence Scale): Neuropsychological battery designed to measure intelligence and cognitive ability in adults and older adolescents.

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Introduction

1. Intelligence Quotient (IQ)

1.1. Historical overview of the study and testing of intelligence

The scientific study of intelligence dates to the end of the nineteenth century. Francis Galton pioneered the idea of intelligence as a hereditary trait and carried out psychometric and statistical research that laid the foundations for the development of modern tests. Mayr divided the paradigms of intelligence into two groups, the "lumpers" and the "splitters" (Mayr, 1982). The lumper paradigm refers to generalist theories that consider intelligence as a general ability to acquire knowledge, reason and solve problems. In this line, Alfred Binet and Théodore Simon understood intelligence as a fundamental faculty (Binet & Simon, 1948). Spearman proposed that intelligence is a general cognitive ability, called the g factor, which underlies other specific cognitive functions (Spearman, 1904). On the contrary, the splitter paradigm suggest that intelligence is built by separate mental abilities that operate with a certain degree of independence. That is the case of the models by Louis Thurstone or Howard Gardner (Thurstone, 1946). For Gardner (1995), there are multiple intelligences, which follow different developmental paths.

There is a third group of paradigms with an intermediate position, which advocates a hierarchical organization of intelligence, with both general and specific factors. Horn and Cattell's two-factor theory distinguished two components of intelligence, called crystallised and fluid (Horn & Cattell, 1966). Crystallised intelligence refers to knowledge acquired throughout life, including vocabulary, general knowledge, culture and specific skills (Horn & Cattell, 1966). Fluid intelligence refers to the ability to reason, solve problems and adapt to new situations (Horn & Cattell, 1966). This theory recognizes that the crystallised and fluid aspects are related, although they have different characteristics and should be measured by different tests.

From a testing perspective, early attempts to assess intelligence relied on anthropometric measurements, as seen in Galton's use of line bisection (Galton, 1885). Later, the called mental tests were implemented to evaluate students' admissions and placement in educational institutions. The first intelligence scale was developed in 1905 by Binet and Simon to evaluate the intellectual abilities of children and determine their cognitive development about their chronological age (Plucker & Shelton, 2015). The scale underwent revision and was subsequently known as the Stanford-Binet (1916), which emerged as the most widely used intelligence test during that time (Plucker & Shelton, 2015).

The First World War was a significant accelerator of group intelligence testing. There was a need to quickly screen recruits for the army and classify them according to their general intelligence (Resing, 2005). These tests also had to be free of bias caused by ethnic, cultural, and linguistic differences. The result was the Army Beta, a non-verbal test that is the basis of current measures of fluid intelligence (Spring, 1972).

Currently, there are comprehensive intelligence tests available such as the Wechsler Intelligence Scale for both children and adults (Wechsler, 1997, 2003, 2012). These scales are designed for individual administration and include different subtests aimed at assessing different specific factors of intelligence. The Wechsler scales have the advantage of being validated and adapted to different populations. They provide normative population data after being administered to large samples.

1.2. Definition of intelligence, crystallised intelligence, and IQ

Wechsler (1997) defined intelligence as the aggregate or global capacity of the individual to act purposefully, to think rationally, and to deal effectively with the environment. From a cognitive perspective, intelligence can be understood as the degree to which people can learn, and retain in long-term memory, the knowledge and skills that can be learned from the environment (Carroll, 1997).

The construct of “intelligence quotient” (IQ) is useful for operationalizing intelligence in quantitative terms. It was used for the first time in 1912 by William Stern and referred to the score obtained by dividing an individual's mental age by their chronological age and then multiplying it by 100 (Stern, 1912). This measure was not suitable for older children and adults and is no longer used. Current IQ tests provide deviation scores, which compare an individual's raw score to their peers' average score, adjusted for age. Modern tests are also adapted and validated for different regions and languages. IQ scores below 90 would indicate low intelligence, while scores between 90 and 110 would indicate average intelligence, and scores above 110 would indicate high intelligence (Wechsler, 2001), as shown in Table 1 and Figure 1.

It is important to recognize the limitations of psychometric measures in providing a comprehensive measure of intelligence. These tests assess an individual's intelligence based on their performance on a specific set of tasks, providing an estimate of intelligence at a specific moment. Furthermore, current intelligence tests primarily assess academic intelligence and may overlook other facets of cognitive ability (Resing, 2005).

Table 1. Correspondence of IQ scores and other standard scales

	Category	Theoretical percentage [a]	Sample percentage [b]	Standard Deviations	T scores
130 or more	Very Superior	2.3	2.8	+3	80
120-129	Superior	6.7	7.9	+2	70
110-119	Average-high	16.1	16.1	+1	60
90-109	Average	50.0	49.5	0	50
80-89	Average-low	16.1	15.4	-1	40
70-79	Inferior	6.7	6.3	-2	30
69 or less	Very inferior	2.2	2.0	-3	20

Note: Adapted from Wechsler (2001).
[a] Distribution of the expected normal curve.
[b] Data from the sample was used to validate the Spanish version of the WAIS-III scale (Wechsler, 2001).

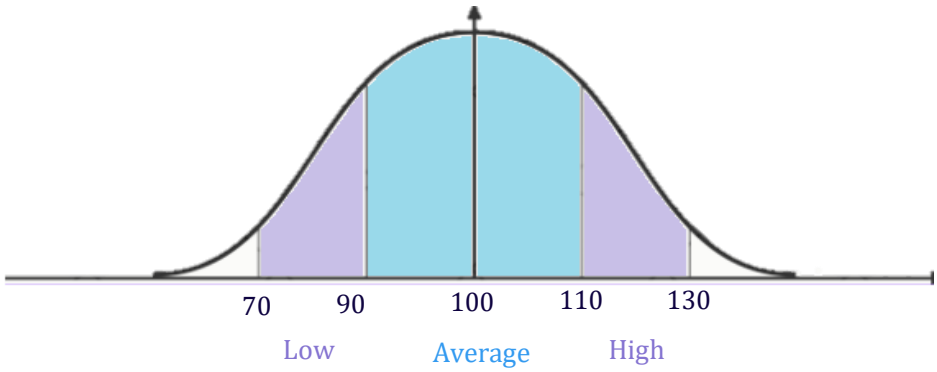

Figure 1. Interpretation of IQ scores based on the expected normal curve.

Adapted from Wechsler (2001). Modern neuropsychological tests define low IQ as ranging from 70 to 89, average IQ as ranging from 90 to 110, and high IQ as ranging from 111 to 130.

1.3. Characteristics of crystallised intelligence

Based on the hierarchical model of intelligence, crystallised intelligence is the type of intelligence referring to the accumulation of knowledge and skills acquired over one's lifetime, encompassing vocabulary, general information, cultural understanding, and specific competencies (Cattell, 1971; Horn & Cattell, 1966). This store of information and problem-solving strategies serves as a resource that individuals use to solve everyday challenges (Ellingsen & Ackerman, 2015). It is most useful for solving familiar circumstances, but limited for solving novel problems (Ellingsen & Ackerman, 2015). This relatively inflexible nature explains its description as crystallised and is what distinguishes it from fluid intelligence.

Crystallised intelligence tends to increase during childhood and adolescence and remain relatively stable throughout adulthood (Kaufman & Horn, 1996; Wang & Kaufman, 1993). Studies in the general population have shown that vocabulary learning continues into adulthood, possibly due to

environmental factors such as continued exposure to new information (Hartshorne & Germine, 2015; Kaufman & Horn, 1996). The decline in this intelligence may occur after the age of 60 and is much slower than fluid intelligence, which has been reported to decline earlier in adulthood (Kaufman & Horn, 1996; Wang & Kaufman, 1993).

1.3.1. Proxy measures of crystallised IQ

In clinical and research settings, it is common to use proxy measures for IQ estimation. A proxy measure is used as an indirect estimate of the trait or ability of interest. The most common proxy measures for crystallised IQ are academic achievement or performance on an intelligence subtest (Spinks et al., 2009), such as the vocabulary of the Wechsler Adults Intelligence Scale (WAIS) (Wechsler, 2001). The specific tests that assess crystallised intelligence involve items on general information, vocabulary knowledge and skills acquired through experience or formal schooling (Wechsler, 1997, 2001).

Proxy IQ measures have advantages over comprehensive IQ batteries in terms of accessibility, cost-effectiveness, and efficiency. They can be more easily administered in a variety of settings without special training or equipment and provide rapid assessments of cognitive ability. Proxy measures correlate with other IQ tests in the general population and clinical groups (Lezak, 1995; Ringe et al., 2002). Despite their advantages, proxy IQ measures have limitations as they may only capture certain aspects of intelligence.

1.4. Heritability and polygenic structure of IQ

IQ is known to be one of the most inheritable cognitive traits. Its heritability estimates vary throughout life, increasing from about 40% in childhood to about 70% in adulthood (Haworth et al., 2010; Willoughby et al., 2021). These findings indicate that IQ is more influenced by environmental factors in early life (Sauce & Matzel, 2018), while genetic influences gain more dominance in adult intelligence (Willoughby et al., 2021). It is essential to highlight that heritability estimates are population-level statistics and do not describe the extent to which an individual's IQ is influenced by genetics or the environment.

According to large-scale genomic studies (GWAS), the genetic architecture of IQ is polygenic (Coleman et al., 2019; Genç et al., 2021; Hill et al., 2019; Savage et al., 2018; Zabaneh et al., 2018). The largest GWAS of intelligence to date has identified 205 genomic loci and 1016 genes associated with this trait (Savage et al., 2018) (see Figure 2). Genetic variants such as single nucleotide polymorphisms (SNPs)

and copy number variants (CNVs) (see Figure 3), collectively contribute to individual differences through the combined influence of thousands of small effects. The genes linked to these variants show robust expression in the brain, particularly in striatal medium spiny neurons and hippocampal pyramidal neurons (Savage et al., 2018; Sniekers et al., 2017). Gene set analyses have implicated pathways relevant to nervous system development and synaptic structure (Savage et al., 2018). Intelligence may have protective effects against Alzheimer's disease and attention deficit hyperactivity disorder, but bidirectional causality with pleiotropic effects towards schizophrenia (Lencz et al., 2014; Savage et al., 2018).

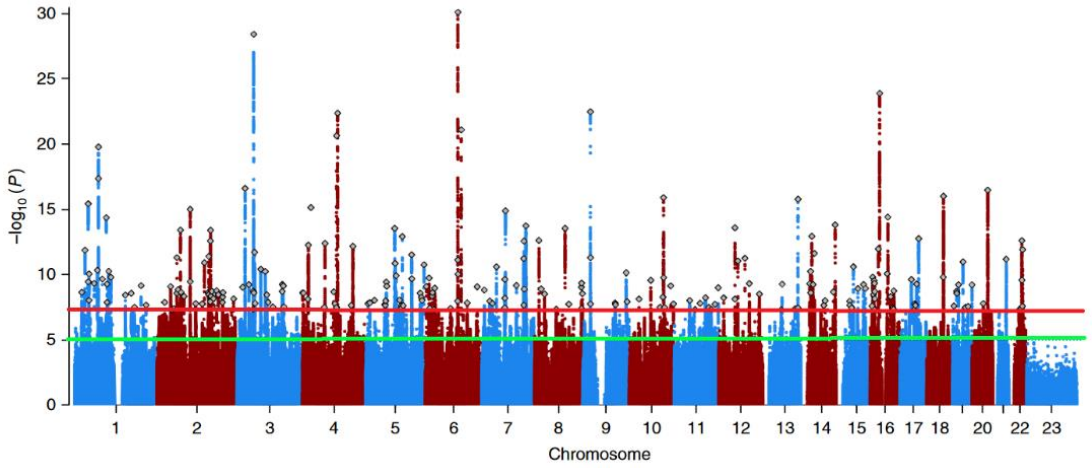

Figure 2. SNP-based associations with intelligence in the GWAS meta-analysis of n = 269,867 independent individuals by Savage et al. (2018).

Reproduced from Savage et al. (2018) with permission from Springer Nature (License Number 5771410239208, https://doi.org/10.1038/s41588-018-0152-6) This Manhattan plot summarizes the findings of a large GWAS investigating intelligence. Each dot represents a SNP positioned along its corresponding chromosome on the X-axis. The Y-axis reflects the strength of the association between each SNP and intelligence, with lower values indicating stronger links. The horizontal red line highlights SNPs with very strong connections to intelligence (genome-wide significance), while the horizontal green line suggests potential associations that require further investigation. Diamonds pinpoint the most crucial SNPs identified in the study, representing independent lead candidates for further exploration.

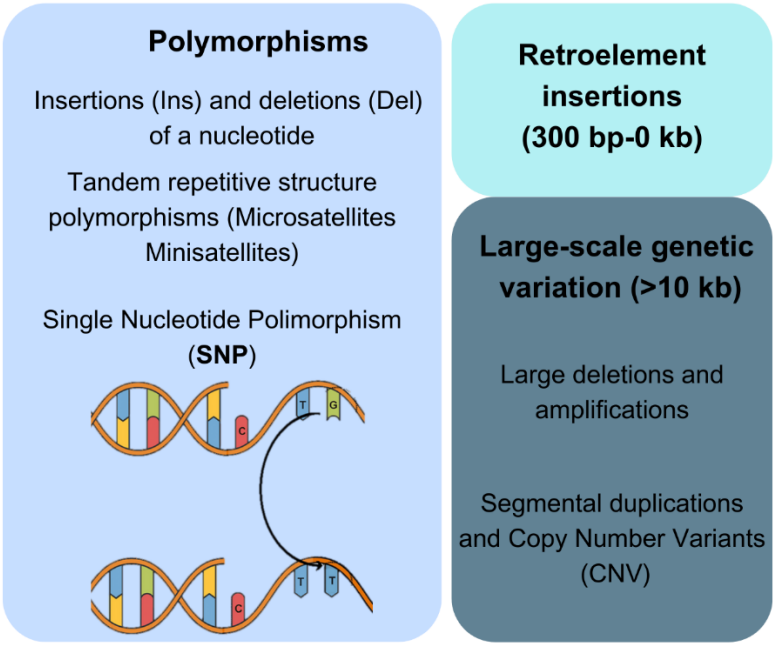

Figure 3. Main forms of genetic variation or polymorphisms.

Adapted from Rosa, Arias and Fatjó-Vilas (2014). A polymorphism occurs when there is a variation in a specific location or locus of the genome, and this translates into the existence of more than one variant present in the population with frequencies greater than 1%. SNPs are the most common type; these are changes in a single nucleotide of the DNA code. They can influence traits, but individual effects are often small.

2. Intelligence and Schizophrenia Spectrum Disorders (SSDs)

2.1. Characterization of SSDs

Schizophrenia Spectrum Disorder (SSD) is a diagnostic category that includes several mental disorders that share similar features with schizophrenia but differ in severity, duration, and clinical presentation (American Psychiatric Association, 2013). The term spectrum is used because people with SSDs can present a wide range of symptoms and levels of functioning, with schizophrenia being the most severe and chronic form (Tandon, 2012). Table 2 lists specific disorders in the SSD category according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013). Despite the varying degrees of severity and presentation of SSDs, they share the common symptom of psychosis.

Table 2. Category of schizophrenia spectrum and other psychotic disorders according to DSM-5.

Diagnosis	Associated features
Delusional disorder	Isolated delusions in absence of other psychotic symptoms.
Brief psychotic disorder	Transient psychosis with return to premorbid functioning.
Schizophreniform disorder	Sub-syndromal schizophrenia with multiple psychotic symptoms of duration longer than 1 month and less than 6 months.
Schizophrenia	Two or more psychotic symptoms for 6 or more months.
Schizoaffective disorder	Psychotic symptoms for 2 weeks in the absence of mood symptoms and symptoms that meet criteria for a mood episode during a majority of the duration of illness.
Substance/medication-induced psychotic disorder	Psychotic symptoms the direct result of a substance or medication.
Psychotic disorder due to another medical condition	Psychotic symptoms the direct result of a medical condition.
Catatonia (specifier)	Used to describe psychiatric disorders but can have catatonia due to medial conditions, etc.
Other specified schizophrenia spectrum and other psychotic disorder	Other psychotic disorders that do not meet criteria for another disorder.
Unspecified schizophrenia spectrum and psychotic disorder	Psychotic disorder due to unknown or undetermined causes.
Schizotypal personality disorder	Pervasive pattern of reduced capacity for close relationships as well as cognitive and perceptual distortions.

Notes: Specific diagnoses included in the SSD category according to DSM-5, adapted from Bhati (2013).

2.1.1. Definition of psychosis and First episode of psychosis (FEP)

Psychosis is a condition in which there is a breakdown in the distinction between oneself and the outside world, or a significant difficulty in distinguishing reality, often accompanied by false beliefs (delusions) or remarkable sensory experiences without external stimuli (hallucinations) (APA, 1994; World Health Organization, WHO, 1992). Psychosis symptoms may also include disorganized thinking, and changes in behaviour and emotions (APA, 1994; WHO, 1992).

The term FEP is used in clinical and research settings to refer to individuals who experience their initial psychotic symptoms. The term also encompasses the initial encounter with treatment and a short length of time on antipsychotic medication (from 3 to 12 weeks) (Breitborde et al., 2009). This stage of the illness is extremely relevant because it is a crucial starting point for the early detection, diagnosis, and treatment of SSDs (Reynolds et al., 2019). At the FEP, most patients are drug-naïve, and their cognitive and social functioning may still be preserved from chronic deterioration (Breitborde et al., 2009). Studying FEP patients has several advantages. It enables us to ensure that our observations correspond to the onset of psychosis, without being overly influenced by antipsychotic medication or the progression of the illness. Additionally, studying the FEP population provides a valuable opportunity to follow patients over time and identify different patterns of progression.

Despite its common use, there are limitations to the conceptualisation of FEP. There is currently no consensus on its definition and existing diagnostic systems do not provide clear diagnostic criteria (Breitborde et al., 2009; Kingdon et al., 2024). The FEP category is heterogeneous, including individuals with recent onset of psychosis but with different clinical courses. Clinicians often do not make a definitive diagnosis until several months after the FEP, depending on the course and severity of the individual's illness. Therefore, findings in the FEP population should be interpreted with this in mind.

2.1.2. Epidemiology and impact

In Spain, the prevalence of SSDs among people aged 15-34 years was 6.2 per 1,000 individuals (about 0.62% of the population), and an incidence rate of 50.25 per 100,000 individuals (0.05%) (Orrico-Sánchez et al., 2020). This age group is at risk since the onset of psychosis often occurs in adolescence or early adulthood. Also, the prevalence of SSDs was 76% higher among men than women (Orrico-Sánchez et al., 2020). In the region of Cantabria, the incidence was 1.38 per 10,000 inhabitants (0.01%) in the 15-55 age group (Pelayo-Terán et al., 2008). In Finnish and Danish cohorts with a wider age range, incidence rates increase to 1.3%-1.5% (Kühl et al., 2016; Mäki et al., 2003).

For schizophrenia, there is also a variance in the epidemiological data across studies. A systematic review including several incidence studies over the world reported that the prevalence of schizophrenia ranged from 4.05 to 5.75 per 1,000 for men (0.40%-0.57%) and 4.05 to 4.26 per 1,000 for women (0.40%-0.52%) (Saha et al., 2008). The incidence per 100,000 people was from 7.2 to 67.0 (Saha et al., 2008). The characteristics more frequently associated with developing schizophrenia are being male, migrant status, being born or living in an urban area, and older paternal age (Mcgrath & Susser, 2009).

Although SSDs are less prevalent than other mental disorders such as anxiety or depression (Bryant et al., 2008; Lie et al., 2015), they have a strong impact on patients and the health system. SSDs significantly affect the functionality of the individual in activities of daily living (Liberman, 2012; Reichenberg et al., 2014), their social functioning (Dickerson et al., 2000; Etchepare et al., 2019), and their subjective well-being (Vothknecht et al., 2011). Even increased mortality rates have been reported among patients with SSDs (Moreno-Küstner et al., 2021). The costs of health care caused by SSDs are also significant, with estimations of €48,353 per patient during the first year in the local region of Cantabria (Mayoral-van Son et al., 2019).

2.1.3. Diagnosis and treatment

The diagnosis of SSDs involves a thorough clinical assessment by a qualified mental health professional. This process includes a detailed clinical interview, evaluation of symptoms against diagnostic criteria, medical assessment to rule out other causes, consideration of symptom duration and impairment, differential diagnosis, and integration of cultural and contextual factors (APA, 1994; WHO, 1992). Table 3 presents the diagnostic criteria for schizophrenia, the most chronic and severe disorder of the SSD category.

Table 3. DSM-5 diagnostic criteria for schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3): o 1.Delusions. o 2.Hallucinations. o 3.Disorganized speech (e.g., frequent derailment or incoherence). o 4.Grossly disorganized or catatonic behavior. o 5.Negative symptoms (i.e., diminished emotional expression or avolition).
B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).
Specify if: The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria. • First episode, currently in acute episode: First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An acute episode is a time period in which the symptom criteria are fulfilled. • First episode, currently in partial remission: Partial remission is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled. • First episode, currently in full remission: Full remission is a period of time after a previous episode during which no disorder-specific symptoms are present.

- Multiple episodes, currently in acute episode: Multiple episodes may be determined after a minimum of two episodes (i.e. after a first episode, a remission and a minimum of one relapse).
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous: Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.
- Unspecified

Specify if: With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119–120, for definition).

- Coding note: Use additional code 293.89 (F06.1) catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). (See Clinician-Rated Dimensions of Psychosis Symptom Severity in the chapter "Assessment Measures").

Notes: adapted from DSM-5 (American Psychiatric Association, 2013).

Treatment usually involves a combination of antipsychotic medication, psychological therapy, and psychosocial support to help people manage their symptoms and improve their quality of life (Alvarez-Jimenez et al., 2012; Bell et al., 2014; Bhati, 2013; Gómez-Revuelta et al., 2020). Psychoeducation is also a relevant intervention for SSDs, with significant effects on relapse prevention (Lincoln et al., 2007). Evidence suggests that treatment should be multidisciplinary to ensure stable improvement over time (Alvarez-Jimenez et al., 2012; Burton & Twamley, 2015; Pillet et al., 2015). New strategies are being introduced, such as cognitive remediation, which appears to be effective in improving people's cognitive functioning and thus their functioning in daily activities (Bell et al., 2014).

2.1.4. Neurocognitive symptoms

Neurocognitive symptoms are a key feature of SSDs. People with SSDs often experience a global cognitive deficit compared with healthy controls (Asarnow et al., 2002; Ayesa-Arriola, Rodríguez-Sánchez, et al., 2016a; Fioravanti et al., 2005; Jiménez-López et al., 2017). The domains most affected are attention (Cornblatt & Keilp, 1994; Elvevåg & Goldberg, 2000; Laurent et al., 1999), verbal memory (Ayesa-Arriola, Rodríguez-Sánchez, et al., 2016b; Rodríguez-Sánchez et al., 2013), visual memory (Townsend et al., 2002), processing speed (Badcock et al., 2004; Carey et al., 2019; Karbasforoushan et al., 2015), executive function (Adan et al., 2017; Bhatia et al., 2009; Wongupparaj et al., 2015), motor dexterity (Carey et al., 2019; Lehoux et al., 2003) and social cognition (Ayesa-Arriola, Setién-Suero, et al., 2016; Bliksted et al., 2017). Neurocognitive deficits appear with the onset of psychosis and vary

in severity and progression based on the specific disorder. The greatest neurocognitive deficits are observed in FEP patients with confirmed diagnosis of schizophrenia, while the least deficits are associated with brief psychotic disorder (Ayesa-Arriola, Rodríguez-Sánchez, et al., 2016a; Inamura et al., 2015). Thus, comprehensive neuropsychological assessments in the FEP may be helpful in determining the severity of the disorder, and in guiding a personalised treatment.

Research suggests that neurocognitive symptoms in SSD are associated with abnormalities in brain structure and function, particularly in regions involved in information processing and integration, such as the prefrontal cortex (Owens et al., 2012; Zoubovsky et al., 2011) and hippocampus (Chen et al., 2018; Harrisberger et al., 2016). Neurocognitive deficits often persist even when other symptoms, such as hallucinations or delusions, are effectively treated (Ayesa-Arriola et al., 2013; Frías et al., 2017; Rodríguez-Sánchez et al., 2013). Such findings suggest that neurocognitive deficits are characteristics intrinsic to SSD. Research on the neurocognitive performance of patients with SSDs allows us to study vulnerability to psychosis, to explore risk factors associated with its aetiology, and to propose complementary treatment strategies (such as cognitive remediation) that contribute to improving functioning in daily activities and quality of life.

2.1.5. Aetiology

The aetiology of SSDs is multifactorial (see Figure 4), involving a complex interplay of genetic, neurobiological, environmental, and psychosocial factors (Adorjan & Papiol, 2019; Ayesa-Arriola et al., 2020; Brown, 2011; Trubetskoy et al., 2022; van Os et al., 2008). Genetic predisposition plays a significant role, with heritability estimates suggesting a strong genetic component (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020; Trubetskoy et al., 2022). Neurobiological factors include abnormalities in brain structure and function (Carment et al., 2020; Di Carlo et al., 2019; Owens et al., 2012). Environmental factors such as prenatal and perinatal complications, exposure to toxins, stress, and substance abuse during critical developmental periods can also increase the risk of psychosis (Martin et al., 2014; Woods et al., 2021; Zinellu et al., 2023). Exposure to various viruses during neurodevelopment, including prenatal exposure to influenza and other viral infections, is associated with an increased risk of developing schizophrenia, possibly through effects on brain development and cognitive function (Ayesa-Arriola et al., 2023; Khandaker et al., 2012). In addition, psychosocial stressors, trauma, and social adversity may contribute to the onset and course

of the disorder, highlighting the complex nature of SSD development (Bailey et al., 2018; Pruessner et al., 2021).

The neurodevelopmental model of schizophrenia suggests that the disorder arises from abnormalities in brain development, particularly during the prenatal or early postnatal period (Owen & O'Donovan, 2017). According to this hypothesis, genetic and environmental factors disrupt normal neurodevelopmental processes, leading to structural and functional abnormalities in the brain that manifest as schizophrenia symptoms later in life. Evidence for this model includes the identification of subtle brain abnormalities in individuals at high risk for schizophrenia prior to the onset of symptoms, and the presence of genetic risk factors linked to neurodevelopmental processes (Agnew-Blais et al., 2015; Agnew-Blais & Seidman, 2013; Bora et al., 2014).

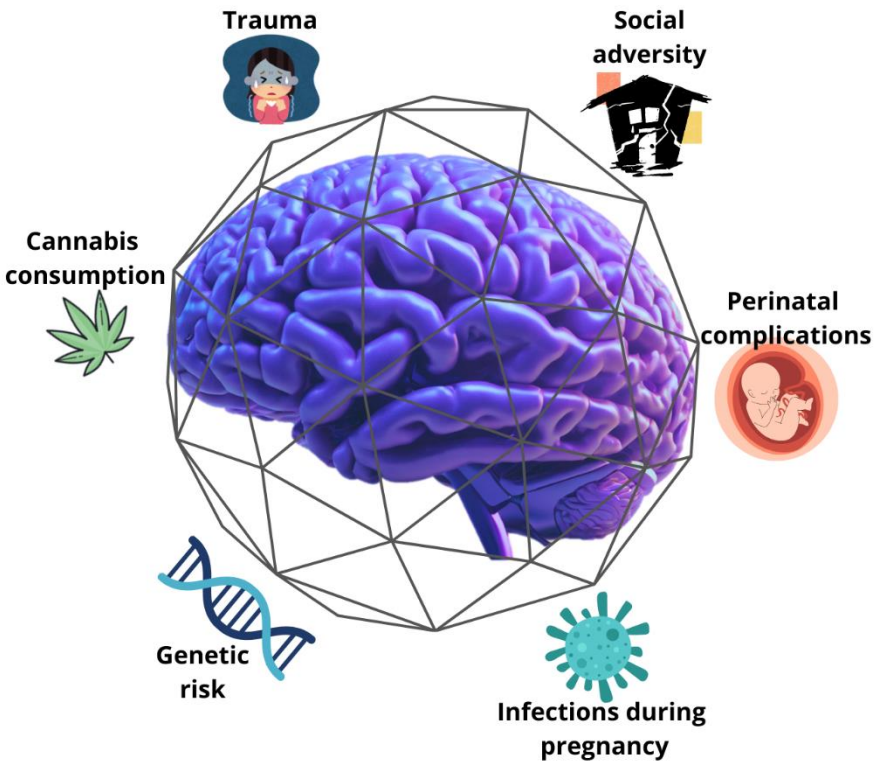

Figure 4. Illustration of the multifactorial model of SSDs.

The multifactorial model explains that the aetiology of SSDs is a complex interplay of genetic, neurobiological, environmental, and psychosocial factors. Adverse factors such as genetic risk, infections during pregnancy, perinatal complications, and environmental insults may interact and disrupt optimal neurodevelopment.

In contrast, the neurodegeneration hypothesis proposes that schizophrenia involves progressive degenerative changes in the brain over time (Kochunov & Hong, 2014). This perspective suggests that factors such as chronic stress, neuroinflammation and oxidative stress contribute to neuronal damage and loss, leading to the worsening of symptoms and cognitive decline observed in some people with schizophrenia (Anderson et al., 1998; Knoll et al., 1998). However, the evidence for neurodegeneration in schizophrenia remains less clear than in other neurodegenerative disorders such as Alzheimer's disease (Stone et al., 2022).

2.1.6. Heritability and polygenic structure of SSDs

Schizophrenia is a complex trait with a polygenic architecture. Genetic studies have estimated the heritability of schizophrenia to be between 64% and 80% (Lichtenstein et al., 2009; Sullivan et al., 2003). Current genomic approaches can potentially explain about 40% of these heritability estimates (Owen et al., 2023), with a significant contribution from the global effect of thousands of SNPs (SNP heritability=24%) (Trubetskoy et al., 2022). Rare copy number variants and rare coding variants have also been found to be associated with schizophrenia, although at a lower frequency than common variants (Georgieva et al., 2014; Rees et al., 2016).

The largest GWAS at present on schizophrenia population includes data on 76,755 affected individuals and 243,649 healthy controls (Trubetskoy et al., 2022). Schizophrenia was found to be associated with common variants at 287 genomic loci, predominantly in genes that are expressed in excitatory and inhibitory neurons of the central nervous system (Trubetskoy et al., 2022). There are 120 genes identified (106 of which are protein-coding) as potential contributors to the genetic architecture of schizophrenia, including 16 genes with potentially causative variations in non-coding or untranslated regions, as shown in Figure 5 (Trubetskoy et al., 2022). The evidence shows that these genetic variations related to schizophrenia play role in key neuronal functions such as synaptic structure, differentiation, and signalling (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Some key genes associated with schizophrenia include *DISC1*, *C4*, and *Neurexin 1* (Owen et al., 2023).

In addition, schizophrenia is pleiotropic, meaning that genetic factors associated with the disorder may influence multiple traits or phenotypes beyond the primary diagnosis of schizophrenia itself. Genetic factors associated with the schizophrenia polygenic risk score have been shown to be associated with other psychiatric disorders, such as bipolar disorder (Bigdeli et al., 2022; The Brain Consortium et al.,

2018), and neurodevelopmental disorders (Owen & O'Donovan, 2017). There is also evidence of pleiotropy between schizophrenia and cognitive traits (Hubbard et al., 2016; Lencz et al., 2014), psychosocial factors (Owen et al., 2023) and physical health outcomes (Muntané et al., 2023; Zhang et al., 2024).

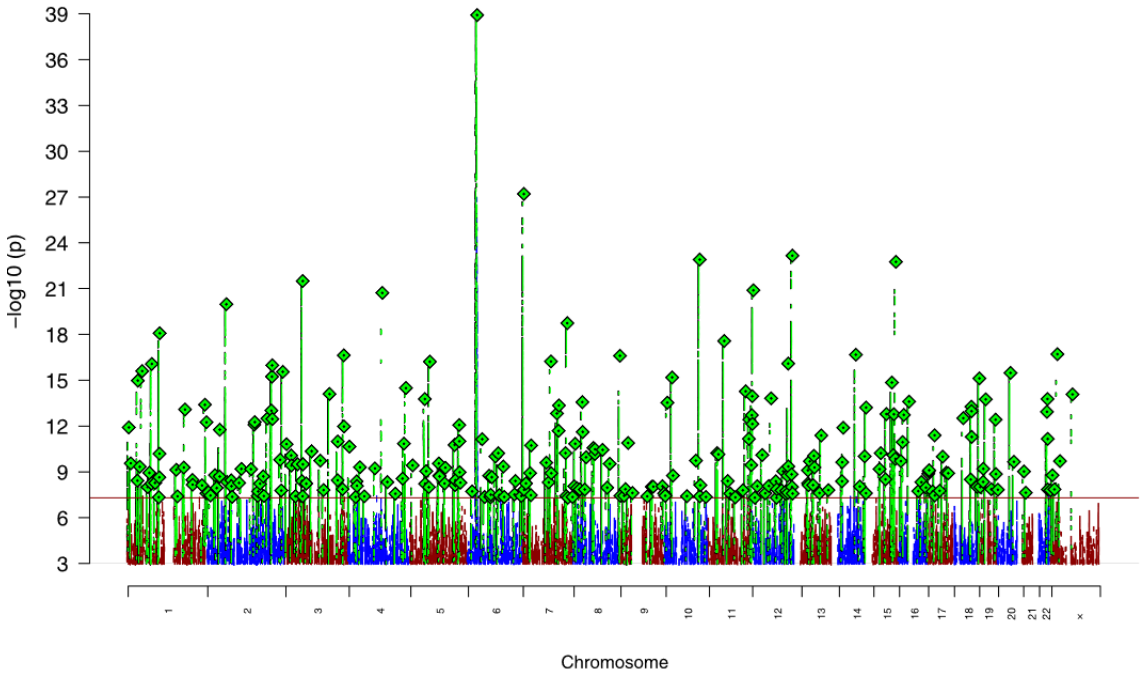

Figure 5. SNP-based associations with schizophrenia in the GWAS meta-analysis of n=76,755 individuals with schizophrenia and n=243,649 control individuals by Trubetskoy et al. (2022).

Reproduced from Trubetskoy et al. (2022) with permission from Springer Nature (License Number 5771420539539, 10.1038/s41586-022-04434-5). This graph shows the location of SNPs on chromosomes (X-axis) and how strongly they're linked to a specific trait (Y-axis). The lower the Y-axis value (higher -log10(P)), the stronger the association. The horizontal red line indicates a very strong link that is considered significant across the entire genome. Green dots represent SNPs that are closely related (linkage disequilibrium, LD) to the most important SNPs in this study (diamonds). These diamonds highlight independent associations that are also very strong across the genome (genome-wide significant), meaning they are not simply "carried along" by the effect of another nearby SNP. The minimum threshold for this close relationship is set at 10% shared genetic variation ($r2 > 0.1$).

2.2. Intelligence as a candidate endophenotype of SSDs

An endophenotype, or intermediate phenotype, is a heritable and stable trait that is indirectly related to a disease. In psychiatry, the endophenotype concept refers to measurable behavioural traits that are located along the pathway connecting a disease to its fundamental genetic factors (Gottesman & Gould, 2003). There are several benefits to studying and validating the endophenotypes of a condition. Endophenotypes can offer insights into the genetic background of the primary disease, assist in

subtyping patients for classification and diagnostic purposes, and provide guidance for the development of animal models for psychiatric disorders (Gottesman & Gould, 2003; Lenzenweger, 2013). However, to establish a valid endophenotype of a disease, criteria presented in Table 4 must be met.

Table 4. Criteria for establishing an endophenotype in the context of psychiatric disorders.

Criterion		Description
1.	Association with Illness	The endophenotype should be associated with the specific illness in the population being studied.
2.	Heritability	The endophenotype should demonstrate heritability, indicating that it is passed down through generations.
3.	State-Independence	The endophenotype should manifest in individuals regardless of whether the illness is active or not.
4.	Co-Segregation	Within families, the endophenotype and the illness should co-segregate, meaning they are found together in affected family members.
5.	Higher Rate in Nonaffected Family Members	The endophenotype should be found in nonaffected family members at a higher rate than in the general population, especially for diseases with complex inheritance patterns.

Notes: Adapted from Gottesman & Gould (2003).

Research in the field of SSD has focused on identifying endophenotypes of the disorder (Aukes et al., 2009; Bertisch et al., 2009; Owens et al., 2012). IQ is a candidate endophenotype for schizophrenia for several reasons. In line with Gottesman & Gould (2003) first criterion, low IQ have been identified as a marker trait for the disorder. Individuals with SSDs tend to have lower IQs than healthy controls, and such underachievement tends to be premorbid (Aylward et al., 1984; G. M. Khandaker et al., 2011). Children who went on to develop SSDs have been described as having low IQ from an early age (Agnew-Blais et al., 2015; Aylward et al., 1984; Jones et al., 1994; Koenen et al., 2009). People at high risk of psychosis also show IQ deviations from the general population (Agnew-Blais & Seidman, 2013; Bora et al., 2014; Bora & Pantelis, 2013; Cosway et al., 2000).

A previous study by our research group found that low IQ (<90) was more common in FEP patients (28.8%) than in healthy controls (14.6%). FEP patients with low IQ were more likely to have poor premorbid adjustment, low socioeconomic status, and lower educational attainment (Ayesa-Arriola et al., 2018). These findings are consistent with evidence that lower IQ is associated with poorer prognosis and symptom severity in SSDs (Nelson et al., 1990). There is also evidence that IQ is

heritable, not only in the general population but also in the FEP population (Blokland et al., 2017; Savage et al., 2018).

Research suggests that deficits in IQ are evident both before the onset of psychosis and persist even after positive symptoms have resolved, suggesting that these deficits are state-independent (Hedman et al., 2013; Jones & Offord, 1975). Several studies, including those by Leeson et al. (2011) and Hedman et al. (2012), have shown that IQ scores in FEP patients remain relatively stable over follow-up periods of 3 to 5 years. However, a meta-analysis by Hedman et al. (2013) reported a modest average annual increase in IQ of 0.33 points. Another body of research indicates a potential decline in IQ following the onset of psychosis (Fujino et al., 2017; Ohi et al., 2019; Zanelli et al., 2019). These different findings suggest the presence of diverse intellectual trajectories in FEP patients, likely influenced by different clinical, neurocognitive, and genetic factors.

Co-segregation refers to the phenomenon where two or more traits or genetic markers tend to be inherited together. There are studies suggesting that IQ and schizophrenia do co-segregate within families, potentially due to shared genetic factors and chromosomal abnormalities (Blackwood et al., 2001; Gur et al., 2007). However, evidence on this matter is inconclusive, and further studies in families affected by SSDs are needed to elucidate the extent of co-segregation with IQ. This line of research is linked to the final criterion of Gottesman & Gould (2003). The study of non-affected relatives of individuals with SSDs is increasing and shows interesting insights. Zhang et al. (2018) found that relatives of SSD patients underperformed healthy controls on IQ tests, and these deficits were greater in families with increased genetic risk for schizophrenia. Goldberg et al. (2012) also described IQ resemblance within families that included a proband with SSD, and this similarity was stronger for patients with early-onset schizophrenia, which is considered a more severe condition than adult-onset schizophrenia. Thus, IQ may be affected in first-degree relatives of people with SSD, and that the degree of familial transmission may be greater for severe disorders on the spectrum.

Although the evidence for IQ as an endophenotype of SSDs is currently inconclusive, there is emerging data to suggest that it may be an observable and measurable marker of schizophrenia. Its validation would contribute to better characterization of the disorder, prevention and early diagnosis, and personalized intervention.

2.2.1. Genetic overlap between IQ and SSDs

The co-segregation of IQ and SSDs requires evidence of a genetic basis underlying the consistent presence of the endophenotype in the condition. As described before, both IQ and SSDs are complex behavioral traits that are heritable and have a polygenic genetic architecture. There is evidence for a negative genetic correlation between common alleles associated with IQ and those associated with SSDs, suggesting a common genetic basis between cognitive deficit and the disorder (Owen et al., 2023).

Previous GWAS have indicated that genetic variants overlapping between IQ and SSDs are expressed in the central nervous system and play key roles in neurogenesis, nervous system development regulation, neuronal differentiation, and cell development. A SNP within the *DTNBP1* gene (rs1011313) has been associated with both neurocognitive function and susceptibility to schizophrenia, potentially due to its involvement in the glutamatergic system (Yang et al., 2020). Another locus linked to elevated schizophrenia risk and diminished overall cognition is *TCF20* (rs134873, intron variant), which codes for a transcriptional coregulator (Smeland et al., 2017). In addition, the risk allele of rs134873 correlates with increased expression of the *NAGA* gene (involved in regulating glycosylation-associated enzymes, glutamatergic, and GABAergic systems); and with decreased expression of the *CYP2D6* gene (which plays a role in serotonin and dopamine metabolism) in human brain (Smeland et al., 2017).

From a broader perspective, additional research endeavours have delved into examining the correlation between polygenic loading for IQ and for SSDs. Lencz et al. (2014) confirmed genetic overlap between IQ and schizophrenia, as the genetic burden for schizophrenia was associated with lower general cognitive ability in both general population and clinical cohorts. Similarly, Ohi et al. (2021) found that the genetic load for schizophrenia significantly predicted intelligence in patients and healthy controls, in contrast to the genetic predisposition for bipolar disorder. This suggests that possible schizophrenia-specific genetic factors may explain the clinical differences between SSDs and other disorders and may influence premorbid IQ.

3. Approaches to advance in the knowledge of low IQ as a risk factor for SSDs

3.1. Family designs

Family designs are key to the study of complex traits such as IQ and SSDs. First-degree relatives share genetic and environmental factors, making them ideal for studying risk and protective factors that contribute to individual differences. Twin and adoption studies have provided valuable insights into the heritability of IQ and SSDs. Other family designs include sibling pairs, first-degree unaffected relatives, and offspring of probands.

Family studies have revealed the complex interplay between genetic and environmental factors in shaping IQ, highlighting the need for further research to elucidate these mechanisms fully. Adoption studies further support the role of genetics, as adopted children' IQ show strong correlations with that of their biological relatives (Harden et al., 2007). However, environmental factors also play a significant role, as evidenced by the Flynn effect, which shows an increase in average IQ scores over time (Flynn, 1984). Factors such as education, socioeconomic status, nutrition, and early childhood experiences can have a significant impact on cognitive development and IQ (Beam et al., 2015).

The family approach has been also relevant in the study of SSDs, as it provides a unique opportunity into understanding the heritability and genetic transmission of the disorder. Studies with family design have consistently shown an increased risk of schizophrenia in first-degree relatives of affected individuals (Blackwood et al., 2001; Bora & Pantelis, 2013; Gur et al., 2007; Haren et al., 2019). The meta-analysis by Rasic et al. (2014) found that the risk of developing schizophrenia was approximately 10 times higher in siblings of patients with schizophrenia compared to the general population. In addition to investigating heritability, family designs are essential to elucidate the underlying mechanisms and biological pathways involved in the pathophysiology of SSDs. Genetic linkage and association studies have identified several chromosomal regions and candidate genes that may be involved in genetic susceptibility to SSDs (Blackwood et al., 2001; Faraone et al., 1998; Shih et al., 2004).

Another important aspect of family designs is their role in identifying endophenotypes. As mentioned in Table 4, one criterion for the validation of an endophenotype is that it should be observable in the proband's relatives. Family designs are therefore necessary. In this regard, several family studies have

reported that relatives of FEP patients display intermediate performance between the proband and healthy controls in IQ, executive functions, memory, and theory of mind (Barrantes-Vidal et al., 2007; Cella et al., 2015; Mondragón-Maya et al., 2017; Scala et al., 2014; Varela et al., 2021). Due to the similar background shared by siblings, it may be expected that members of the same family would have similar outcomes. However, FEP patients deviate from their unaffected relatives by developing symptoms of psychosis, including neurocognitive deficit.

Kendler et al. studied the neurocognitive abilities of FEP patients and compared them with the performance of their first-degree relatives (Kendler et al., 2016a). The results suggest that it is not low IQ that increases the risk of developing schizophrenia, but a deviation from family cognitive ability. The authors suggest that such neurocognitive deviations are likely to result from qualitative developmental impairments (Kendler et al., 2016a). Further investigation, including familial studies, is essential to understand the role of deviation from familial neurocognitive performance in the development of SSDs.

3.2. Polygenic Scores

The use of polygenic scores (PGS) has increased in recent years for studying the genetic loading for complex traits. The PGS is a method that predicts the cumulative effect of genetic variants in an individual's genome towards a phenotype, providing a quantitative measure of genetic load. PGS are obtained by multiplying the number of risk alleles of a person by the effect size of each variant, and then summing each of these products across all loci of interest (Martin et al., 2019). When the studied phenotype is of risk, such as SSDs, the term polygenic risk score is often employed.

Currently, it is possible to calculate PGS for IQ (PGS-IQ) based on large GWAS studies that have identified thousands of SNPs associated with the trait (Savage et al., 2018; Sniekers et al., 2017). PGS-IQ are highly correlated with crystallised intelligence and explain up to 5.1% of the variation in general cognitive ability (Loughnan et al., 2023).

PGS can also be calculated for schizophrenia (PGS-SZ) based on the largest GWAS available on the disorder (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020; Trubetskoy et al., 2022). PGS-SZ explain between 2.4% and 7.3% of the susceptibility to schizophrenia and are elevated in patients with the disorder compared to healthy controls (Ferraro et al., 2023; Harrisberger et al., 2016).

PGS is still a developing field with limitations since its predictive power varies depending on the specific trait and is generally modest. Although the PGS approach has no current use in clinical context, it has diverse applications in research. PGS can provide a more comprehensive assessment of an individual's genetic predisposition for complex traits compared to focusing on individual genes. In the study of IQ as an endophenotype of SSDs, the use of PGS can help identifying the genetic architecture of both traits and exploring its interactions. There could be a correlation between PGS-IQ and PGS-SZ, as many genetic variants are contributing factors to both intelligence and schizophrenia (Hill et al., 2016). Similarly, PGS discriminating schizophrenia from bipolar disorder was found to be specifically related to intelligence (Lencz et al., 2014).

This knowledge can lead to a deeper understanding of the aetiology of SSDs and pave the way for the development of novel therapies. In the future, PGS can contribute to the advancement of personalized medicine by tailoring preventive and treatment strategies based on an individual's unique genetic makeup. By understanding their genetic risk profile, individuals and healthcare professionals can make more informed decisions about disease prevention, early detection, and treatment options.

4. Justification

Despite significant advancements in the field, understanding the aetiology of SSDs remains a critical task that has yet to be accomplished. This thesis explores one potential piece of the puzzle: the relationship between intelligence, operationalized as IQ, and SSDs. Unravelling this association holds considerable promise. If a lower IQ is found to be a reliable endophenotype of psychosis, then the earlier identification of those at risk could become a reality. Moreover, a deeper understanding of the IQ-SSD link could shed light on the biological mechanisms underlying psychosis, potentially leading to more targeted interventions.

This dissertation takes a multifaceted approach to studying a sample of FEP patients in order to address the complex interplay between IQ and SSDs. The FEP population is valuable for studying neuropsychological performance early in the development of SSD. In addition to reducing the likelihood of capturing the effects of chronicity of the disorder, performance on IQ tests close to the onset of psychosis can serve as a proxy measure of premorbid neurocognitive functioning.

A longitudinal study is needed to analyse the intellectual trajectory of FEP patients over time. While previous research has documented lower IQs in individuals experiencing a FEP, the long-term course of intellectual functioning remains unclear. The longitudinal study addresses this gap by using a 10-year follow-up period. This extended timeframe allows us to investigate whether people with SSDs show intellectual decline, stability or even improvement at the long-term.

Interestingly, recent research suggests that the risk of SSDs may not be due to low IQ, but rather to a significant deviation from expected neurocognitive abilities within the family. To explore this assumption, a family study is required. By studying unaffected relatives of FEP patients, it would be possible to estimate the familiality of IQ and whether affected individuals deviate from their family potential.

A growing body of evidence points to a possible genetic basis for the IQ-SSD association. Therefore, a systematic review is necessary to investigate current research on genetic variations linked to both IQ and SSDs. The study of common genetic polymorphisms between the two phenotypes could lead to the identification of promising targets for further investigation into the biological mechanisms of SSDs.

To explore the potential genetic underpinnings of the IQ-SSD association, a family-based design incorporating PGS may be valuable. PGS provide a robust approach for investigating the complex

genetic architecture of polygenic traits such as IQ and SSDs. By estimating PGS-SZ within families, it can be examined whether the proband with FEP has a greater genetic burden for the disorder compared to their unaffected siblings and parents. Similarly, PGS-IQ can be estimated within families to analyse whether the observed lower IQ in FEP patients compared to their family members and healthy controls has a genetic basis.

In summary, this dissertation uses a multi-method approach that combines endophenotypic and genetic data to comprehensively analyse the relationship between IQ and SSDs. The availability of neuropsychological and DNA data from a well-defined sample within the PAFIP (Programa de Atención a Fases Iniciales de Psicosis) cohort makes this project feasible. The PAFIP program was conducted in Spain from 2001 to 2018 and includes a sample of FEP patients and a sample of healthy controls (see Figure 6). The family-based studies are possible through access to the PAFIP-FAMILIAS project (PI17/00221), which was conducted from 2018 to 2021. The PAFIP-FAMILIAS project collected data from siblings and parents of the previous sample of FEP patients.

This thesis has the potential to significantly improve our understanding of the complex relationship between IQ and SSDs. By investigating a potential neuropsychological endophenotype of SSDs, this research has significant clinical relevance. Improved knowledge of these risk markers could pave the way for the development of more effective prevention strategies and earlier intervention in psychosis. In addition, by characterizing the heterogeneity of intellectual profiles within the SSD spectrum, this research may inform the development of individualized treatment plans tailored to the specific needs of each patient. Furthermore, the identification of environmental and genetic factors associated with SSDs may open new avenues of research into the aetiology of psychosis.

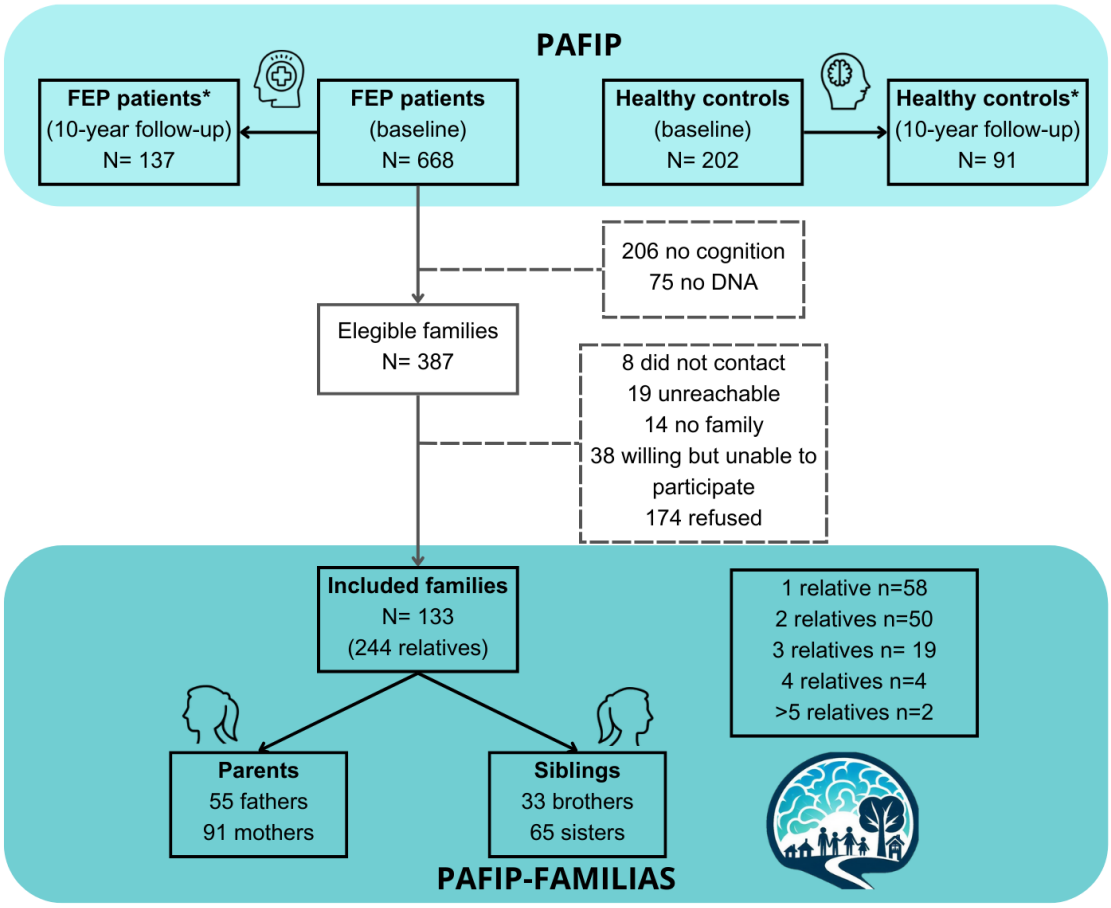

Figure 6. Flow diagram of PAFIP and PAFIP-FAMILIAS.
The participants in this dissertation were selected from the PAFIP and PAFIP-FAMILIAS projects. Final sample sizes for each study are detailed in the results section. *The longitudinal study included FEP patients and healthy controls with IQ measures at baseline and a 10-year follow-up.

General hypothesis and objectives

1. General hypothesis

Based on the literature presented in the introduction, we expected to find strong evidence at the phenotypic and genetic level of IQ as an endophenotype for SSDs (see Figure 7). More specifically:

- Hypothesis 1: The IQ of FEP patients is expected to remain stable in the long term, even 10 years after the onset of psychosis.
- Hypothesis 2: The IQ of first-degree relatives of FEP patients is potentially lower than that of healthy controls, but higher than that of probands. This indicates that neurocognitive deficits may be heritable and stable markers of SSDs.
- Hypothesis 3: IQ is a highly heritable neurocognitive trait and is expected to exhibit low to moderate familiality in FEP patients and their first-degree relatives. Deviation from family IQ is associated with more adverse features in patients.
- Hypothesis 4: The available evidence indicates that several pleiotropic genes contribute to both IQ and schizophrenia risk, suggesting a genetic overlap between the two traits.
- Hypothesis 5: The polygenic score for schizophrenia will have a negative association with IQ in FEP patients and their relatives due to the genetic overlap between the disorder and intelligence.

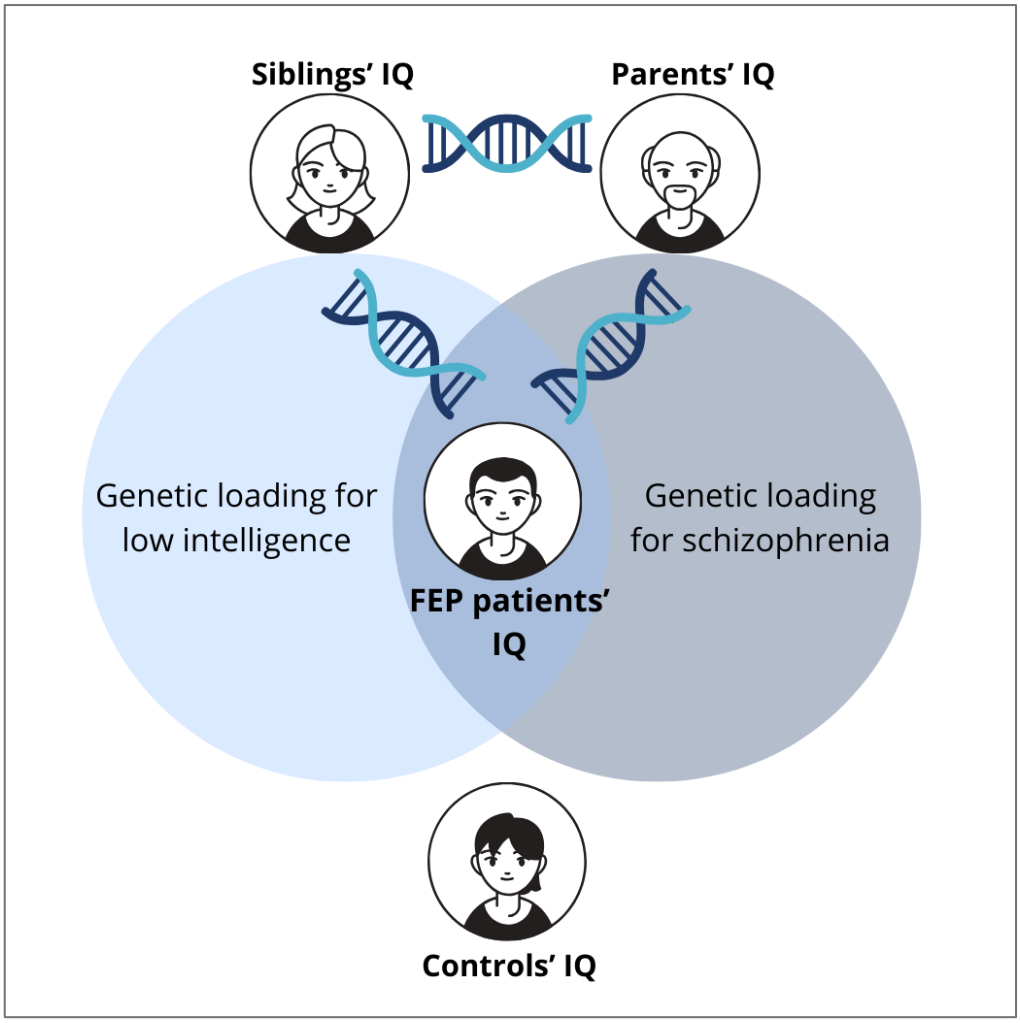

Figure 7. General hypothesis diagram.

The tendency of FEP patients to have low IQ is expected to be influenced by genetic factors for intelligence and schizophrenia. The IQ of FEP patients is expected to deviate negatively from the IQ of their siblings and parents, which is a risk marker for SSDs.

2. Objectives

The aim of this thesis was to investigate the validity of IQ as an endophenotype of SSDs. To achieve this, several specific aims were established:

1. To investigate whether the FEP patients exhibit a decline in IQ over the long term compared to healthy controls.
2. To compare the IQ of first-degree relatives with that of FEP patients and healthy controls to confirm a potential deviation from controls.
3. To examine the intellectual similarity among family members (familiality) and evaluate if patients who differ from their family IQ have more adverse characteristics.
4. To systematically review current evidence on the possible genetic overlap between IQ and SSDs.
5. To test if the genetic burden of schizophrenia measured by polygenic risk scores predicts low IQ in FEP patients and their relatives.

Publications

Study 1: Intelligence quotient changes over 10 years: Diversity of cognitive profiles in first episode of psychosis and healthy controls.

Murillo-García, N., Ortíz-García de la Foz, V., Miguel-Corredera, M., Vázquez-Bourgon, J., Setién-Suero, E., Neergaard, K., Moya-Higueras, J., Crespo-Facorro, B., & Ayesa-Arriola, R.

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Intelligence quotient changes over 10 years: Diversity of cognitive profiles in first episode of psychosis and healthy controls

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ABSTRACT

Objective: This study aimed to analyse whether intelligence quotient (IQ) improves, declines, or remains stable over 10 years among FEP patients and healthy subjects.
Methods: A group of FEP patients enrolled in a Program of First Episode Psychosis in Spain called PAFIP, and a sample of Healthy Controls (HC) completed the same neuropsychological battery at baseline and approximately 10 years later, which included the WAIS vocabulary subtest to estimate premorbid IQ and 10-year IQ. Cluster analysis was performed separately in the patient group and the HC group to determine their profiles of intellectual change.
Results: One hundred and thirty-seven FEP patients were grouped into five clusters: "Improved low IQ" (9.49 % of patients), "Improved average IQ" (14.6 %), "Preserved low IQ" (17.52 %), "Preserved average IQ" (43.06 %), and "Preserved high IQ" (15.33 %). Ninety HC were grouped into three clusters: "Preserved low IQ" (32.22 % of the HC), "Preserved average IQ" (44.44 %), and "Preserved high IQ" (23.33 %). The first two clusters of FEP patients, characterized by a low IQ, earlier age at illness onset, and lower educational attainment, showed a substantial cognitive improvement. The remaining clusters demonstrated cognitive stability.
Conclusions: The FEP patients showed intellectual improvement or stability, but no decline post-onset of psy- chosis. However, their profiles of intellectual change are more heterogeneous than that of HC over 10 years. Particularly, there is a subgroup of FEP patients with a significant potential for long-term cognitive enhancement.

1. Introduction

Extensive research has shown a generalized cognitive impairment in schizophrenia spectrum disorders (Ayesa-Arriola et al., 2018; Fioravanti et al., 2005; Sørensen et al., 2010). The identification of premorbid intelligence quotient (IQ) deficits in childhood and adolescence of affected individuals (Cosway et al., 2000; Dickson et al., 2012) supports the theory that schizophrenia is a neurodevelopmental disorder (Khandaker et al., 2011; Murray and Lewis, 1987). Agnew-Blais et al. (2015) re- ported that low IQ, along with behavioural problems during childhood, were specific markers of risk for schizophrenia. Furthermore, a meta-analysis found that the risk of schizophrenia had a dose-response effect on IQ, both in verbal and nonverbal abilities (Khandaker et al., 2011). However, although the literature shows evidence of IQ deficits prior to a first episode of psychosis (FEP), the subsequent long-term intellectual course is unclear.

To date, results on the trajectory of intellectual course post-FEP have varied. Several studies have found IQ stability in FEP patients after follow-up periods of 3-years (Leeson et al., 2011) and 5-years (Hedman et al., 2012). This stands in contrast to a meta-analysis that reported an

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increase of IQ by 0.33 points per year on average (Hedman et al., 2013). To put this into context, Jepsen et al. (2010) proposed that while patients can acquire new intellectual information and increase their IQ scores, they do so ultimately slower than healthy people. In contrast to evidence supporting either stability or increase, a third group of studies has indicated a trend toward IQ decline post-FEP (Fujino et al., 2017; Ohi et al., 2021), including Zanelli et al. (2019), who identified a decrease in IQ, verbal knowledge, and memory at 10-year follow-up. This heterogeneity of results suggests the existence of different intellectual trajectories among FEP patients, probably associated with other clinical, neurocognitive, and genetic characteristics. In fact, Panayiotou et al. (2020) proposed studying the intellectual course of schizophrenia patients taking into account whether their IQ is low or high.

It is important to recognize and describe the diversity of cognitive profiles among individuals who have experienced a FEP, as they are associated with different patterns of functional outcomes and treatment needs (Ayesa-Arriola et al., 2021). Recently, Dickinson et al. (2020) grouped individuals with schizophrenia into three clusters based on premorbid and current IQ, one of which showed preadolescent impairment, another adolescent decline, and the last one cognitive stability. Knowing the intellectual trajectory of FEP patients and comparing it with that of healthy people could be relevant to understand the role of premorbid factors in the evolution of the disorder. For instance, a trajectory of cognitive decline could indicate a post-FEP neurodegenerative process, requiring treatment strategies that slow deterioration. Other- wise, trajectories suggesting that the cognitive impairment in FEP re- mains stable or improves may indicate underlying neurodevelopmental alterations that require prevention and cognitive stimulation.

The main objective of this study was to analyse whether IQ improves, declines, or remains stable over 10 years in a sample of FEP patients and healthy controls (HC). Furthermore, we aimed to identify different in- tellectual profiles among FEP patients, and then compare their socio- demographic, clinical, and neurocognitive characteristics. Based on previous findings, we hypothesized that both FEP patients and HC would show IQ stability rather than improvement or decline.

2. Methods

2.1. Study design and setting

This is a retrospective observational study that analyses the cohort of first episode psychosis in Spain named PAFIP (Ayesa-Arriola et al., 2021), a longitudinal intervention program conducted at the University Hospital Marqu´es de Valdecilla where patients were referred from health-care services located in the region (Ayesa-Arriola et al., 2020). From February 2001 to July 2008, PAFIP patients completed a baseline evaluation, and approximately 10 years later (within a range between 8 and 12 years) they were invited to carry out a follow-up reassessment (Ayesa-Arriola et al., 2021).

The program was approved by the local institutional review board (ethics committee for research with medicine, CEIm Cantabria) according to international standards for research ethics (clinical trial numbers NCT0235832 and NCT02534363). All participants gave written informed consent.

2.2. Subjects

Out of the 307 patients assessed at baseline, 209 individuals completed the 10-year reassessment (Ayesa-Arriola et al., 2020, 2021). Baseline inclusion criteria were age between 15 and 60 years; living in the catchment area; experiencing a first episode of psychosis; and being antipsychotic medication naïve, or if previously treated, a total lifetime of adequate antipsychotic treatment of <6 weeks. Exclusion criteria were meeting the DSM-IV criteria for drug or alcohol dependence, having an intellectual disability, and/or 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) (Spitzer et al., 1992) conducted by an experienced psychiatrist within 6 months of the baseline visit.

A group of 229 healthy controls (HC) underwent the same neurocognitive assessment as patients at baseline, while 91 of them completed the 10-year reassessment. They were recruited through advertisements from the local community and had no history of psychiatric disorders, mental disability, neurological or general medical illnesses, as established by the abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, 1987). HC were selected to have a similar distribution in age and sex to the patients.

2.3. Sociodemographic and clinical assessment

At baseline, sociodemographic data (sex, age, age of psychosis onset, years of education, cannabis consumption) were obtained from patients, their relatives and medical records on admission. Age at psychosis onset was defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred. Social premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), with ratings from 0 (indicating the "better") to 6 (denoting the "worse").

Clinical assessment was performed at baseline and after 6 weeks, 3 months, 12 months, 24 months and 36-month-follow-up by a trained psychiatrist (B.C.F.). Symptoms of psychosis were measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The duration of untreated illness (DUI, defined as the time from the first nonspecific symptom related to psychosis) and the duration of untreated psychosis (DUP, defined as the time from the first continuous psychotic symptom to initiation of adequate antipsychotic drug treatment) were estimated. At the 10-year follow-up, information on positive symptoms (using the SAPS), negative symptoms (using the SANS) and cannabis use was re-explored.

2.4. Estimation of premorbid IQ and 10-year IQ

We estimated premorbid IQ and 10-year IQ through the WAIS-III Vocabulary subtest. Previous research has demonstrated that Vocabulary is an appropriate measure of premorbid IQ (de Oliveira et al., 2014; Ringe et al., 2002; Wechsler, 1997), since it assess crystallized intelligence in both in the general population and in individuals with FEP (Lezak et al., 2004). Crystallized intelligence differs from fluid intelligence at the genetic level (Christoforou et al., 2014), is more stable allowing to estimate the cognitive ability previous to the onset of the disorder, and is related to the education attainment and the linguistic information of the native language (de Oliveira et al., 2014). Based on this evidence, our group has previously used Vocabulary as a proxy measure for premorbid intelligence, showing utility to study the IQ of FEP patients (Ayesa-Arriola et al., 2018).

Because the trajectory of crystallized intelligence is less age- dependent (Ardila, 2007; Beier and Ackerman, 2005), we used again Vocabulary to estimate IQ at the 10-year follow-up. This measure has a high test-retest reliability (Iverson, 2001), so we consider it provides a proxy measure of 10-year IQ that could detect non-age related cognitive change. Furthermore, by using the same test at both moments of the evaluation, we could avoid possible biases derived from comparing different measurement tools.

2.5. Neurocognitive assessment

At baseline, patients answered the neuropsychological battery on average 10.5 weeks (SD 6.17) after entering the PAFIP program (once they were stable). Verbal memory was measured with the Rey Auditory Verbal Learning Test (RAVT) (Rey, 1964); visual memory with the Rey Complex Figure (RFC) (Osterrieth, 1944); processing speed with the

WAIS-III Digit Symbol subtest (Wechsler, 1997); working memory with the WAIS-III Digits Backward subtest (Wechsler, 1997); executive function with the Trail Making Test part B (TMTB) (Lezak et al., 2004); motor dexterity with the The Grooved Pegboard Test (Lezak et al., 2004); and attention with the Continuous Performance Test (CPT) (Cegalis and Bowlin, 1991). Raw scores were transformed into Z scores using a sample of 187 healthy volunteers described in previous studies (Seti´en-Suero et al., 2019).

Afterward, the Global Cognitive Functioning (GCF) score was estimated following Reichenberg et al. (2009). First, the T scores of each neuropsychological test were converted to deficit scores ranging from 0 to 5. The deficit score of 0 (T score > 40) indicates absence of impairment; a score of 1 (T score 39 to 35) mild impairment, a score of 2 (T score 34 to 30) mild to moderate impairment, a score of 3 (T score 29 to 25) moderate impairment, 4 (T score < 20) moderate to severe impairment (T score 24 to 20), and a score of 5 a severe impairment. Second, the GCF was calculated from the mean of the deficit scores of all the neuropsychological tests. Previous studies have established that a GCF greater than or equal to 0.5 indicates overall impairment (Reichenberg et al., 2009).

At the 10-year re-evaluation the same neuropsychological battery was carried out.

2.6. Statistical analysis

The data were analysed using the Statistical Package for Social Sci- ence (SPSS) 21.0. First, a hierarchical cluster analysis was performed to determine the patients' clusters by inputting their estimated premorbid IQ and their 10-year IQ. The hierarchical cluster analysis was based on Ward's linkage method and squared Euclidean distance. After visual inspection of the resulting dendrogram and the analysis of agglomeration coefficient changes, the definitive number of clusters was established. Next, a K-means cluster analysis was carried out and the final solution was confirmed by discriminant function analysis. Analysis of variance (ANOVA) or χ2 were used to compare sociodemographic, clinical, and neurocognitive variables between clusters. Neurocognitive comparisons were covariated with age, sex, and years of education. Post- hoc comparisons with Bonferroni correction were conducted to examine pairwise relationships.

Finally, the HC group was subjected to a hierarchical cluster and a K-means cluster analysis using their premorbid IQ and their 10-year IQ, following the same process.

3. Results

3.1. Clusters of FEP patients

Out of the 209 FEP patients that completed the 10-year follow-up evaluation, 137 (55.47 % males) had available information to esti- mate their premorbid IQ and their 10-year IQ (see Fig. 1). When comparing FEP patients completing and no completing the follow-up assessment (Supplementary material Table 1A), we observed that non- completers had a worse premorbid adjustment in childhood (p 0.007) and consumed cannabis at a higher rate in baseline (p 0.003).

After introducing these two variables in the hierarchical cluster analysis a five-cluster solution was suggested, and therefore introduced in the K-means analysis. This solution was confirmed by discriminant function analysis (see Fig. 2). From the five clusters of FEP patients, two showed an IQ improvement, while the other three showed IQ stability at the 10-year reassessment (see Table 1 and Fig. 3). No evidence of IQ decline was observed in our sample. The neurocognitive profile of each cluster is plotted in Supplementary material, Fig. 1A.

3.1.1. Cluster 1 (improved low IQ)

Despite of the IQ improvement observed, these patients (9.49 % of the FEP patients) obtained a low IQ at both assessments. They had completed significantly less years of education and showed worse premorbid adjustment in childhood and early adolescence compared to other clusters. They had the lowest neurocognitive performance of all patients, particularly in attention and executive functions. At 10-year follow-up, they had more negative symptoms than other clusters (Table 2).

3.1.2. Cluster 2 (improved average IQ)

These patients (14.60 % of the patients) showed the greatest improvement in IQ, going from a low premorbid IQ to an average IQ at the 10-year re-assessment. They were younger at the psychosis onset and had completed less years of education than others. There were more

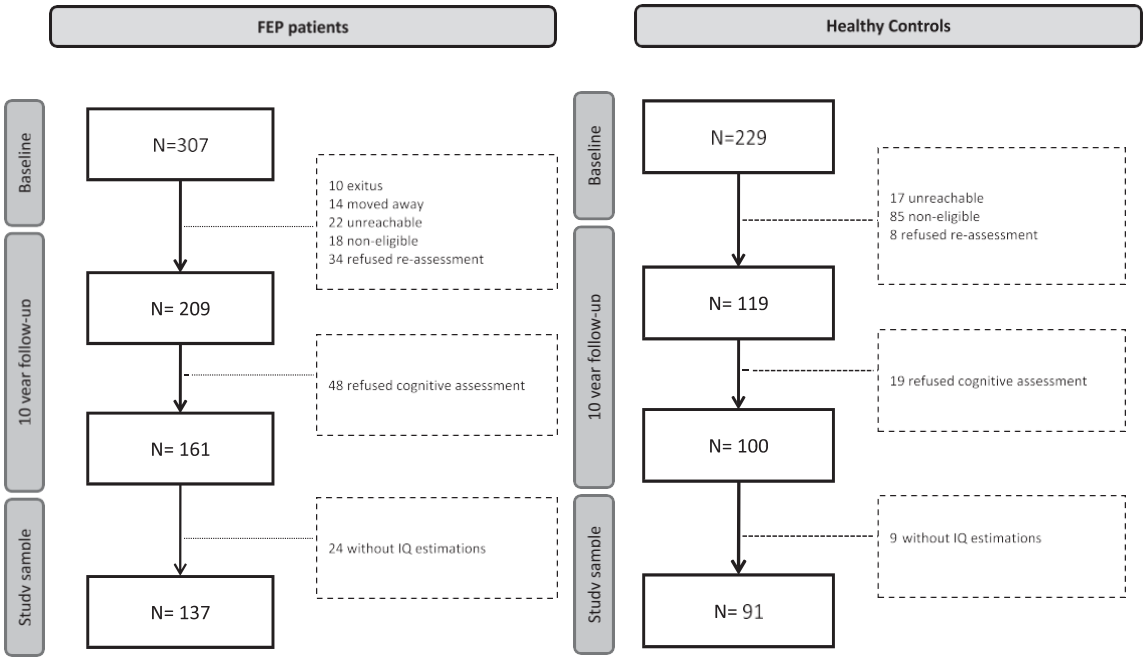

Fig. 1. Flow diagram for study participants. Representation of individuals recruited at baseline and reassessed at 10-year follow-up. The "non-elegible" label refers to people who, at the time of the follow-up evaluation, had passed <8 years since completing the baseline evaluation.

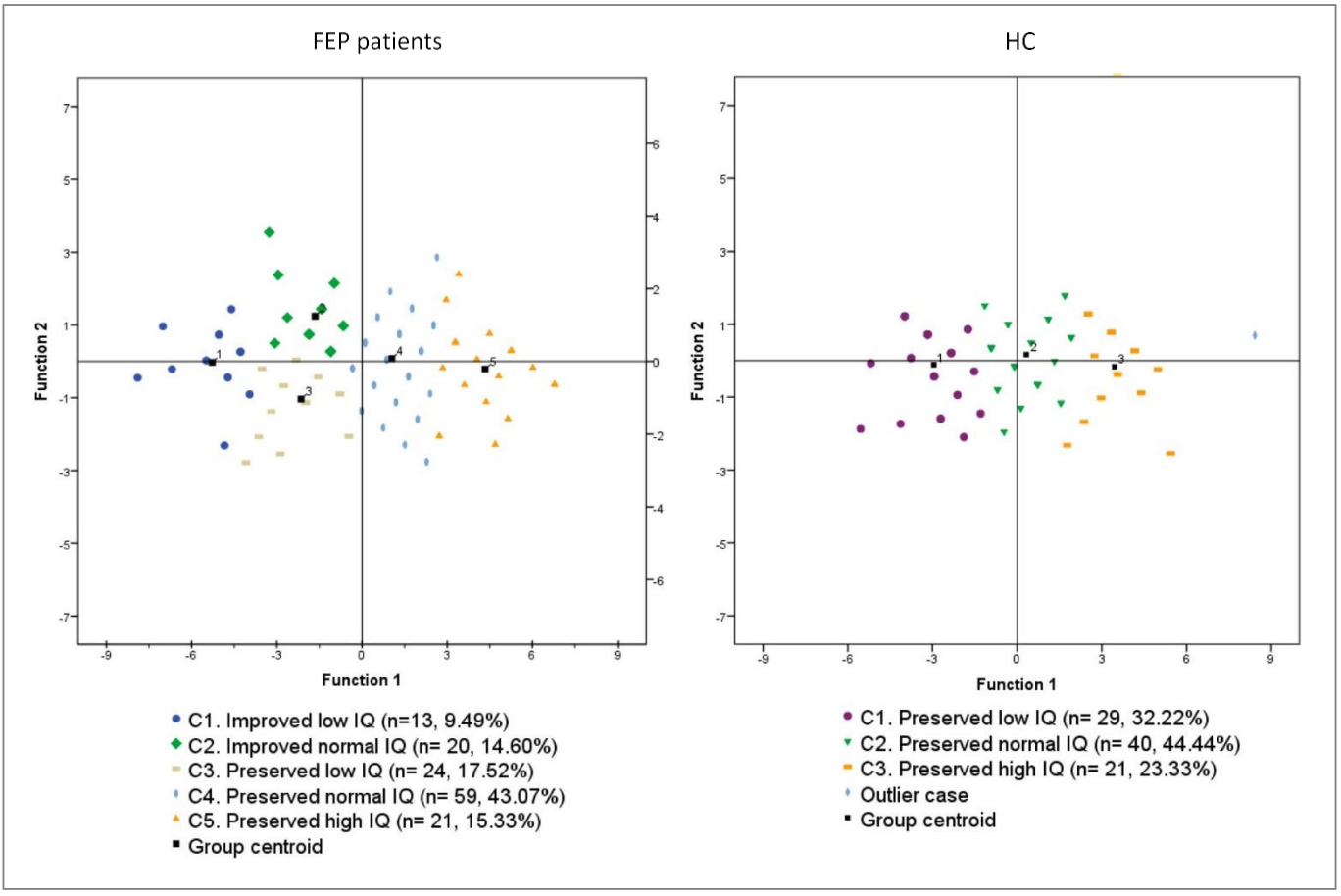

Fig. 2. Cluster membership of FEP patients and HC. Using discriminant analysis, standardized coefficients of two discriminant functions were estimated after setting premorbid IQ and 10-year IQ as predictor variables and cluster membership as grouping variable. This diagram represents the dispersion of the participants in the resulting functions. Wilks' lambda test showed that the mean of the discriminant functions was significantly different between the groups ($p < 0.001$), confirming that the clusters behave differently.

male patients and cannabis users at baseline in this cluster than in others. At baseline, they performed like patients with high IQ in working memory, and at 10-year follow-up, they outperformed those with low IQ (clusters 1 and 3) in several neurocognitive domains.

3.1.3. Cluster 3 (preserved low IQ)

Patients with a stable low IQ (17.52 % of the patients). They were younger at onset, had completed less years of education, and had worse childhood adjustment and worse general premorbid adjustment than others. They underperformed other patients in attention at baseline, and in motor dexterity at 10-year follow-up.

3.1.4. Cluster 4 (preserved average IQ)

Patients with a stable average IQ (43.07 % of the patients). Their educational attainment and neurocognitive performance was intermediate between the previous clusters and the cluster with high IQ at both moments of assessment.

3.1.5. Cluster 5 (preserved high IQ)

Patients with a stable high premorbid IQ (15.33 % of the patients). Compared to other patients, these were older at the psychosis onset, had completed more years of education, and showed a better adjustment during childhood and early adolescence. Overall, they had a better neurocognitive performance than others at both assessments.

3.2. Clusters of healthy controls (HC)

Ninety-one HC had estimations of premorbid IQ and 10-year IQ, butan outlier with scores of 130 and 135 respectively was eliminated fromthe analysis (see Fig. 1). When comparing completers and non-completers at baseline (Supplementary material, Table 2A), weobserved that the first ones had completed fewer years of education (p 0.002). The results of the hierarchical cluster analysis suggested a three-cluster solution, so a K-means analysis with this characteristic was run(see Table 3, Figs. 2, 3).

All three clusters of HC had a preserved IQ since their premorbid IQ remained similar after 10 years. Cluster 1 (32.22 % of the HC) had a low IQ, had completed less years of education and underperformed others in most neurocognitive domains. Cluster 2 (44.44 % of the HC) had an average premorbid IQ, and an intermediate neurocognitive performance between others. Cluster 3 (23.33 % of the HC) had a high premorbid IQ, had completed more years of education and performed better in most neurocognitive domains. The neurocognitive profile of each cluster is plotted in Supplementary material, Fig. 2A.

4. Discussion

In this study, we analysed whether IQ scores improve, decline, or remain stable over 10 years in FEP patients and HC, and identified different intellectual profiles through cluster analysis. We found that the intellectual course of FEP patients differs from that of unaffected in- dividuals because they were grouped differently based on their IQ

Table 1. Sociodemographic and clinical characteristics of FEP patients according to their membership cluster.

	Improved low IQ (C1) N= 13	Improved average IQ (C2) N= 20	Preserved low IQ (C3) N= 24	Preserved average IQ (C4) N= 59	Preserved high IQ (C5) N= 21			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	P	Paired comparisons
Premorbid IQ	71.15 (6.50)	84.50 (5.10)	88.96 (5.31)	100.76 (4.90)	117.14 (7.34)	180.87	<0.001	1<2*, 1<3*, 1<4*, 1<5*, 2<4*, 2<5*, 3<4*, 3<5*, 4<5*
10-year IQ	85.38 (5.94)	103.25 (4.06)	90.00 (5.32)	105.76 (6.49)	114.52 (6.87)	77.47	<0.001	1<2*, 1<4*, 1<5*, 2>3*, 2<5*, 3<4*, 3<5*, 4<5*
Points of IQ change	14.23 (8.13)	18.75 (7.23)	1.04 (6.59)	5.00 (8.51)	-2.62 (10.08)	23.21	<0.001	1>3*, 1>4**, 1>5*, 2>3*, 2>4*, 2>5*, 4>5**
Age	26.44 (6.07)	24.85 (4.08)	25.99 (8.49)	30.86 (9.54)	33.20 (8.81)	4.350	0.002	2<5**, 3<5***
Age under 20 (yes %)¶	2 (15.4%)	2 (10%)	5 (20.8%)	6 (10.2%)	0	χ2= 5.304	0.257	-
Age of onset	25.54 (5.81)	24.11 (4.19)	25.46 (8.41)	29.68 (9.26)	32.14 (8.48)	3.993	0.004	2<5***
Sex (male %)	7 (53.8%)	15 (80%)	15 (62.5%)	29 (49.1%)	9 (42.8%)	χ2= 7.672	0.104	2>4***; 2> 5***
Years of education	8.31 (2.14)	9.00 (2.10)	9.00 (2.13)	11.63 (3.39)	14.38 (3.15)	15.818	<0.001	1<4**, 1<5*, 2<4**, 2<5*, 3<4**, 3<5*, 4<5**
PAS Childhood	2.95 (1.10)	2.48 (1.45)	2.74 (1.48)	1.90 (1.18)	1.46 (0.98)	4.889	0.001	1>5**, 3>5**
PAS Early adolescence	3.27 (0.75)	2.93 (1.36)	2.95 (1.47)	2.15 (1.17)	1.95 (0.99)	4.869	0.001	1>4***, 1>5***
PAS Late adolescence	2.71 (1.53)	3.21 (1.68)	3.33 (1.82)	2.44 (1.47)	2.31 (1.48)	2.066	0.089	-
PAS Adulthood	2.83 (2.26)	2.39 (2.36)	3.04 (2.97)	1.71 (1.89)	2.06 (2.49)	1.403	0.238	-
PAS General	3.62 (1.69)	3.56 (2.00)	3.99 (2.23)	2.79 (1.72)	2.21 (1.72)	3.241	0.014	3>5***
Cannabis at baseline (yes%)	6 (46.15%)	12 (60%)	9 (37.50%)	15 (25.42%)	7 (33.33%)	χ2= 8.556	0.073	2>4**
Cannabis at 10-years (yes%)	2 (15.3%)	1 (5%)	3 (12.50%)	3 (5.08%)	0	χ2= 4.790	0.310	-
DUP (months)	10.77 (16.50)	8.94 (9.79)	6.42 (9.47)	14.08 (28.46)	12.77 (20.02)	0.628	0.643	-
Schizophrenia diagnosis (yes%)	7 (53.8%)	14 (70%)	17 (70.8%)	35 (59.3%)	12 (57.1%)	2.096	0.718	-
SAPS at baseline	12.69 (3.61)	13.00 (4.09)	12.79 (4.15)	13.56 (4.76)	12.19 (4.57)	0.432	0.785	-
SANS at baseline	8.62 (5.90)	7.75 (7.43)	10.38 (6.6)	7.63 (6.05)	5.86 (5.42)	1.563	0.188	-
SAPS at 10-years	2.77 (5.96)	1.90 (4.16)	2.50 (3.57)	0.76 (1.41)	0.10 (0.30)	3.312	0.013	-
SANS at 10-years	7.23 (6.47)	2.60 (4.68)	6.17 (5.81)	3.39 (3.63)	2.95 (3.20)	4.109	0.004	1>2***

DUP: duration of untreated psychosis; FEP: First Episode Psychosis; IQ: Intelligence Quotient; PAS: Premorbid Adjustment Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms. Note: all paired comparisons were conducted with Bonferroni correction.
*** $p < 0.050$. ** $p < 0.010$. * $p \leq 0.001$. [a] Age ranges: C1 = 17.92–34.33; C2 = 18.95–30.55; C3 = 17.18–49.07; C4 = 15.91–57.84; C5 = 20.47–51.66.

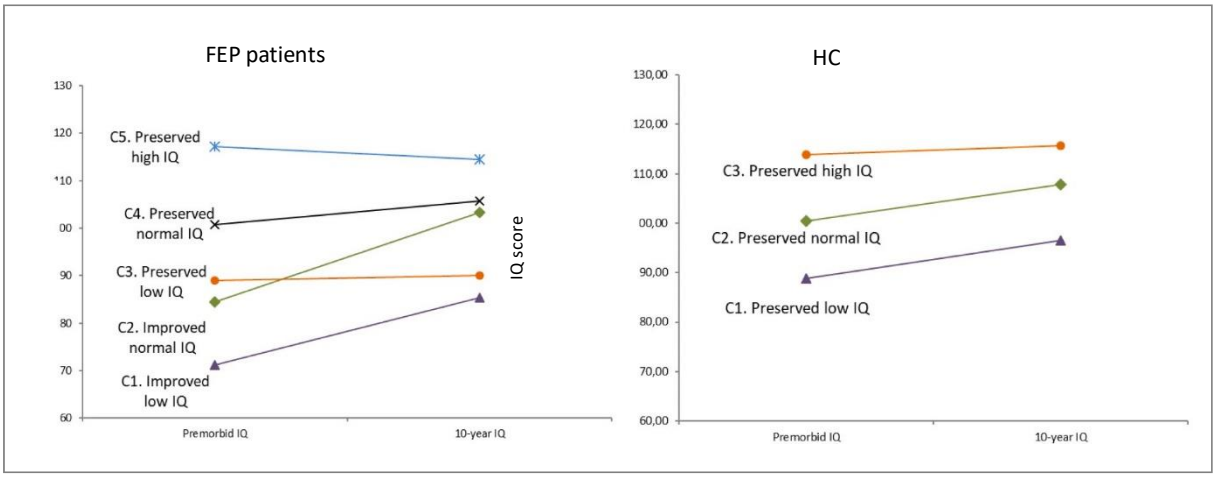

Fig. 3. IQ change of FEP patients and HC from baseline to 10-year follow-up. The graphs show the mean points of IQ change among the obtained clusters, where steep slopes indicate improvement.

estimations. While HC were classified into three clusters, FEP patients were subdivided into five groups with different neurocognitive profiles. This result replicates previous findings on the heterogeneity of cognitive course after the psychosis onset (Fett et al., 2020; Hedman et al., 2013; Ohi et al., 2021; Zanelli et al., 2019). But contrasts with others showing three instead of five different patterns of cognitive change among FEP patients (Badcock et al., 2005; Dickinson et al., 2020).

Generally, we found that all participants, both patients and HC, can

Table 2. Neurocognitive performance of FEP patients according to their membership cluster.

	Improved low IQ (C1) N= 13	**Improved average IQ** (C2) N= 20	**Preserved low IQ** (C3) N= 24	**Preserved average IQ** (C4) N= 59	**Preserved high IQ** (C5) N= 21			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	P	Paired comparisons
Baseline								
Verbal memory	-3.09 (1.42)	-2.97 (0.95)	-2.38 (1.31)	-2.18 (1.21)	-1.41 (1.55)	3.93	0.005	1<4*** 1<5* 2<4*** 2<5* 3<5*** 4<5***
Visual memory	-1.22 (1.12)	-0.56 (0.88)	-0.58 (0.98)	-0.43 (1.00)	0.03 (0.91)	2.76	0.030	1<4*** 1<5*
Processing speed	-1.77 (0.98)	-2.13 (0.89)	-1.65 (0.95)	-1.46 (0.99)	-0.73 (0.95)	4.36	0.002	1<5** 2<4** 2<5* 3<5** 4<5**
Working memory	-0.82 (0.52)	-0.10 (0.70)	-0.68 (0.64)	-0.54 (0.77)	0.03 (1.11)	4.07	0.004	1<2** 1<5** 3<2*** 3<5** 4<2*** 4<5**
Executive function	-2.87 (2.69)	-1.14 (1.54)	-0.51 (1.87)	-1.00 (1.70)	-0.23 (0.57)	4.97	0.001	1<2** 1<3*1<4* 1<5*
Motor dexterity	-1.85 (2.54)	-0.99 (1.52)	-2.38 (6.05)	-0.95 (1.22)	-0.68 (1.04)	1.17	0.326	ns
Attention	-3.14 (3.24)	-3.97 (5.97)	-4.93 (6.07)	-1.59 (3.33)	-1.41 (3.89)	2.20	0.073	3<4** 3<5***
GCF	2.15 (0.90)	1.71 (0.95)	1.65 (1.13)	1.24 (0.84)	0.76 (0.63)	3.92	0.005	4<1** 5<1* 5<2** 5<3**
10 years								
Verbal memory	-2.59 (1.46)	-2.29 (0.96)	-2.64 (1.35)	-1.67 (1.23)	-0.75 (1.26)	6.09	<0.001	1<4***1<5*2<5* 3<4** 3<5* 4<5**
Visual memory	-1.40 (0.59)	-0.51 (0.74)	-0.81 (0.82)	-0.42 (0.72)	-0.09 (0.73)	6.18	<0.001	1<2* 1<3*** 1<4* 1<5* 3<4*** 3<5**
Processing speed	-1.34 (0.92)	-0.56 (1.04)	-1.16 (0.69)	-0.49 (0.91)	-0.48 (0.90)	4.38	0.002	1<2** 1<4** 1<5**3<2*** 3<5***
Working memory	-1.19 (0.54)	-0.22 (0.84)	-0.78 (0.72)	-0.42 (0.73)	0.17 (0.73)	7.25	<0.001	1<2* 1<4* 1<5* 3<2*** 3<5* 4<5**
Executive function	-1.67 (1.71)	-0.25 (1.40)	-1.55 (1.85)	-0.51 (1.35)	-0.59 (1.48)	3.49	0.010	1<2*** 1<4*** 3<2** 3<4**
Motor dexterity	-1.46 (1.10)	-1.41 (3.33)	-2.53 (3.91)	-0.63 (1.43)	-0.39 (1.40)	2.85	0.027	3<4* 3<5**
Attention	-4.98 (6.60)	-1.57 (2.71)	-3.94 (6.38)	-0.76 (2.65)	-1.23 (4.55)	3.75	0.006	1<2*** 1<4** 1<5*** 3<4**
GCF	1.84 (0.84)	0.99 (0.78)	1.54 (0.83)	0.79 (0.77)	0.59 (0.67)	6.50	<0.001	2<1** 2<3*** 4<1* 4<3* 5<1* 5<3*
Z-score change						Time effect		
Verbal memory	0.50	0.68	0.19	-0.50	- 0.68	0.64	0.424	-
Visual memory	- 0.18	0.06	0.23	0.18	- 0.06	4.07	**0.046**	-
Processing speed	0.42	1.57	1.15	-0.42	- 1.57	0.85	0.358	-
Working memory	- 0.37	- 0.12	0.24	0.37	0.12	2.61	0.108	-
Executive function	1.20	0.89	-0.32	-1.20	- 0.89	0.73	0.392	-
Motor dexterity	0.39	-0.43	-0.81	-0.39	0.43	7.01	**0.009**	-
Attention	- 1.84	2.39	4.24	1.84	- 2.39	1.77	0.185	-
GCF	- 0.31	- 0.73	-0.41	0.31	0.73	0.73	0.394	-

GCF: Global Cognitive Functioning; FEP: First Episode Psychosis. Notes: neurocognitive comparisons are covariated by sex, age and years of education. All paired comparisons were conducted with Bonferroni correction. *** $p < 0.050$. ** $p \leq 0.010$. * $p \leq 0.001$.

improve their IQ scores in the long term. According to Hartshorne and Germine (2015), crystallized intelligence peaks around age 50 in the general population, therefore, the HC's slight improvement in the vocabulary subtest can be considered normal. However, the greater increase of FEP patients might suggest that at baseline they performed below their cognitive abilities, thus having a bigger window for improvement in the long term, probably due to a neurodevelopmental alteration. A similar intellectual rise over time post-FEP has been previously reported and linked to the practice effect (Van Haren et al., 2019), which allows to improve the cognitive performance after repeated exposures (Albus et al., 2006; Hedman et al., 2013). Our finding demonstrates that FEP patients can manage new information despite their underlying intellectual deficit. Since age influences this effect (Granholm et al., 2010), the great increase of patients in the clusters "Improved low IQ" and "Improved average IQ" could be explained in part by the fact that they were younger than HC. However, after comparing the proportion of individuals under age 20 in each cluster, we observed no significant differences. Therefore, we can rule out that these patients had an underestimation of their premorbid IQ due to a young age at baseline, and their IQ gain would be related to other features. Although our results differ from others indicating a lack of cognitive improvement post-FEP (Albus et al., 2006; Fujino et al., 2017; Zanelli et al., 2019), the discrepancies may be related to the data analysis strategy. The cluster analyses used in this study might have identified two subgroups of FEP patients with an outstanding potential for cognitive improvement. They were characterized by an earlier age at onset of psychosis and lower educational attainment. Consequently, these results could justify the early treatment of psychosis, both in its clinical and cognitive dimensions.

In total 49 patients from our sample were cannabis users at baseline, of whom 9 continued to use at 10 years of follow-up. Although our sample size lacks the statistical power to draw conclusions in this regard, it is relevant to further study the possible effects of cannabis withdraw on the intellectual course. A pattern of cognitive improvement was described in a previous study of our group (Setien-Suero et al., 2019), and agrees with Weibell et al. (2019) who observed that early substance discontinuation among FEP patients was related to cognitive, clinical, and functional improvements. Hence, stopping cannabis use could

Table 3. Sociodemographic characteristics and neurocognitive performance of HC according to their membership cluster.

	Preserved low IQ (*N* = 29) Mean (SD)	Preserved average IQ (*N* = 40) Mean (SD)	Preserved high IQ (*N* = 21) Mean (SD)	F	P	Paired comparisons
IQ at baseline	88.79 (5.61)	100.50 (4.64)	113.81 (5.90)	137.71	<0.001	1 < 2*. 1 < 3*. 2 < 3*
10-Year IQ	96.55 (5.84)	107.88 (5.76)	115.71 (5.76)	70.33	<0.001	1 < 2*. 1 < 3*. 2 < 3*
Points of IQ change	7.76 (8.82)	7.38 (7.59)	1.90 (9.81)	3.513	0.034	–
Age	30.58 (8.28)	29.63 (9.66)	28.40 (6.03)	0.40	0.670	–
Age under 20 (yes %)[a]	5 (17.2 %)	7 (17.5 %)	3 (14.3 %)	χ2 = 0.113	0.945	
Sex (male %)	13 (44.82 %)	23 (57.50 %)	11 (52.3 %)	1.08	0.582	–
Years of education	10.34 (1.52)	10.68 (2.80)	13.89 (2.56)	14.82	<0.001	1 < 3*. 2 < 3*
Neurocognitive performance at baseline						
Verbal memory	−1.45(1.17)	−1.14 (1.32)	−0.81 (1.06)	1.51	0.227	–
Visual memory	−0.44(1.23)	0.15 (0.90)	0.05 (0.71)	3.83	0.026	1 < 2**
Processing speed	−0.17(1.04)	0.10 (0.86)	0.65 (0.88)	3.33	0.041	1 < 3***
Working memory	−0.25(0.97)	0.15 (0.99)	0.25 (0.97)	1.74	0.182	–
EXecutive function	−0.40(1.24)	0.16 (0.73)	0.26 (0.87)	3.27	0.043	1 < 2*** 1 < 3***
Motor dexterity	0.15(0.78)	−0.04 (0.93)	0.26 (0.56)	0.86	0.429	–
Attention	−0.55(1.38)	0.04 (1.02)	0.22 (0.54)	2.82	0.066	1 < 2*** 1 < 3 (p = 0.051)
GCF	0.70(0.61)	0.36 (0.43)	0.29 (0.28)	5.43	0.006	2 < 1** 3 < 1**
Neurocognitive performance at 10-year follow-up						
Verbal memory	−1.00 (1.12)	−0.56 (1.13)	−0.52 (1.04)	1.73	0.184	–
Visual memory	0.13 (0.81)	0.34 (0.65)	0.47 (0.69)	1.44	0.243	–
Processing speed	0.36 (0.85)	0.65 (0.69)	1.03 (0.72)	3.76	0.028	1 < 3**
Working memory	−0.27 (0.94)	0.33 (1.04)	0.38 (0.91)	3.93	0.024	1 < 2** 1 < 3***
EXecutive function	−0.05 (0.77)	0.01 (0.71)	0.12 (0.59)	0.25	0.781	–
Motor dexterity	0.59 (0.63)	0.41 (0.99)	0.64 (0.45)	0.70	0.500	–
Attention	−0.66 (2.66)	−0.05 (0.89)	0.68 (0.27)	2.81	0.066	1 < 3***
GCF	0.39 (0.45)	0.21 (0.37)	0.15 (0.21)	2.81	0.066	2 < 1*** 3 < 1 (p = 0.054)
Z-score change				Time effect		
Verbal memory	0.45	0.58	0.29	2.46	0.121	–
Visual memory	0.57	0.19	0.43	0.18	0.674	–
Processing speed	0.53	0.55	0.39	1.31	0.256	–
Working memory	−0.02	0.18	0.13	1.23	0.271	–
EXecutive function	0.34	−0.15	−0.15	0.24	0.624	–
Motor dexterity	0.43	0.45	0.38	4.24	0.043	–
Attention	−0.11	−0.09	0.45	2.83	0.067	–
GCF	−0.30	−0.15	−0.14	1.71	0.195	–

GCF: Global Cognitive Functioning; IQ: Intelligence Quotient; FEP: First Episode Psychosis. Notes: neurocognitive comparisons are covariated by sex, age, and years of education. All paired comparisons were conducted with Bonferroni correction.

*** $p < 0.050$. ** $p < 0.010$. * $p \leq 0.001$. [a] Age ranges: C1 = 18.18–50.16; C2 = 15.15–51.48; C3 = 18.84–39.69.

reverse its potential negative effects on cognition (Setién-Suero et al., 2019), but it is important to consider moderating variables such as the amount and pattern of consumption (Schoeler et al., 2016), sex (Ayesa-Arriola et al., 2020; Setién-Suero et al., 2017), age (Barnes et al., 2006), and genetic factors (Van Winkel et al., 2011). However, there is literature reporting better cognitive functioning associated with cannabis use in FEP (Hájková et al., 2021; Kayir et al., 2022), so current evidence is inconclusive (Ahmed et al., 2021).

The specific neurocognitive profile among clusters of FEP patients may also contribute to their intellectual course. The cluster with the greatest IQ increase showed a relative spare performance in working memory ("Improved average IQ"), while the cluster with the lowest IQ ("Improved low IQ") had the poorer performance in working memory at both assessments. Previous research has described that adolescents at familial high-risk for psychosis have impaired working memory function and altered brain activity during this task (van Gool et al., 2022). Therefore, FEP patients with a noticeable deficit in this domain may represent a subgroup of individuals at higher liability for psychosis from early ages. Other cognitive domains potentially related to this differential profile are attention and executive functioning, since patients in the "Improved low IQ" cluster showed a marked executive dysfunction at baseline and a marked attentional deficit at 10-year follow-up.

A recent study of our group found that these same domains were especially affected in first-degree relatives of FEP patients, which make them suitable endophenotypes for psychotic disorders (Murillo-García et al., 2022).

Our findings corresponds with evidence on low premorbid IQ and cognitive impairment as potential endophenotypes of schizophrenia spectrum disorders (Burdick et al., 2006; Lemvigh et al., 2020; McCarthy et al., 2018). Despite the long-term cognitive improvement of FEP patients, they had a significant higher rate of low premorbid IQ than HC (27.7 % and 13.3 % respectively, χ2 6.609, p 0.037), and obtained worse neurocognitive outcomes at 10-year follow-up. This finding agrees with a previous study from our research group describing that low IQ was more frequent in FEP patients than in controls (Ayesa-Arriola et al., 2018). Even patients in the "preserved" clusters with average and high IQ showed significant impairments in most cognitive domains, contrary to HC with equivalent IQ scores. Which suggests cognitive deficits as markers of the disorder and could be a result of a neuro- developmental alteration (Bertisch et al., 2009; Gur et al., 2015). Moreover, the substantial processing speed deficit in the FEP patients from our sample could have affect their performance in the rest of do- mains (Bechi et al., 2019) despite having an average or high IQ. In addition, HC could have a higher cognitive reserve contributing to a better performance in different cognitive functions (Magdaleno Herreroet al., 2021).

In particular, the FEP cluster "Improved low IQ" allows us to make substantial interpretations. First, they showed more unfavourable pre- morbid characteristics than other patients during childhood and early adolescence, which suggest neurodevelopmental disruption (Dickinsonet al., 2020). Second, their cognitive trajectory was associated with more severe negative symptomatology at 10-year follow-up, replicating previous findings (Leeson et al., 2011). Based on a family approach, Zhang et al. (2018) confirmed the same relationship in first-degree relatives of individuals with schizophrenia, proposing that negative symptoms together with cognitive impairment could indicate a higher genetic riskburden for the disorder. This body of evidence supports the notion of the psychosis spectrum as a continuum over limited diagnostic categories, with patients cognitively impaired and substantial negative symptoms at one end, and patients with high premorbid IQ, better global functioning, and greater insight at the other (Černis et al., 2015).

In this study, no evidence of cognitive decline at 10 years was observed in FEP patients or HC, which is consistent with a recent finding from our group on general cognitive stability across the entire group of patients and healthy subjects (Rodríguez-Sánchez et al., 2020). This result agrees with a systematic review comprised of 26 studies (Bozikasand Andreou, 2011) that described cognitive stability after a FEP and indicated that the cognitive impairment preceded the psychosis onset. Interestingly, our findings suggest that FEP patients cognitively stable (the three clusters of preserved IQ) improved to a lesser degree than HC.This result corresponds with Jepsen et al. (2010), who described adiminished capacity of FEP patients to acquire intellectual information, probably due to a neurodevelopmental alteration. Patients in the "Pre- served high IQ" cluster diminished their 10-year IQ, but their intellectual trajectory could be considered stable because the decrease was minimal. Members of this cluster evidenced protective variables including high premorbid IQ, older age at onset, more years of education, and better premorbid social adjustment, all related to a cognitive reserve that allows coping better with brain pathology (Amoretti et al., 2016; Leeson et al., 2011). In addition, FEP patients with average and high IQ were more frequently women, which replicates previous resultsof our group (Ayesa-Arriola et al., 2018; Rodríguez-Sánchez et al., 2020) and others reporting better cognitive functioning among female patients, and a better course a few years after commencing the treatment of psychosis (Seeman, 2019). In fact, a recent work by our group showed that a higher educational attainment was more frequent among female patients, which was associated with better long-term outcomes (Ayesa- Arriola et al., 2021). Other advantageous situations more frequently found in women than in men with a FEP are older age at onset, lower rates of cannabis use (Ochoa et al., 2012), having employment, marrying, and having children (Ayesa-Arriola et al., 2020; Seeman, 2019), as well as better coping strategies (Li et al., 2014).

Our evidence on cognitive improvement and stability among FEP patients contradicts several findings that reported an IQ decline (Fettet al., 2020; Fujino et al., 2017; Ohi et al., 2021; Zanelli et al., 2019). Theheterogeneity of results might be due to methodological differences such as the characteristics of the participants. For instance, some studies included patients with affective and non-affective psychosis (Agnew- Blais et al., 2015; Jepsen et al., 2010; Leeson et al., 2011), while others (Dickinson et al., 2020; Heaton et al., 2001; Hoff et al., 2005), like ours, exclusively selected non-affective psychosis patients. Likewise, the inclusion of outpatients with probable better cognitive functioning mightcause a loss about inpatients with lower functionality (Fett et al., 2020). Furthermore, the follow-up periods of the studies must be considered because they can inform on cognition at different stages of the disease. However, it would not be appropriate to directly compare their results. Therefore, the cognitive profile described a few years post-FEP (Jepsen et al., 2010; Leeson et al., 2011) could change over the longterm (Fett et al., 2020; Hoff et al., 2005; Zanelli et al., 2019). The evaluation procedure could also explain the variability of the findings, as some authors estimated premorbid and current IQ using different neuropsychological tests in a cross-sectional assessment (Fujino et al., 2017), while others administered the same measure at baseline and follow-up (Jepsen et al., 2010). Finally, the inclusion of HC is relevant due to the need to know the cognitive course in unaffected individuals toproperly interpret the results (Albus et al., 2006; Hedman et al., 2013; Hoff et al., 2005; Ohi et al., 2021).

4.1. Strengths and limitations

The main strength of this study was the long-term design that allows the evaluation of neuropsychological performance at 10-year follow-up.In addition, having the same longitudinal data from a group of HC was valuable as comparisons between outcomes of patients and healthy individuals. However, some limitations were identified. When performingcluster analysis and subdividing the total sample, some groups includedfew members, hindering the generalizations of the findings. Another limitation refers to the retrospective estimation of the premorbid IQ. The patients in our sample were assessed after the FEP; hence this estimation could be less precise than prospective measures in subjects at risk before psychosis onset. Regarding the HC sample, subjects were volunteers not randomly chosen from the population, which could represent a recruitment bias. In addition, both for the sample of FEP patients and HC there were dropouts at the 10-year follow-up, and group comparisons (Supplementary material) showed that patients' non-completers had a worse premorbid adjustment and higher rates of cannabis consumption, while HC non-completers had accomplished fewer years of education. Thus, we could have lost information on participants with possibleworse cognitive outcomes.

5. Conclusions

This study has identified more heterogeneity of intellectual change among FEP patients than in HC at 10-year follow-up, showing stability and different degrees of improvement. Affected individuals with worse premorbid characteristics and low IQ had significant potential for long-term cognitive enhancement, so this subgroup should be a primary target for early drug treatment and cognitive remediation. Our results on the cognitive course of FEP patients suggest a more gradual intellectualrise than healthy people rather than a post-FEP decline. This is consistent with the neurodevelopmental hypothesis of schizophrenia that states that neurocognitive deficits of patients precede the onset of psychosis.

CRediT authorship contribution statement

NMG and RAA formulated the research question and carried out the design of this study. MMC, JVB and ESS participated in the recruitmentand evaluation of the subjects. BCF led the PAFIP cohort and assessed the included patients. VOG participated in data management and analysis. KN and JMH participated in the writing of the article.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.02.025.

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Study 2: A family study on first episode of psychosis patients: Exploring neuropsychological performance as an endophenotype.

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ORIGINAL ARTICLE

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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 re- search in SSD.

KEYWORDS
Cognition, Endophenotypes, Psychotic Disorders, Relatives, Schizophrenia Spectrum Disorders

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

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 geneticand environmental factors potentially related to the dis- ease.[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]

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 functionsassociated with the risk for psychosis is needed. Zhanget 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 subsequentlydeveloped 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]

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.

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 thesuitability 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 specializedin 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 base- line 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, 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.

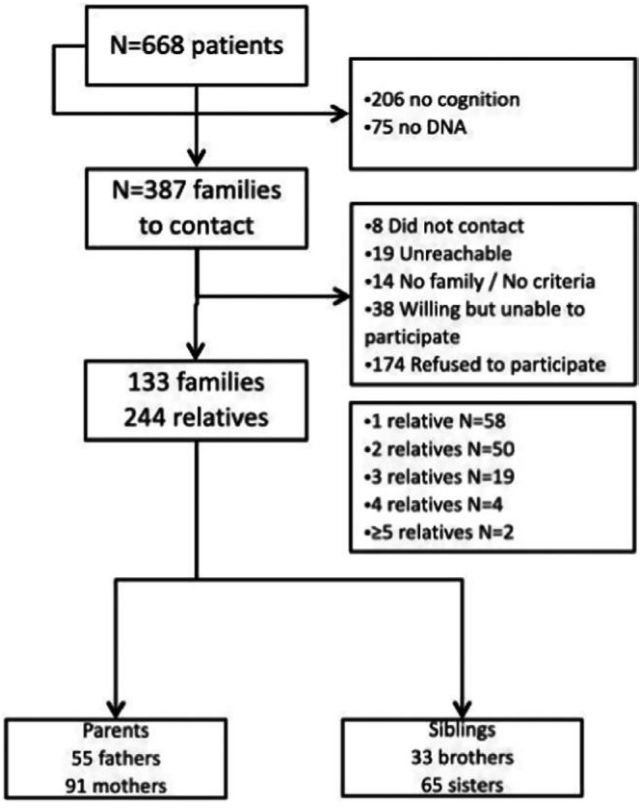

FIGURE 1 Flow diagram for patients and their first-degreerelatives enrolled in the PAFIP-FAMILIAS project

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

2.4 | Sociodemographic andclinical 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 shownto 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 avalid proxy measure of crystallized intelligence.[40] Different tests were used to assess: (1) verbal memory (Rey AuditoryVerbal Learning Test, RAVT[41]); (2) visual memory (ReyComplex Figure, RFC[42]); (3) processing speed (WAIS-III Digit Symbol subtest[39]); (4) working memory (WAIS-IIIDigits Backward subtest[39]); (5) executive function (TrailMaking Test part B, TMTB[43]); (6) motor dexterity (TheGrooved Pegboard Test[43]); (7) attention (ContinuousPerformance Test, CPT[44]); and (8) theory of mind (TheReading the Mind in the Eyes Task, RMET[45]). In order tomake direct comparisons between the performance of thesubjects, the T-scores derived from the WAIS-III subtests(Vocabulary, Digit Symbol, and Digits Backward), and theraw 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 theaverage of the deficit scores of each test. Previous studieshave 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 covariatedwith sex, age, and years of education. When ANCOVA yielded significant differences, pairwise comparisons were conducted with Bonferroni correction. All statisticaltests 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 andclinical 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 siblingswere 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 his- tory of psychopathology, HC reported significantly lower percentage of symptoms throughout life (9.42%) than therest 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 ($p < 0.001$). Regardingattention, 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 scoresin 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 restwith 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)		Parents (P)		Siblings (S)	Controls (HC)			Paired comparisons
		(*N* = 133)		(*N* = 146)		(*N* = 98)	(*N* = 202)	Statistics		
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.

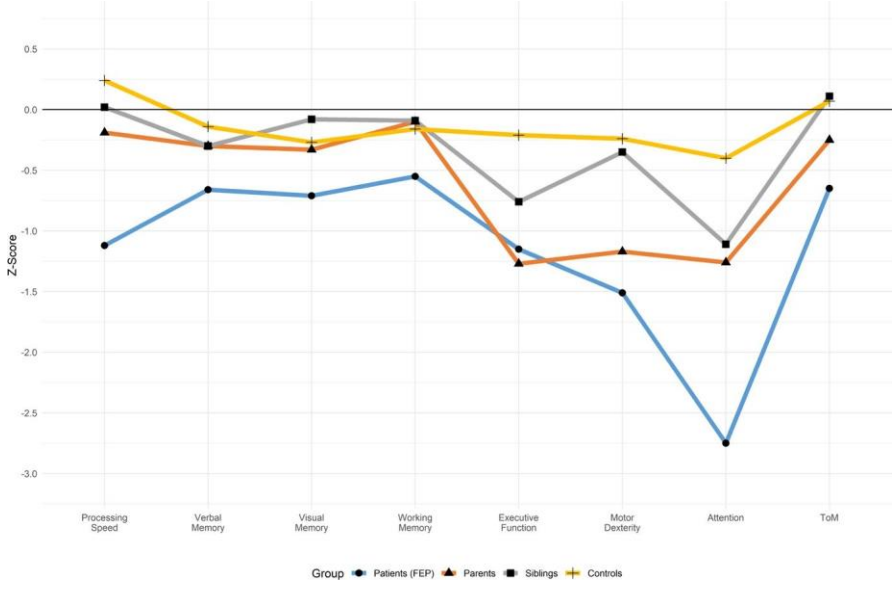

FIGURE 2 Neurocognitive profile of the participants in the PAFIP-FAMILIAS project (*Note*: Scores corrected by sex, age, and years of education)

by FEP patients, their parents, and their siblings, may be the best candidates. These findings could be explained byboth 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 amongmen.[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 caregiversof 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 effectof sex on the cognitive endophenotypes of SSD will be ofgreat interest.

Regarding years of education, we found that siblings had completed significantly more years of education thanFEP 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 psycho- sis. 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 differencesin education, and given that FEP patients were evaluated at a younger age than their siblings, they had less timeto accomplish higher educational levels. Also, it shouldbe 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 educationallevel due to environmental factors. While it is likely that patients and their siblings shared a similar environment during childhood and adolescence, the differences be-tween 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) 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]; there- fore, 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 ac- cumulation of stressful life events causing psychosocial stress could precipitate the FEP.[3,76] Another environmental factor potentially related to psychosis onset is canna- bis 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 featuresin 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 accordingto their relationship with the proband. Likewise, the inclusion of HC allowed us to compare the participants witha 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 eth-nic 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 thegroup of FEP patients. However, previous studies by our group indicated that the use of different antipsychoticsdid 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

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13404.

DATA AVAILABILITY STATEMENT

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

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Study 3: Familiality of the Intelligence Quotient in First Episode Psychosis: Is the degree of family resemblance associated with different profiles?

Murillo-García, N., Soler, J., Ortiz-García de la Foz, V., Miguel-Corredera, M., Barrio-Martinez, S., Setién-Suero, E., Papiol, S., Fatjó-Vilas, M., & Ayesa-Arriola, R.

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Study 4: Overlap between genetic variants associated with schizophrenia spectrum disorders and intelligence quotient: A systematic review.

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Research Paper

Overlap between genetic variants associated with schizophrenia spectrum disorders and intelligence quotient: a systematic review

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Background: To study whether there is genetic overlap underlying the risk for schizophrenia spectrum disorders (SSD) and low intelligence quotient (IQ), we reviewed and summarized the evidence on genetic variants associated with both traits. **Methods**: We performed this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and pre-registered it in PROSPERO. We searched the databases of MEDLINE via PubMed, PsycINFO, Web of Science, and Scopus. We included studies on adults with a diagnosis of SSD that explored their genetic variants (single nucleotide polymorphisms [SNPs], copy number variations [CNVs], genomic insertions, or genomic deletions), estimated their IQ, and studied the relationship between genetic variability and both traits (SSD and IQ). We synthesized the results and assessed their risk of bias using the Quality of Genetic Association Studies (Q-Genie) tool. **Results**: Fifty-five studies met the inclusion criteria (45 case–control, 9 cross-sectional, 1 cohort), of which 55% reported significant associations between the genetic variant addressed with IQ in SSD patients. The SNPs more frequently explored through candidate gene studies were located at *COMT*, *DTNBP1*, *BDNF*, and *TCF4*. Through genome-wide association studies, two SNPs located in *CHD7* and *GATAD2A* were reported to be associated with IQ in SSD patients. The studies on CNVs suggested significant associations of structural variants with low IQ in SSD patients. **Limitations**: Overall, primary studies used heterogenous IQ measurement tools and had small samples. Grey literature was not screened. **Conclusions**: Genetic overlap between SSD and IQ supports the neurodevelopmental hypothesis of schizophrenia. Most of the risk polymorphisms identified are located in genes relevant for brain development, neural proliferation and differentiation, and synaptic plasticity.

Introduction

Schizophrenia spectrum disorders (SSDs) are characterized by hallucinations, delusions, disorganized thinking, negative symptoms, and cognitive dysfunctions that compromise functionality [1,2]. SSDs differ from each other according to the type of symptoms, their duration and aetiology, wherein schizophrenia is the most severe and disabling disorder with a lifetime prevalence of 0.7 to 0.9% [3]. The aetiology of SSD is unknown, but its onset is influenced by the interaction of genetic and environmental factors [4]. Genetic studies have estimated the heritability of schizophrenia to be approximately 80% [5,6], which is explained in part by the global effect of thousands of single nucleotide polymorphisms (SNPs) (SNP heritability=24%)[7]. In addition, the polygenic burden of risk variants, the so-called polygenic risk scores (PRS), explains 7.3% of the variance in liability for schizophrenia according to the most recent estimates [7-9].

In recent years, there has been widespread interest in establishing endophenotypes of SSD that allow the identification of the disorder through observable and quantitative traits [10,11]. One of these candidate endophenotypes is the intelligence quotient (IQ) [12-16], which is a quantitative score obtained through a standardized intelligence test that represents an individual's intellectual ability [17]. Thanks to this quantitative estimation of the general cognitive function, it is possible to make comparisons between subjects, so it is common to use the IQ score to assess intelligence in the population[17]. Current evidence indicates that IQ is heritable and its genetic architecture is highly polygenic [18-21]. In addition, people with SSD have shown poorer intellectual performance compared to healthy

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subjects [22,23], which in some cases are already present during childhood [24]. Along the same line, it has been demonstrated that adolescents at high risk of psychosis exhibit a lower IQ than healthy controls [25] and that the unaffected relatives of SSD patients present similar deficits [26]. Taken together, this evidence indicates that SSD might be caused by pathological neurodevelopment processes that would be observable as premorbid intellectual deficits.

Genetic overlap between vulnerability to SSD and low intelligence has been identified in large studies involving individuals with schizophrenia [10] and healthy subjects [27]. This evidence is consistent with a population-based study including over one hundred thousand participants that described significant associations between polygenic risk for schizophrenia and other neuropsychiatric disorders and poorer cognitive functioning, specially in processing of speed and memory [28]. Accordingly, the large-scale GWAS of Savage et al.[29] identified 205 genomic loci associated with intelligence, which they found to be enriched in genes expressed in the brain. Moreover, Ohi et al. [30] found that genetic factors differentiating schizophrenia from bipolar disorder were specifically related to low premorbid intelligence. Thus, the identification of genetic variants contributing to the risk of schizophrenia and low IQ could provide insight into the biological correlates of the disorder. Generally, different genome-wide association studies (GWAS) have found that the genetic variants associated with both traits are enriched in genes expressed in the central nervous system and participate in neurogenesis, regulation of nervous system development, neuronal differentiation, and regulation of cell development [7,29,31]. For instance, a SNP in the *DTNBP1* gene (rs1011313) has been found to be related to both neurocognition and schizophrenia risk, probably because of its involvement in the glutamatergic system [32]. Another locus associated with increased risk for the disorder and lower general cognition is *TCF20* (rs134873, intron variant), which encodes a transcriptional coregulator [33]. Smeland et al. [33] found that the risk allele of rs134873 was related to higher expression of *NAGA* (involved in regulation of glycosylation-associated enzymes, glutamatergic and GABAergic systems [34]) and reduced expression of *CYP2D6* (with a role in serotonin and dopamine metabolism) in human brain [33]. In addition, other sources of genetic variation, such as copy number variants (CNVs), may also be involved in the aetiology of schizophrenia and intellectual deficits, since schizophrenia patients with at least one rare CNV yielded low IQ [35].

Although several researchers have approached this matter, no systematic review summarizes current findings on different genetic variants associated with SSD and IQ. We believe that a compilation of results from various original studies can contribute in different ways to the field of knowledge. A synthesis with no date limitation allows knowing the evolution in an area of research, contributing to a better level of scientific quality and reducing the possibility of bias. Furthermore, by comparing independent samples, the description of positive and negative results helps to establish whether the results are consistent and can be generalized. Likewise, it is interesting to include both candidate gene studies and GWAS to analyse replicability of results after using different methods. In fact, GWAS yield valuable results, since they have the advantage of reducing possible biases based on the lack of pre-established hypothesis. However, regretfully both GWAS and candidate genes studies are subject to publication bias since they are at risk of not being reported when the results are negative. Therefore, to answer the question of whether overlapping genetic variants underlie the risk of SSD and low IQ, this systematic review aimed to analyse and summarize primary studies on genetic variants associated with both traits. These data will contribute to establishing IQ as a potential endophenotype for SSD and to identifying future lines of research.

Methods

This review is being reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (PRISMA checklist in Supplemental Material). The present review was registered in the International Prospective Registry of Systematic Reviews (PROSPERO, CRD42020218842), and a protocol was elaborated for guiding the review process (https://doi.org/10.21203/rs.3.rs-150210/v1).

Eligibility criteria

The following types of studies were included: published genetic association studies based on IQ, either GWAS or candidate gene studies, with an observational design, including cross-sectional, case–control, and cohort studies. Only manuscripts written in English were considered, but no restrictions were used based on the date of publication. For the participants, we selected studies on the human adult population with a diagnosis of SSD based on DSM [2] or ICD [36] criteria in any stage of the disease (either first episode of psychosis or chronic evolution). We included studies that addressed the association between genetic variability and both traits (SSD and IQ) by exploring the following genetic variants: SNPs, CNVs, genomic insertions, or genomic deletions. Regarding the IQ, only studies estimating the participants' IQ through a standardized test were included. By including studies in SSD patients with IQ estimation, we sought to guide the search strategy and selection process toward research targeting genetic overlap between both traits.

In contrast, the following were reasons for exclusion from this review: a) animal model or cell line studies; b) studies not measuring the outcomes of interest (lacking genotyping, IQ estimation, or their association); c) review or meta-

analysis articles; d) not peer-reviewed literature, single case studies, books, editorials or theses.

Search strategies and information sources

The design of the search strategy was established with the advice of an expert librarian from the University of Cantabria. The search was carried out in November 2020 and updated in October 2021 in the electronic databases of MEDLINE via PubMed, PsycINFO, Web of Science (WOS) and Scopus. In accordance with PRISMA guidelines, the search strategy was adapted to the controlled format of each database when appropriate. For MEDLINE, MeSH format was used ("Schizophrenia"[MeSH] OR "Psychotic Disorders"[MeSH] OR "Psychosis") AND ("Genetic Variation"[MeSH] OR "Genetic Variant" OR "Polymorphism, Genetic"[MeSH] OR "Polymorphism, Single Nucleotide"[MeSH] OR "Polymorphism") AND ("Intelligence" [MeSH] OR "Intelligence Quotient" OR "IQ"). For PsycINFO, the Thesaurus format was used ((DE"Schizophrenia" OR "Psychotic Disorders" OR DE"Psychosis")) AND (("Genetic Variation" OR "Genetic Variant" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR DE"Polymorphism")) AND ((DE"Intelligence quotient" OR "IQ")). The WOS and Scopus databases were screened by using the aforementioned terms in free text, and the results in Scopus were limited to document type (article) and language (English) due to the large number of records obtained. In addition, we examined the reference lists of the articles included in this manuscript to identify eligible studies.

Study selection and data collection process

After the results of the databases were retrieved, they were recorded in the bibliographic manager EndNote (Clarivate Analytics, Philadelphia, USA). Once the duplicated records were eliminated, two reviewers (NMG, SBM) proceeded to screen each record independently by reviewing all titles and abstracts. Afterwards, the full texts of the eligible studies were analysed, and those that met the inclusion criteria were selected. These tasks were carried out separately by the reviewers, who finally selected the studies by consensus. Doubts or discrepancies were resolved by the reviewers, and if necessary, the postdoctoral researcher (ESS) and the senior researcher (RAA) were consulted.

Data from the selected studies were recorded in a standardized table designed by the reviewers. The information extracted from each study included the author, year of publication, country of origin, study design, genetic variants and genes investigated, sample size (patients and healthy controls if applicable), instruments for IQ measuring, mean IQ, and main findings. Each reviewer collected the information from half of the included records, which were subsequently exchanged for verification by their partner.

Outcomes

Among genetic variants for SSD, we considered SNPs, CNVs, genomic insertions, or genomic deletions as eligible. Only the studies that reported the location of the genetic variant were included. As for IQ outcomes, we considered the global intelligence score estimated through any standardized measure, such as the Wechsler Adult Intelligence Scale (WAIS), the Weschler test of Adult Reading (WTAR), the National Adult Reading Test-revised (NART), or the Wechsler Abbreviated Scale of Intelligence (WASI). All types of IQ were included: verbal , performance, or full. Verbal IQ is an intelligence index estimated by results on tests of verbal comprehension and working memory; Performance IQ is estimated by scores on tests of perceptual organization and processing speed; while full IQ provides a mean of both verbal and performance IQ [17].

Quality assessment of primary studies

The reviewers used the Quality of Genetic association studies (Q-Genie) tool to assess the risk of bias of the studies included in this review [37]. This is a questionnaire of 11 items rated on a 7-point Likert scale, where scores of 1 indicate poor quality and 7 suggest excellent quality. The included items evaluated different categories, including the rationale of the study, ascertainment of comparison groups, and technical and nontechnical classification of genetic variants tested. The Q-Genie allows us to obtain a global score that indicates the overall quality of the study, which can be poor (scores ≤35 for studies with control groups and scores ≤32 for studies without control groups), moderate (scores between >35 and ≤45 for studies with control groups and >32 and ≤40 for studies without control groups) or good (scores >45 for studies with control groups and scores >40 for studies without control groups).

Data synthesis

A narrative synthesis of all the analysed studies is presented in the results section. For greater clarity and organization of the results, these were grouped into two sections, one comprising candidate gene studies and the other covering GWAS.

Results

For the present systematic review, a total of 2438 records were identified through database searching. After duplicates were eliminated, 2153 results were screened for eligibility, from which 2007 records were discarded for meeting exclusion criteria (3 book chapters, 9 letters to the editor, 24 case studies, 44 meta-analyses, 166 reviews, 226 animal or cellular models, and 1535 did not address the topic of interest). From the 146 full-text articles that were reviewed, 93 were excluded for not meeting the inclusion criteria. In addition, 2 records were included via citation searching.

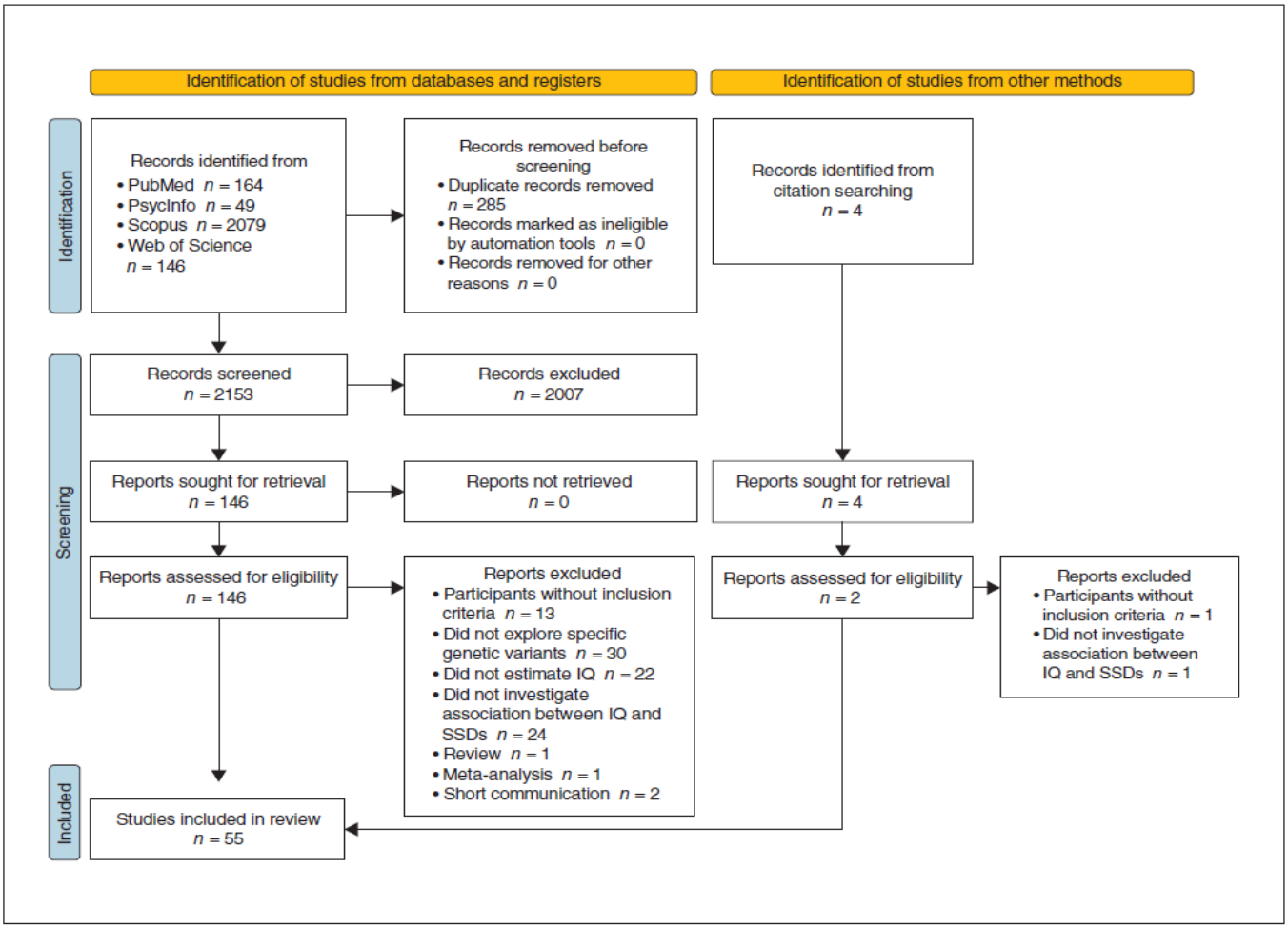

Figure 1: PRISMA 2020 flow diagram36 for new systematic reviews which included searches of databases, registers and other sources. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SSD = schizophrenia spectrum disorder.

Finally, 55 articles that explored genetic variants associated with both SSD and IQ were included in this review (see Figure 1).

Among the included studies, 47 (85.45%) obtained global scores in the Q-Genie tool that indicated good quality, and 8 (14.55%) had scores of overall moderate quality. None of the studies was rated as low quality (see Supplemental Material).

From the total of studies with a case-control design (n= 45), 86.6% (n= 39) reported that SSD patients scored significantly lower than healthy controls, regardless of the evaluation tool used. One of the remaining case-control studies [38] found no significant differences, while the rest (n= 5) did not report the participants' IQ. Different polymorphisms were explored by the reviewed studies, yielding heterogeneous results. However, the most frequent genes addressed through the candidate gene strategy were *COMT*, *BDNF*, *DTNBP1*, and *TCF4*, as described below. Although fewer studies have used the GWAS strategy, their results are also presented. Tables 1-6 summarize the findings of the selected studies.

Candidate genes studies

COMT

Seven studies examined the association of the *COMT* genotype with both SSD and IQ, of which six had a case–control design and one had a cross-sectional design. Mixed results were found, as shown in Table 1. Four of these studies (57.14%) [39-42] did not observe a significant association between the SNP rs4680 (which is also denominated Val158Met polymorphism) and the IQ in people with SSD. Despite this, three studies (42.86%)[43-45] did find significant associations. Green et al. [44] found in their entire sample of patients that the Val158Met polymorphism was a significant predictor of IQ, as Val homozygotes performed worse on the intelligence test. Two other studies reported similar results, although with certain specifications. Kontis et al. [45] reported that *COMT*-Val homozygotes had lower IQ, but this effect was reduced by the interaction with the rs1801133 allele *MTHFR-T*. Rebollo-Mesa et al. [43] observed that the Val158Met polymorphism was only significantly related to IQ in patients who were taking antipsychotics at the time, wherein Val carriers with a high dose of antipsychotic medication had a lower IQ than Met carriers.

Table 1: Studies exploring the *COMT* gene and IQ in patients with schizophrenia

Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
					Patients	Healthy controls		Patients	Healthy controls	
rs4680†	Galderisi et al.[39] (2005)	Cross-sectional	Italy	Caucasian	106 (schizophrenia)	NA	WAIS	NA	NA	No
rs4680	Ho et al.[40] (2005)	Case–control	United States	Caucasian	159 (schizophrenia)	84	WAIS§	91.0 ± 12.45	109.0 ± 12.05	No
rs4680	Prata et al.[41] (2009)	Case–control	United Kingdom	90% Caucasian	42 (schizophrenia)	48	WAIS, WASI§	97.2 ± 16.4	118.2 ± 11.5	No
rs4680	Wirgenes et al.[42] (2010)	Case–control	Norway	Caucasian	171 (SSD)	340	WASI§	103.5 ± 13.8	113.6 ± 9.9	No
rs4680	Rebollo-Mesa et al.[43] (2011)	Case–control	United Kingdom	84% Caucasian	68 (SSD)	208	WAIS	NA	NA	Yes (only with antipsychotics)
rs4680	Green et al.[44] (2014)	Case–control	Australia	Caucasian	617 (SSD)	659	WTAR§	97.49 ± 15.04	105.47 ± 10.67	Yes
rs4680, rs1801133‡	Kontis et al.[45] (2013)	Case–control	Greece	NA	90 (schizophrenia)	55	WAIS	81.06 ± 11.35	NA	Yes

NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.
*Terminology taken from the original articles.
†rs4680 is commonly known as the Val158Met polymorphism.
‡rs1801133 is located in the *MTHFR* gene.
§Patients had significantly lower IQs than healthy controls.

Table 2: Studies exploring the *BDNF* gene and IQ in patients with schizophrenia

Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
					Patients	Healthy controls		Patients	Healthy controls	
rs6265†	Ho et al.[46] (2006)	Case–control	United States	NA	293 (SSD)	144	WAIS‡	91.49 ± 13.49	110.41 ± 11.66	No
rs6265	Chung et al.[47] (2010)	Case–control	South Korea	East Asian	101 (schizophrenia)	50	WAIS‡	102.45 ± 14.1	107.9 ± 10.4	Yes (only before statistical correction)
rs6265	Lu et al.[48] (2012)	Case–control	China	East Asian	112 (SSD)	63	WAIS‡	87.8 ± 14.7	113.4 ± 14.2	Yes
rs6265	Smith et al.[49] (2012)	Case–control	Canada	72% Caucasian, 10% South Asian, 9% East Asian, 9% Other	58 (first episode of psychosis)	39	NAART	100.4 ± 8.7	NA	No
rs6265	Abbasian et al.[50] (2021)	Case–control	Iran	Asian	71 (schizophrenia)	88	WAIS‡	85.48 ± 13.6	98.30 ± 15.12	No

NA = not available; NAART = North American Adult Reading Test; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale.
*Terminology taken from the original articles.
†rs6265 is commonly known as the Val66Met polymorphism.
‡Patients had significantly lower IQs than healthy controls.

Table 3: Studies exploring the *DTNBP1* gene and IQ in patients with schizophrenia

Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
					Patients	Healthy controls		Patients	Healthy controls	
rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs1011313	Burdick et al.[51] (2007)	Cross-sectional	United States	Caucasian	183 (SSD)	NA	WRAT	NA	NA	Yes
rs2619539, rs3213207, rs261953	Donohoe et al.[52] (2007)	Cross-sectional	Ireland	Caucasian	52 (SSD)	NA	WTAR	93.05 ± 11.85	NA	No
rs2619539, rs3213207, rs1011313, rs2619528, rs760761, rs2619522, rs2619538	Zinkstok et al.[53] (2007)	Case–control	Netherlands	Caucasian, Turkish, Moroccan, Surinamese	76 (FEP)	31	WAIS†	86.7 ± 13.8	107.0 ± 15.5	Yes (only rs2619528, rs760761, rs2619522, rs2619538)
rs261953	Hashimoto et al.[54] (2009)	Case–control	Japan	East Asian	70 (schizophrenia)	165	WAIS†	87.06 ± 18.86	109.73 ± 10.73	No
rs2619539, rs2619528, rs2619538, rs3213207, rs760761	Varela-Gomez et al.[55] (2015)	Case–control	Spain	NA	238 (FEP)	47	WAIS	NA	NA	Yes (only rs2619539 and rs3213207)

FEP = first episode of psychosis; NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WRAT = Wide Range Achievement Test; WTAR = Wechsler Test of Adult Reading.
*Terminology taken from the original articles.
†Patients had significantly lower IQs than healthy controls.

Table 4: Studies exploring the *TCF4* gene and IQ in patients with schizophrenia

Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
					Patients	Healthy controls		Patients	Healthy controls	
rs9960767	Lennertz et al.[56] (2011)	Cross-sectional	Germany	NA	401 (schizophrenia)	NA	MWT-B, WAIS	105.28 ± 17.7	NA	No
rs2958182	Zhu et al.[57] (2013)	Case–control	China	East Asian	526 (schizophrenia)	421	WAIS†	96.01 ± 14.99	110.13 ± 11.6	Yes
rs9960767	Albanna et al.[58] (2014)	Cross-sectional	Canada	103 Caucasian, 70 Other	173 (FEP)	NA	WAIS	90.9 ± 15.25	NA	No

FEP = first episode of psychosis; MWT-B = Mehrfachwahl-Wortschatz Test B; NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale.
*Terminology taken from the original articles.
†Patients had significantly lower IQs than healthy controls.

Table 5 (part 1 of 2): Studies exploring different candidate genes and IQ in patients with schizophrenia

Gene	Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
						Patients	Healthy controls		Patients	Healthy controls	
5HT1A-R	–1019	Bosia et al.[59] (2011)	Cross-sectional	Italy	NA	118 (schizophrenia)	NA	WAIS	83.46 ± 12.54	NA	No
AKT1	rs2494732	Van Winkel et al.[60] (2011)	Case–control	Netherlands, Belgium	Caucasian	611 (NAP)	590	WAIS	94.6 ± 16.5	NA	No
ANK3	rs1938526	Cassidy et al.[61] (2014)	Cross-sectional	Canada	102 Caucasian, 71 Other	173 (FEP)	NA	WAIS	92.6 ± 15.7	NA	Yes
APOE	rs7412, rs429358	Vila-Rodriguez et al.[62] (2017)	Case–control	Canada	60 Caucasian, 13 Asian, 13 Other 60:13:13 (69.8% Caucasian)	86 (FEP)	39	NAART†	100.45 ± 8.01	107.54 ± 6.75	No
CNNM2	rs7914558	Rose et al.[63] (2014)	Case–control	Ireland	NA	400 (SSD)	160	WAIS†	91.23 ± 18.39	121.4 ± 14.6	No
CPLX2	rs6868608, rs2443541, rs2243404, rs4242187, rs10072860, rs4868539, rs1366116, rs3892909, rs3822674, rs56934064	Begemann et al.[64] (2010)	Case–control	Germany	Caucasian	1071 (SSD)	1079	MWT-B	NA	NA	No
CSMD1	rs10503253	Donohoe et al.[65] (2013)	Case–control	Ireland	Caucasian	387 (SSD)	205	WAIS†	89.74 ± 17.46	118.3 ± 13.89	Yes
FKBP5	rs1360780, rs9470080, rs4713902, rs9394309	Green et al.[66] (2015)	Case–control	Australia	98% Caucasian	617 (SSD)	659	WTAR†	97.49 ± 15.04	105.47 ± 10.67	No
FOLH1	rs202676	Zink et al.[67] (2020)	Case–control	United States	Caucasian and African American	57 (FEP)	65	HART	100.7 ± 10.6	104.3 ± 10.6	Yes
GRIN2A, GRIN2B, GRIN3A, GRM1, GRM3, GRM4, GRM5, GRM7, GRM8	43 SNPs	Chaumette et al.[68] (2020)	Cohort	Canada	Caucasian	148 (FEP)	NA	WAIS	92.8 ± 15.4	NA	Yes (only rs1396409 in *GRM7*)
GRM5	rs60954128, rs3824927	Matosin et al.[69] (2018)	Case–control	Australia	Caucasian	249 (schizophrenia)	261	WASI†	102.69 ± 13.94	118.01 ± 10.26	Yes (only rs3824927)
HPS4	rs4822724, rs61276843, rs9608491, rs713998, rs2014410	Kuratomi et al.[70] (2013)	Case–control	Japan	East Asian	240 (schizophrenia)	240	JART†	92.4 ± 10.4	103.4 ± 10.7	No
IL1B	rs16944	Fatjó-Vilas et al.[71] (2012)	Case–control	Spain	European	48 (schizophrenia)	46	WAIS†	89.04 ± 15.27	107.81 ± 12.81	No
LOC100128714	rs4906844	Bakken et al.[72] (2011)	Case–control	Norway	Caucasian	208 (SSD)	368	WASI†	103.4 ± 14.0	113.5 ± 9.7	No
MHC, TCF4, NRGN	rs6904071, rs13219354, rs3131296, rs6932590, rs9960767, rs12807809	Walters et al.[73] (2013)	Case–control	Germany	Caucasian	342 (schizophrenia)	2244	WAIS†	102.2 ± 18.0	113.76 ± 14.3	Yes (only rs6904071 in *MHC*)
MIR137	rs1625579	Green et al.[74] (2013)	Case–control	Australia	Australian	617 (SSD)	764	WTAR†	97.49 ± 15.04	105.47 ± 10.67	Yes (only together with negative symptoms)
NOS1	rs6490121	Donohoe et al.[75] (2009)	Case–control	Ireland	Caucasian	349 (SSD)	230	WAIS†	91.53 ± 18.2	122.93 ± 15.13	Yes (only for verbal IQ)

Table 5 (part 2 of 2): Studies exploring different candidate genes and IQ in patients with schizophrenia

Gene	Polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Association between polymorphism and IQ in patients with SSD
						Patients	Healthy controls		Patients	Healthy controls	
NOS1	rs6490121, rs3782206	Zhang et al.[76] (2015)	Case–control	China	East Asian	580 (schizophrenia)	720	WAIS†	95.99 ± 14.67	106.49 ± 13.99	No
NRG1	rs2439272, rs6988339	Ananloo et al.[77] (2020)	Case–control	Iran	Asian	276 (schizophrenia)	193	WAIS†	74.35 ± 11.07	105.19 ± 7.25	Yes
NRGN	rs12807809, rs12278912	Ohi et al.[78] (2013)	Case–control	Japan	East Asian	157 (schizophrenia)	257	WAIS†	NA	NA	Yes (only for the diplotype)
NRN1	19 SNPs	Chandler et al.[79] (2010)	Case–control	Australia	Caucasian	336 (schizophrenia)	172	SILS†	89.9 ± 14.2	108.2 ± 8.4	Yes (for rs1475157, rs9405890)
NRN1	11 SNPs	Fatjo-Vilas et al.[80] (2016)	Case–control	Spain	Caucasian	697 (SSD)	668	WAIS†	89.02 ± 15.37	99.48 ± 13.64	Yes (for the haplotype rs9763180, rs1048432, rs4960155, rs9379002, rs9405890, rs1475157, before statistical correction)
OXTR	rs2254298, rs53576, rs115324487	Montag et al.[81] (2012)	Case–control	Germany	Caucasian	145 (schizophrenia)	145	MWT-B†	103.96 ± 13.5	108.96 ± 13.4	No
OXTR	rs143908202, rs150746704, rs115324487, rs61740241	Veras et al.[82] (2018)	Case–control	United States	Caucasian, Hispanic, African American and Other	48 (SSD)	25	WAIS†	84.05 ± 11.75	102.9 ± 15.3	Yes (only for nonverbal IQ)
S100B	rs2839357, rs1051169, rs9722	Zhai et al.[83] (2012)	Case–control	China	East Asian	434 (schizophrenia)	412	WAIS†	97.13 ± 14.87	108.52 ± 13.89	No
ST8SIA2	rs4586379, rs2035645, rs4777974, rs3784735	Fullerton et al.[84] (2018)	Case–control	Australia	88.1% European, 3.5% Asian, 8.4% Unknown	281 (SSD)	172	WASI†	104	119	No
TH	rs10770141	Horiguchi et al.[85] (2014)	Case–control	Japan	East Asian	132 (schizophrenia)	282	WAIS†	103.75 ± 11.15	106.9 ± 8.7	Yes
ZNF804A	rs1344706	Walters et al.[86] (2010)	Case–control	Ireland	Caucasian	297 (schizophrenia)	165	WAIS†	88.0 ± 16.26	122.26 ± 13.83	Yes (only for high IQ)
ZNF804A	rs1344706	Chen et al.[87] (2012)	Case–control	China	East Asian	531 (schizophrenia)	442	WAIS†	97.09 ± 14.72	109.50 ± 11.88	Yes (only for high IQ)

FEP = first episode of psychosis; HART = Hopkins Adult Reading Test; JART = Japanese version of the National Adult Reading Test; MWT-B = Mehrfachwahl-Wortschatz Test B; NA = not available; NAART = North American Adult Reading Test; NAP = non-affective psychosis; SD = standard deviation; SILS = Shipley Institute of Living Scale test; SNP = single nucleotide polymorphism; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.
*Terminology taken from the original articles.
†Patients had significantly lower IQs than healthy controls.

Table 6: Overview of genome-wide association studies related to IQ and schizophrenia

Type of polymorphism	Study	Design	Country	Ancestry*	Participants, *n*		IQ measure	Mean IQ ± SD		Findings
					Patients	Healthy controls		Patients	Healthy controls	
SNP	LeBlanc et al.[88] (2012)	Case–control	Norway	European	190 (SSD)	353	WASI	NA	NA	No significant association with IQ
SNP	Whitton et al.[89] (2016)	Case–control	Ireland	NA	670 (SSD)	330	WTAR	90.29 ± 18.08	119.81 ± 15.57	rs6984242 (*CHD7*) and rs2905426 (*GATAD2A*) associated with IQ
CNV	Derks et al.[90] (2013)	Case–control	United Kingdom	Caucasian	64 (schizophrenia)	NA	WAIS	NA	NA	14 CNVs related to low IQ at chromosomes 15q11.2 and 22q11.21
CNV	Martin et al.[91] (2014)	Case–control	Australia	Caucasian	82 (schizophrenia)	50	WASI†	86.57 ± 16.16	116.44 ± 11.58	Large, rare deletions related to lower IQ in patients
CNV	Lowther et al.[35] (2017)	Cross-sectional	Canada	Caucasian	546 (SSD)	NA	NA	NA	NA	Pathogenic CNVs related to lower IQ
CNV	Hubbard et al.[92] (2021)	Cross-sectional	United Kingdom	Caucasian	875 (SSD)	NA	WAIS	NA	NA	CNV carriers with schizophrenia had lower IQ

CNV = copy number variant; NA = not available; SNP = single nucleotide polymorphism; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.
*Terminology taken from the original articles.
†Patients had significantly lower IQs than healthy controls.

BDNF

Five studies explored the link between variations in the *BDNF* gene and the IQ in SSD (see Table 2). All studies included a control group and focused on the Val66Met polymorphism (rs6265). Three of them (60%) [46-48] reported negative results, but Chung et al. [49] and Lu et al. [50] found a significant correlation between the Val66Met SNP and the patients' IQ. The Met allele was associated with lower IQ in patients with SSD in both studies [49,50], although in the case of Chung et al. (2010), this relationship lost significance after Bonferroni correction.

DTNBP1

Five studies targeted polymorphisms at *DTNBP1* (see Table 3), of which three had a case–control methodology and two had a cross-sectional design. Two studies (40%) found no association between different SNPs in *DTNBP1* and the patients' IQ [51,52], while the remaining studies (60%) did confirm this association [53-55]. Burdick et al. [53] observed that the genotype of six SNPs in *DTNBP1* (rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs1011313) was associated with intellectual decline in patients, with carriers of the CTCTAC haplotype demonstrating a significantly greater IQ decline than noncarriers. Zinkstok et al. [54] found that carriers of the low-frequency allele in the SNPs rs760761 (T) and rs2619522 (G) had lower IQ, while the common allele in rs2619538 (A) was related to better IQ. Varela-Gomez et al. [55] found that the patients' homozygotes for the risk genotype in rs2619539 (GG) and in rs3213207 (AA) had lower IQ.

TCF4

Three studies assessed the relationship between IQ in patients with SSD and polymorphisms in *TCF4* (Table 4). Two of them (66.66%) were cross-sectional and did not find a significant association [56,57]. In contrast, a study [58] with a case–control design observed that T-carrier patients at rs2958182 had higher IQ than A-carrier patients.

Other candidate genes

Twenty-nine studies explored different candidate genes from those mentioned above, wherein twenty-six had a case–control design, 2 were cross-sectional and 1 was longitudinal. From these, sixteen studies (55.17%) reported significant associations between the investigated polymorphisms and the patients' IQ in different directions (see Table 5). In most cases, the minor frequent allele was associated with lower IQ in patients, including SNPs at *ANK3* [59], *CSMD1* [60], *FOLH1*[38], *GRM7* [61], *GRM5* [62], *MHC* [63], *MIR137* [64], *NOS1* [65], *NRG1* [66], *NRGN* [67], and *OXTR* [68]. Regarding *NRGN* [67], an association with IQ was found only for the diplotype rs12807809–rs12278912, where the risk allele combination TG/TG was related to lower IQ. In contrast, the minor frequent allele in some SNPs at *NRN1* [69,70], *TH* [71] and *ZNF804A* [72,73] showed a protective effect on IQ, as patients who were carriers had higher IQ. Furthermore, two studies specified that the relationship between genetic variants and IQ was conditioned by the type of IQ. Donohoe et al. [65] found that carriers of the risk genotype in rs6490121 (GG) at *NOS1* had lower verbal IQ in both patients and controls, but full IQ was not significantly different. Additionally, some rare variants at *OXTR* demonstrated a specific link with low nonverbal IQ [68]. Thirteen studies obtained non-significant results [74-86].

1.1. Genome-wide association studies (GWAS)

Six GWAS were included, of which two were cross-sectional, while the rest had a case–control design (see Table 6). Two studies explored SNPs while four searched CNVs. One of the SNP studies (50%) did not find significant associations [87], but the other [88] reported two SNPs associated with patient IQ. The risk alleles were related to lower global IQ for the two SNPs located at genes *CHD7* and *GATAD2A* [88]. Specifically, the risk allele in rs6984242 (*CHD7*) was the most strongly associated with low verbal IQ.

From the remaining GWAS exploring CNVs, all reported significant associations with low IQ. Martin et al. [89] found that patients with large (>500 kb) and rare (<1% frequency) deletions had a lower IQ than those without such polymorphisms. Similarly, Lowther et al. [35] observed that patients with pathogenic CNVs showed lower IQ, in contrast to patients with average IQ who had the lowest yield of pathogenic CNVs. Derks et al. [90] identified 14 CNVs, mostly at chromosome 15q11.2, related to intellectual disability after studying patients with schizophrenia and IQ scores below 70. Finally, Hubbard et al. [91] found that patients carrying CNVs related to SSD showed a significantly lower IQ than noncarriers.

Discussion

This is the first systematic review to date to analyse current evidence on the genetic association between SSD and IQ. Fifty-five studies were summarized, some of which found that variability in several genes was significantly related to the disorder and the IQ in different directions. At the trait level, the results were consistent in showing lower IQ estimations in patients with SSD compared to healthy controls, which corresponds to other reviews and meta-analysis[92-94]. Taken together, these findings show a possible common biological correlate between the two traits, indicating that IQ is a strong candidate endophenotype for SSD. Our review synthesizes the current data emerging from a line of research that has yielded heterogeneous results through diverse study strategies. For this reason, we believe that the present work provides relevant insights into the hypotheses with more consistent results to continue researching promising proposals. In this vein, our results point to the study of novel genes such as *NRN1, ZNF804A, CHD7* and *GATAD2A*, instead of others traditionally studied

(*COMT*, *BDNF* and *DTNBP1*) that have not been supported by GWAS results.

Catechol-O-Methyltransferase (*COMT)*

We found that the most frequently studied polymorphism was Val158Met (rs4680), located at *COMT*. This gene encodes the enzyme catechol-O-methyltransferase (COMT), which degrades catecholamines, including dopamine, thus helping to maintain appropriate levels of this neurotransmitter, particularly in the prefrontal cortex [95]. The Val158Met polymorphism leads to a substitution of valine with methionine, wherein the Val allele results in increased enzymatic activity of COMT, which in turn reduces dopamine concentration [96]. Some studies described here established that patients with the Val genotype showed lower IQ than Met carriers [43-45], but others did not replicate this finding [39-42]. The possible IQ deficit of Val carriers might be explained by the dopamine reduction in the prefrontal cortex associated with this variant, which, in turn, is linked to worse performance in executive function and working memory [97]. Moreover, a study on intellectual disability suggested that Val158Met may contribute to intelligence by affecting the white matter architecture in the prefrontal lobe and hippocampal formation [98].

The discrepancy in results could be due to differences when controlling for mediating variables such as the medication and the type of intelligence. Rebollo-Mesa et al. [43] described that Val carriers had a lower verbal IQ, but no differences were observed in their performance IQ, and this effect was exclusive for patients who were taking high doses of antipsychotics. This indicates that the Val158Met polymorphism could modulate the effects of antipsychotics on verbal IQ, wherein carriers of the risk allele would be more susceptible to the deterioration of verbal skills as a result of medication [99]. This corresponds with the findings by Schacht [100], who stated that this same polymorphism is key in identifying patients who are most likely to respond adequately to dopaminergic drugs. For clinical practice, these outcomes suggest that there is a subgroup of SSD patients with a higher genetic risk of cognitive decline who need long-term follow-up.

Further research on the Val158Met polymorphism must explore possible interactions with other SNPs, such as rs1801133 at *MTHFR*, since these interactions may influence the expression of *COMT* [45]. In fact, it has previously been demonstrated that polymorphisms in these two genes may be associated with IQ, especially since the *MTHFR* T-allele decreases the beneficial role of the *COMT-Met* allele in patients with schizophrenia [101].

Brain-Derived Neurotrophic Factor (*BDNF*)

All included studies on the *BDNF* gene analysed the Val66Met polymorphism, probably due to its demonstrated link to schizophrenia [102] and cognitive processes [103]. This gene encodes brain-derived neurotrophic factor (BDNF), a neurotrophin that has a relevant role in neurodevelopment, synapse regulation, and synaptic plasticity [104]. Variations in this gene may lead to alterations in the BDNF protein that could cause impaired brain development and synapse and neuroplasticity failures, which have been associated with schizophrenia [104,105]. The results found in this review regarding the Val66Met polymorphism are controversial. Chung et al. [49] and Lu et al. [50] established that SSD patients who were Met carriers had a lower IQ than Val carriers. This corresponds with previous research describing that the *BDNF* Met allele was associated with lower IQ in healthy women [106].

The Val66Met polymorphism is believed to contribute to the aetiology of SSD by affecting brain morphology as a result of lower levels of BDNF, with Met allele carriers showing reductions in the dorsolateral prefrontal cortex, caudate nucleus, and frontal grey matter volume [107-109]. The decreased secretion of BDNF caused by Val/Met substitution may also alter synaptic plasticity and neurodevelopment [105], which could influence cognition by disrupting the learning process [104]. However, three other studies included in this review found no association between the Val66Met polymorphism and IQ score in people with SSD [46-48]. Once again, the different findings might depend on genetic variability in *BDNF* between populations, since only a significant association was found in individuals from South Korea and China. This is in line with previous literature reporting a higher frequency of the Met allele in the Asian population [110]; thus, future studies must explore the potential differential role of the Val66Met polymorphism in patients with SSD from different genetic backgrounds. Moreover, the association of Val66Met with IQ was only established for full IQ and verbal IQ estimated by the WAIS [49,50] but not with premorbid IQ assessed through the NAART questionnaire [47]. For this reason, Val66Met could be exclusively related to some types of IQ.

Dystrobrevin Binding Protein 1 (*DTNBP1)*

Some associations were reported between SNPs at *DTNBP1* and IQ in patients with SSD. This gene encodes the Dysbindin-1 protein, which has a relevant role in neurotransmission and neurodevelopment [111]. Dysbindin-1 has been found in presynaptic and postsynaptic locations in several brain areas of interest in schizophrenia, including the hippocampus, prefrontal cortex and midbrain [112,113]. Because dysbindin-1 interacts with different proteins involved in the release of neurotransmitters, its alteration could affect synaptic homeostasis[85]. In all studies with significant results, the risk allele was related to lower IQ, including the C allele in rs2619539 [55], the T allele in rs760761 [54], the G allele in rs2619522 [54], and the A allele in rs3213207 [55]. Furthermore, a risk haplotype that included two of the above SNPs

(rs2619522 and rs760761) was found to be associated with a greater IQ decline in SSD patients [53]. The mechanism responsible for this association is unknown, but these polymorphisms might influence intelligence by reducing *DTNBP1* expression in the prefrontal cortex, hippocampus and midbrain [111,112], thus affecting the glutamatergic system [113].

However, other studies did not find this association [51,52], which may be due to the great variety of SNPs analysed. In addition, while most studies considered diagnosis of patients with SSD at early stages, Hashimoto et al. (2009) analysed a sample with chronic SSD, which may affect the results, since there have been described changes in gene expression depending on the different clinical stages of the disorder [114]. Similarly, the discrepancies found may be a consequence of genetic variance in *DTNBP1* between different populations [113,115], since the only study with Asian participants had negative results.

Transcription Factor 4 (*TCF4*)

Few studies have explored the association between genetic variability in *TCF4*, IQ and SSD. This gene encodes transcription Factor 4, a basic helix-loop-helix transcription factor. *TCF4* is widely expressed in the early human embryo and might be relevant for nervous system development [116] because of its role in neural proliferation and differentiation [117]. Disruptions in this gene are associated with neurodevelopmental disorders that occur with intellectual disability, such as Pitt-Hopkins syndrome [116]. However, this review reported insufficient evidence to confirm a relationship between *TCF4* variability and IQ in SSD patients. A single study obtained significant findings [58], wherein carriers of the minor allele in rs2958182 (A) obtained a lower IQ than noncarriers. Lennertz et al. found that SSD patients carrying the risk allele (C) of rs9960767 had worse memory impairment [57], and Albanna et al. observed that the risk allele was related to deficits in the reasoning cognitive domain [56]. Therefore, *TCF4* polymorphisms could be linked to specific cognitive domains rather than general cognition, but further studies are needed to understand their role in the pathophysiology of SSD.

Other candidate genes

Among the results of other candidate genes, *NRN1* and *ZNF804A* were the ones that showed the strongest link with IQ in patients with SSD. The *NRN1* gene encodes a protein from the neuritin family and is expressed both in embryonic development [118] and in the adult brain [119]. It plays a role in neuronal differentiation, synapse formation and maturation, and synaptic plasticity [120,121]. Due to these functions, it is believed that its variations could confer risk for the disorder and for neurocognitive alterations [70]. Two different studies observed that a haplotype (rs1475157 and rs9405890) at *NRN1* was related to the IQ of SSD patients [69,70]. Chandler et al. reported that the SNPs rs1475157 and rs9405890 have a selective influence on fluid intelligence, since carriers of the GA haplotype had lower fluid intelligence scores on both premorbid and current IQ tests [69]. Additionally, variability in rs1475157 and rs9405890 was related to the age at onset, which in turn could modulate the long-term cognitive course of patients with SSD [122]. Although these results must be replicated, the study of *NRN1* variations could help to identify a subgroup of patients at increased risk of cognitive impairment.

Two other studies observed that the risk allele (A) in rs1344706, located at *ZNF804A*, was associated with high IQ in patients with schizophrenia [72,73]. Walters et al. [73] clarified that although patients carrying this allele had higher IQ and fewer cognitive deficits than noncarriers, they still showed cognitive impairments compared to healthy subjects. This polymorphism might be specifically implicated in SSD since it has been more frequently identified in patients with the disorder [8,123,124], and it was related to higher schizotypy scores in healthy individuals [125]. Overall, these results agree on the value of the rs1344706 polymorphism as a potential genetic marker for psychosis risk. The specific function of *ZNF804A* is still unknown, but it encodes a zinc finger binding protein, a type of protein that participates in diverse roles, such as binding to DNA, transcriptional regulation and DNA-protein interactions [126,127]. This gene is expressed in the foetal and adult human brain, including the medial temporal lobe, the dorsolateral prefrontal cortex, the hippocampus, and the amygdala [128-130]. A plausible hypothesis is that the risk allele in rs1344706 may be related to SSD by affecting the expression of *ZNF804A* and other genes relevant for neurodevelopment [128-130] and by disturbing brain connectivity [131].

Genome-wide association studies (GWAS)

In this review, the *COMT*, *BDNF* and *DTNBP1* genes, the most frequent candidates explored in relation to IQ in SSD patients, were not found to be associated with such phenotypes through the GWAS strategy. Different reasons could explain the inconsistency of results. First, since the two GWAS exploring SNPs included here assessed SSD patients [87,88], clinical heterogeneity could have diminished the statistical power to detect the effect of such genes [132]. Moreover, their sample sizes were small, with a limited statistical power that could interfere in the identification of genetic variants related to the traits of interest. Another plausible explanation is that the aforementioned genes (*COMT*, *BDNF* and *DTNBP1*) do not confer risk for SSD, which would be consistent with the larger GWAS in schizophrenia to date [8,9,133]. Instead, other less explored common variations may better explain the genetic correlation between SSD and IQ reported by different GWAS meta-analyses with samples above 100,000 individuals each. The studies by Hagenaars et al. [28], Savage et al. [29] and the Brain

Consortium[134] have described substantial evidence of pleiotropy between schizophrenia and cognition, wherein lower IQ[134] and slower reaction[28] time were genetically correlated with the disorder. Regarding intelligence, Smeland et al. [135] identified 75 distinct genomic loci that may underlie the genetics overlapping with schizophrenia, and the gene set analysis suggests that these loci are implicated in neurodevelopment, synaptic integrity, and neurotransmission. Therefore, it is necessary to carry out future studies that focus on these candidate loci to delve into the biological processes that might cause the clinical and cognitive characteristics of patients with SSD. Several authors have suggested that GWAS with large samples could improve phenotypic characterization by establishing stricter inclusion criteria [132,136,137]. Furthermore, candidate gene studies can provide interesting insights by including homogeneous samples with similar symptoms and clinical manifestations among participants, focusing on unraveling the neurobiological basis of behavior.

Otherwise, recent GWAS have also highlighted the involvement of epigenetic mechanisms involved in SSD and IQ. Whitton et al. [88] explored a list of genes that are chromatin modulators of gene expression and were candidate genes for schizophrenia risk. They found that two SNPs, one in *CHD7* and the other in *GATAD2A*, were related to lower IQ in SSD patients. The strongest association was between rs6984242 (in *CHD7)* and verbal IQ, wherein carriers of the risk allele (G) showed lower IQ. *CHD7* encodes chromodomain helicase DNA binding protein 7 (CHD7), which participates in the organization of chromatin, making it relevant for the regulation of gene transcription, DNA repair, replication and recombination [138]. *GATAD2A* encodes the protein GATA zinc finger domain containing 2A, a subunit of the nucleosome remodelling and histone deacetylation (NuRD) complex, and represses gene expression [139,140]. These findings indicate an interesting line of research that explores the possible involvement of genes with epigenetic regulation functions in the risk for SSD and cognitive dysfunction.

GWAS on CNVs were consistent in showing the relationship between CNV burden and low IQ in SSD patients [35,90,91,141]. This should be interpreted with caution, as a recent meta-analysis including ten studies on subjects with SSD, their unaffected relatives, and unrelated controls did not find evidence of an association between CNV burden and overall IQ [142]. Instead, it was observed that CNVs have greater effects on specific cognitive abilities such as memory and perceptual reasoning; therefore, the potential influence of CNVs on the intellectual deficit in SSD should be confirmed in future studies with larger samples that estimate different types of IQ (e.g., verbal IQ or performance IQ).

Limitations and future directions

Despite the genetic association described above between IQ and SSD, approximately 45% (n= 25) of the included studies reported the absence of such a relationship. These negative results could reflect a true lack of association but could also be due to heterogeneity of the samples when including SSD patients with diverse diagnoses and characteristics. The effect of medication might be another confounding factor because it was not controlled by all primary studies. The IQ measurement instruments and the type of intelligence estimated could also be a possible cause of heterogeneity of results. Even when the same instrument was administered (in most cases, the WAIS scale), some authors used the full scale, while others exclusively used subscales of verbal intelligence or performance intelligence. In addition, the use of different measures makes difficult to analyze the different cognitive functions that encompass the construct of intelligence. Furthermore, most studies excluded patients with IQ<70 from the sample, and because intellectual disability is related to CNV and rare mutations [35], relevant genetic information could be lost. Another major limitation of some primary studies was the sample size, the lack of a control group, and the majority inclusion of Caucasian descendants leaving aside other population groups, which affects the generalizability of results to other underrepresented populations.

Regarding the limitations of this systematic review, its main weakness is that grey literature was not screened, so possible unpublished negative results may not have been included. Furthermore, we found few GWAS studies that could replicate the findings of candidate genes with larger samples and less probability of biases. This could be due to our strict eligibility criteria, including the selection of original studies that addressed both simultaneously SSD diagnosis and IQ estimation. Therefore, large and relevant GWAS such as that by Smeland et al. [135] combining data from separate samples (schizophrenia, bipolar disorder, and general population) were exclude from our results. Therefore, our results may be improved by a broader search strategy in eligibility criteria. Likewise, the number of studies we found for each candidate gene was limited in most cases. This affects the generalizability of the results and highlights the need for further genetic studies that replicate previous studies. Nevertheless, this review offers some insight into the genetic basis underlying SSD and IQ using a systematic methodology. In addition, since a time limitation was not established in the bibliographic search, all the existing evidence on this topic was analysed. Similarly, the development of a protocol and its registration prior to the literature search contributed to preventing bias in the selection of studies.

Future directions in this line of research include analyzing the different cognitive functions within the IQ construct to investigate how the genetic component affects each process separately. In addition, future research should improve

current diversity associated with the ancestry of the sample analysed. Although some recent work is investigating the genetic architecture of schizophrenia in Latin American and East Asian populations[143,144], there is still a lack of representation of other groups, including Africans.

Conclusions

The association between several genetic variants and IQ in SSD patients reported in this systematic review highlights previous findings on the polygenic nature of intelligence and the disorder . However, current evidence regarding the specific genes associated with IQ and SSD is inconclusive. Genes traditionally studied, such as *COMT*, *BDNF* and *DTNBP1*, have not been confirmed through the GWAS approach. Instead, novel genes have been targeted to understand the molecular basis underlying the IQ deficit in SSD, including *NRN1*, *ZNF804A*, *CHD7* and *GATAD2A*. Overall, our results support the neurodevelopmental hypothesis of SSD, since there is evidence of genetic risk factors that predispose individuals both to low IQ and the risk for psychosis. In addition, the results on the IQ deficit of SSD patients compared to healthy individuals and on genetic variants associated with IQ and the disorder suggest that IQ is a valid endophenotype for SSD. Therefore, susceptibility to cognitive deficits might be present from brain development and would not be exclusively a consequence of the disease. Hence, IQ estimation might help detect a subgroup of individuals at risk for psychosis.

Declaration of Interest

None.

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Data Availability

The data supporting this systematic review are available by request from the corresponding author RAA.

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Study 5: Studying the relationship between Intelligence Quotient and Schizophrenia Polygenic Scores in a family design with First-Episode Psychosis population

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Studying the relationship between intelligence quotient and schizophrenia polygenic scores in a family design with first-episode psychosis population

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Abstract

Background: The intelligence quotient (IQ) of patients with first-episode psychosis (FEP) and their unaffected relatives may be related to the genetic burden of schizophrenia. The polygenic score approach can be useful for testing this question.

Aim: To assess the contribution of the polygenic risk scores for schizophrenia (PGS-SCZ) and polygenic scores for IQ (PGS-IQ) to the individual IQ and its difference from the mean IQ of the family (named family-IQ) through a family-based design in a FEP sample.

Methods: The PAFIP-FAMILIES sample (Spain) consists of 122 FEP patients, 131 parents, 94 siblings, and 176 controls. They all completed the WAIS Vocabulary subtest for IQ estimation and provided a DNA sample. We calculated PGS-SCZ and PGS-IQ using the PRS continuous shrinkage method. To account for relatedness in our sample, we performed linear mixed models. We controlled for covariates potentially related to IQ, including age, years of education, sex, and ancestry principal components.

Results: FEP patients significantly deviated from their family-IQ. FEP patients had higher PGS-SCZ than other groups, whereas the relatives had intermediate scores between patients and controls. PGS-IQ did not differ between groups. PGS-SCZ significantly predicted the deviation from family-IQ, whereas PGS-IQ significantly predicted individual IQ.

Conclusions: PGS-SCZ discriminated between different levels of genetic risk for the disorder and was specifically related to patients' lower IQ in relation to family-IQ. The genetic background of the disorder may affect neurocognition through complex pathological processes interacting with environmental factors that prevent the individual from reaching their familial cognitive potential.

Introduction

Intelligence quotient (IQ) is a quantitative estimate of an individual's general cognitive ability (1). Patients experiencing a first episode of psychosis (FEP) tend to have lower IQs than healthy controls (2,3). It has also been described that these IQ deficits precede the onset of psychosis, probably due to neurodevelopmental impairments (4,5). While cognitive abilities aggregate in families, FEP patients tend to perform worse on cognitive tasks than their first-degree relatives, indicating a deviation from familial cognitive aptitude (6–10). Accordingly, IQ and specific neuropsychological functions have been largely investigated as endophenotypic traits of psychosis that may enhance preventive measures and early intervention (11–14).

Both IQ and psychosis are highly heritable, with heritability estimates ranging from 40-70% (15,16) and 60-80% (17,18), respectively. The polygenic score (PGS) method is useful for estimating an individual's genetic make-up for such complex phenotypes (19,20). On the one hand, it is possible to calculate polygenic scores for IQ (PGS-IQ) based on the results of large-scale genome-wide studies that have characterised the genetic architecture of intelligence (21). PGS-IQ is strongly correlated with crystallised intelligence and accounts for up to 5.1% of the variance in general cognitive ability (22). On the other, polygenic risk scores for schizophrenia (PGS-SCZ) can be calculated leveraging the results of genome-wide studies on this disorder (23,24). PGS-SCZ explain between 2.4% and 7.3% of the variance in schizophrenia on the liability scale (23,24) and is increased in FEP patients compared to controls (25,26).

There may be a certain degree of association between these two PGSs, given that numerous genetic variants have been identified as contributing factors to intelligence and schizophrenia (27,28). Similarly, PGS discriminating schizophrenia from bipolar disorder was found to be specifically related to intelligence (29).

We hypothesised that i) FEP patients would have higher PGS-SCZ and lower PGS-IQ than first-degree relatives and healthy controls, and ii) PGS-SCZ would be negatively associated with IQ and the patient's IQ deviation from the mean score of their family (named family-IQ), suggesting that genetic predisposition to schizophrenia is related to worse general cognitive ability. We also expected a positive association of PGS-IQ with IQ.

Our primary aim was to test whether the genetic risk for schizophrenia, as determined by PGS-SCZ, might be associated with IQ and contributed to patient-specific differences from their family-IQ in a sample of FEP patients, their first-degree relatives, and healthy controls. Secondarily, we also aimed to examine to what extent PGS-IQ predicts intelligence and deviation from family-IQ.

Methods

Sample

Participants were drawn from PAFIP-FAMILIES, a family-based study carried out in Cantabria, Spain, from January 2018 to March 2021, funded by the ISCIII (FIS PI17/00221). All participants were of European ancestry. We recruited first-degree relatives of a cohort of FEP patients previously enrolled in the Cantabria Program for Early Intervention in Psychosis (PAFIP) (30,31). The local institutional review committee (CEIm Cantabria) approved both projects (PAFIP and PAFIP-FAMILIES) under international research ethics standards and all participants gave their written informed consent. The initial sample consisted of 133 FEP patients, 146 parents, 98 siblings and 202 controls (32).

FEP patients

The PAFIP program was carried out at the University Hospital Marqués de Valdecilla (Santander, Spain) from 2001 to 2018. FEP patients were referred from the inpatient unit, outreach mental health services, and healthcare centres in the region. Inclusion criteria were: 1) 15-60 years of age; 2) living within the recruitment area; 3) experiencing a first episode of psychosis; 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. Exclusion criteria included meeting the DSM-IV criteria for drug or alcohol dependence, having an intellectual disability, and having a history of neurological disease or head injury.

First-degree relatives

We contacted the parents and siblings of the eligible patients (those with neuropsychological data and DNA samples) and invited them to participate in the study. Inclusion criteria were: 1) age over 15 years, 2) good domain of the Spanish language, and 3) ability to give informed consent in writing. Exclusion criteria included a history of psychiatric diagnosis related to psychotic illness spectrum, organic brain pathology, and intellectual disability or substance use disorders according to DSM-V criteria.

Controls

Controls were retrieved from the PAFIP program, which recruited healthy individuals through advertisements from the local community. They met the same inclusion and exclusion criteria as first-degree relatives. The psychiatric history of controls and relatives was screened by the abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH) (33), a semi-structured psychiatric interview that inquiries about the presence of clinical symptoms for mania, depression, and positive, disorganised, and negative dimensions of psychosis.

Phenotypic Data

Sociodemographic data

We recorded the sex, age and completed years of formal education of all participants. Cannabis consumption was recorded for FEP patients, siblings and controls.

Clinical data

We obtained clinical data from patients at baseline through medical records and interviews. The age at psychosis onset was defined as the age when the emergence of the first continuous psychotic symptom occurred. Duration of untreated illness (DUI) was defined as the time from the first nonspecific symptom related to psychosis. Duration of untreated psychosis (DUP) was established as the time from the first continuous psychotic symptom to initiation of antipsychotic drug treatment. Patients were randomly assigned to treatment with olanzapine, risperidone, or haloperidol (34). Positive symptoms were assessed by the Scale for the Assessment of Positive Symptoms (SAPS) (35), and negative symptoms by the Scale for the Assessment of Negative Symptoms (SANS) (36). Functioning was rated by the Global Assessment of Functioning (GAF) (37). Diagnoses were confirmed through the Structured Clinical Interview for DSM-IV (SCID-I) conducted by an experienced psychiatrist within 6 months of the baseline visit.

Estimation of IQ

Expert neuropsychologists administered the WAIS-III Vocabulary subtest (1) to estimate the IQ of all participants. This subtest has adequate properties as a proxy measure for crystallised intelligence in the general population and FEP (38). Crystallised intelligence is defined as knowledge acquired throughout life, including vocabulary, general information, culture and specific skills (39). It represents the stored information and strategies that individuals draw on to solve common problems (40). Crystallised intelligence is more stable than fluid intelligence (41); thus, the Vocabulary subtest would enable the estimation of cognitive abilities before the onset of psychosis in the FEP sample. This subtest is associated with educational attainment and the linguistic knowledge of one's native language (41). We have previously used Vocabulary as a proxy measure for premorbid intelligence, showing utility in studying the IQ of FEP patients (42).

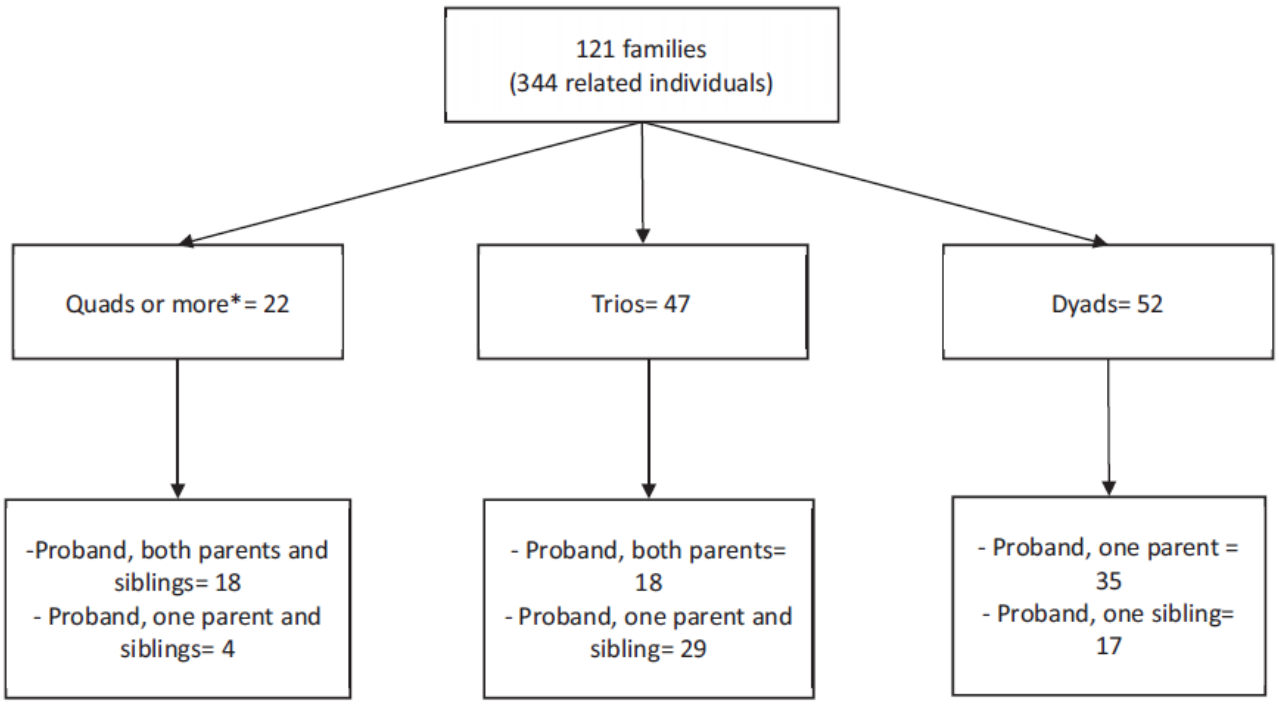

Figure 1. Conformation of the families participating in this study.

Note: Each family was formed by a FEP patient and at least one first-degree relative, either a parent or sibling. All participants completed the same neuropsychological battery and provided a DNA sample that allowed the calculation of polygenic scores. *There was one family with nine members, one with six members, and five with five members.

To estimate a proxy of the potential IQ of FEP patients, we calculated a "family-IQ" for each family. This score represents the mean IQ of all family members, including the FEP patient themself. We included patients in the estimation because 42% of our families consisted of only the proband and one other member (see Figure 1). See the details of family-IQ estimated from unaffected relatives only in the Supplementary Material.

Deviation from family-IQ was determined by calculating the difference between the individual and family scores. Positive deviations indicate that an individual's IQ is above their family-IQ, while negative deviations indicate that it is below their family-IQ.

Genotyping and polygenic scores estimation (PGS)

DNA was extracted from venous blood samples at baseline. Samples and data from patients included in this study were provided by the Biobank Valdecilla (PT20/00067), integrated into the Spanish Biobank Network and they were processed following standard operating procedures with the appropriate approval of the Ethical and Scientific Committees. The genotyping was performed at the Centro Nacional de Genotipado (Human Genotyping laboratory, CeGen) using the Global Screening Array v.3.0 panel (Illumina).

The quality control process was performed using PLINK 1.9. Single nucleotide polymorphisms (SNPs) with a minor allele frequency less than 0.01, missing data exceeding 0.02, or exhibiting deviation from Hardy-Weinberg equilibrium were removed. Participants were excluded if there were discrepancies in sex information or detected heterozygosity. A set of SNPs meeting high-quality criteria (HWE $p>0.001$, MAF>0.01) and subjected to linkage disequilibrium pruning was employed to assess relatedness. We confirmed the participants' recorded relationships, in which PI-HAT values around 0.50 were considered to indicate first-degree relatives. Ancestry outliers were identified through principal component analysis based on 1000 Genomes Project European reference populations and subsequently removed (see Supplementary Material, Figure 1). The final dataset comprised 525 participants and 492,348 SNPs. Genetic imputation was carried out in the Michigan Imputation Server using Minimac4 and individuals from the Haplotype Reference Consortium (HRC; Version r1.1) as the reference dataset. Genetic variants with MAF>0.01 were kept. After imputation, 6,910,431 SNPs were available for downstream analyses.

We calculated PGS for each participant using the latest publicly available summary statistics for schizophrenia (23) and IQ (21) by the method of PRS continuous shrinkage (PRS-CS) (43). PRS-CS shrinks the effect sizes towards the population mean, thereby attenuating the influence of variants with unstable or exaggerated effects. This regularisation technique provides more reliable and interpretable PGS estimates, enhancing their predictive power and generalizability across different populations or cohorts. PGS was then calculated in PLINK 1.9 using imputed dosage data in this cohort.

After obtaining the PGS in our sample, we corrected it by their first five ancestry principal components. The aim was to control for their possible influence on our results. We regressed the effect of the principal components on the PGS using a linear model. Finally, we kept the residuals as the corrected PGS and standardised them.

Statistical Analysis

We performed statistical analysis in R (44). To take into account that our sample was related, we carried out linear mixed models (LMMs) using the 'lme4' package.

$$Y_{ij} = \beta_{(0)} + \beta_1 X + \upsilon_i + \varepsilon_{ij}$$

(Equation 1)

In Equation 1, Y represents the dependent variable. The subscripts i and j on the Y indicate that each observation j is nested within cluster i, in this case, the family. $\beta_{(0)}$ is the overall intercept. $\beta_1 X$ represents the vector of fixed effects. υ_i is the random effect of family code. ε is the error of the model. We adjusted the p-values by False Discovery Rate (FDR) and considered those equal to or less than 0.05 as significant.

Between-group comparisons were performed using separate LMMs, one for each dependent variable (IQ, deviation from family-IQ, PGS-SCZ, PGS-IQ and sociodemographic) according to Equation 1. These models included the grouping variable as a fixed effect (FEP patient, sibling, parent or control) and the family code as a random effect. We covariated IQ comparisons by sex, age and years of education. Post-hoc comparisons were conducted with Bonferroni correction and effect sizes were estimated using beta standardised coefficients.

Then, we performed the main analyses, consisting of four LMMs according to Equation 1, which were fitted to families without controls. All four models included the same covariates (sex, age and years of education) and random effect (family code). The first and second models tested the predictive effect of PGS-SCZ on IQ and deviation from family-IQ, respectively. The third and fourth models tested the predictive effect of PGS-IQ on IQ and deviation from family-IQ, respectively.

We tested the potential effect of antipsychotic medication (chlorpromazine-equivalent dose at baseline) on patients' IQ and found no significant results (p=0.585). Therefore, the antipsychotic variable was excluded from the main analyses.

Results

Descriptive statistics and between-group comparisons

Of all subjects with PGS estimates, five were removed from the LMM analyses because they could not be nested within families (e.g., a dyad whose family member was removed in QC becomes incomplete). The final sample consisted of 344 relatives and 176 controls. Figure 1 displays the distribution of the 121 families included in the LMMs.

There was a higher proportion of men in the FEP and control groups compared to siblings and parents (p<0.001). FEP patients were significantly younger than all other groups and had higher rates of cannabis use than controls and siblings (p<0.050). Siblings were significantly older than controls and had completed more years of education than the other participants had (p<0.001).

Table 1 shows post-hoc comparisons between groups. After correcting for covariates, parents had significantly higher IQs than patients (p=0.024) and controls (p=0.018). FEP patients deviated more from family-IQ (p<0.001) than their relatives. The FEP patients had significantly higher PGS-SCZ than all other groups (p<0.001), and their parents had significantly higher PGS-SCZ than controls (p=0.023) (Figure 2). PGS-IQ was not different between groups.

Predictive effect of the PGSs on IQ and deviation from family-IQ

PGS-SCZ was not associated with IQ (Beta=-0.08, SE=0.04, p=0.53, pFDR=0.63). However, PGS-SCZ significantly predicted IQ deviation from family-IQ (Beta= -0.17, SE=0.05, pFDR=0.003) (see the results detailed in Table 2).

PGS-IQ significantly predicted the individual IQ (Beta=0.13, SE=0.04, pFDR=0.003) but showed a trend towards significance in predicting the deviation from family-IQ (Beta= 0.08, SE=0.04, pFDR= 0.073).

Discussion

Through a family-based design, we add data on the association of the polygenic background of SCZ and IQ with general cognitive performance. We report, as expected, that PGS-SCZ is increased in FEP patients as compared to their relatives and controls. Our data also show that PGS-SCZ significantly predicts the individual's deviation from the mean IQ of their relatives, whereas PGS-IQ is more predictive of the individual's IQ.

Between-group differences in IQ, PGS-SCZ and PGS-IQ

FEP patients had higher PGS-SCZ than other groups, with first-degree relatives having intermediate scores. This supports the efficacy of the PGS method in discerning varying levels of genetic predisposition to psychosis. While previous research indicates that PGS-SCZ can differentiate between FEP patients and controls (25,26), our findings suggest that it can also detect genetic risk variation within families. Although FEP patients showed PGS-IQ similar to other groups, their IQ scores were lower, suggesting unachieved cognitive potential. In addition, FEP patients showed a negative deviation from their family-IQ of 6.84 points on average. This is consistent with previous research describing a strong correlation between deviation from family cognitive ability and risk of schizophrenia (10). Such deviation is aligned with the well-reported cognitive impairments associated with schizophrenia (6), bringing at the same time new questions about the etiological mechanisms underlying the intra-family differences. Thus, deviation from familial aptitude emerges as an important marker of neurodevelopmental processes predisposing to psychosis (10).

Table 1. Between-group comparisons using linear mixed model analysis

	FEP patients (n = 121)			Parents (n = 131)			Siblings (n = 92)			Healthy controls (n = 176)					
	Mean	SD	Effect size (β Std)	Mean	SD	Effect size (β Std)	Mean	SD	Effect size (β Std)	Mean	SD	Effect size (β Std)	*F*	*p*	Post hoc comparisons
IQ	97.44	13.04	−0.06	110.46	10.66	0.39	107.23	11.30	0.26	99.12	10.55	0.00*	49.35	<0.001	P > FEP, HC; S > FEP, HC
IQ with covariates*	99.02	SE= 1.10	−0.02	107.66	SE=1.40	0.22	100.26	SE=1.08	0.13	100.34	SE=0.89	0.00[a]	4.74	0.003	P > FEP (p = 0.024), HC (p = 0.018)
Deviation from family–IQ	−6.84	8.74	−0.46	4.83	7.78	0.12	2.48	7.95	0.00[b]	NA	NA	NA	69.80	<0.001	FEP < P, S
PGS–SCZ	0.79	0.08	0.50	−0.08	0.08	0.12	−0.20	0.09	0.06	−0.38	0.07	0.00[a]	45.83	<0.001	FEP > HC, S, P HC < P (0.023)
PGS–IQ	−0.12	0.09	−0.04	0.03	0.09	0.02	0.14	0.011	0.06	−0.01	0.08	0.00[a]	1.21	0.305	NS
Sociodemographics															
Sex (male %)	73 (60.3%)		–	49 (37.4%)		–	32 (34.8%)		–	106 (60.23%)		–	χ= 29.36	<0.001	FEP> S, P; HC> S, P
Age	26.99	8.61	−0.08	62.06	7.72	0.88	40.72	13.22	0.18	30.20	8.29	0.00[a]	386.72	<0.001	FEP < HC (p = 0.026), S, P; P > all, S>HC
Years of education	10.67	3.47	−0.04	10.20	3.50	−0.11	12.65	3.66	0.19	11.01	2.69	0.00[a]	11.24	<0.001	S > all
Cannabis consumption (yes%)	55 (45.5%)		–	NA		–	5 (5.32%)		–	21 (11.93%)		–	χ = 74.12	<0.001	FEP > HC, S
Clinical at baseline															
Diagnosis (schizophrenia %)	55 (45.08%)														
Age at psychosis onset	26.15	8.42													
SAPS	14.55	4.86													
SANS	6.59	6.28													
DUI	20.09	32.55													
DUP	12.94	29.15													
GAF	51.89	30.28													

Abbreviations: DUI, duration of untreated illness; DUP, duration of untreated psychosis; GAF, global assessment of functioning; IQ, intelligence quotient; NA, not available; SANS, scale for the assessment of negative symptoms, SAPS, scale for the assessment of positive symptoms.

Notes: All post hoc comparisons were Bonferroni corrected and significant at $p < 0.001$ except when indicated. *IQ was covariated with age and years of education.

[a]Controls were used as the reference category in the models (intercept). Therefore, the effect sizes of the other groups represent their differences from the controls.

[b]Siblings were used as the reference category in the models (intercept).

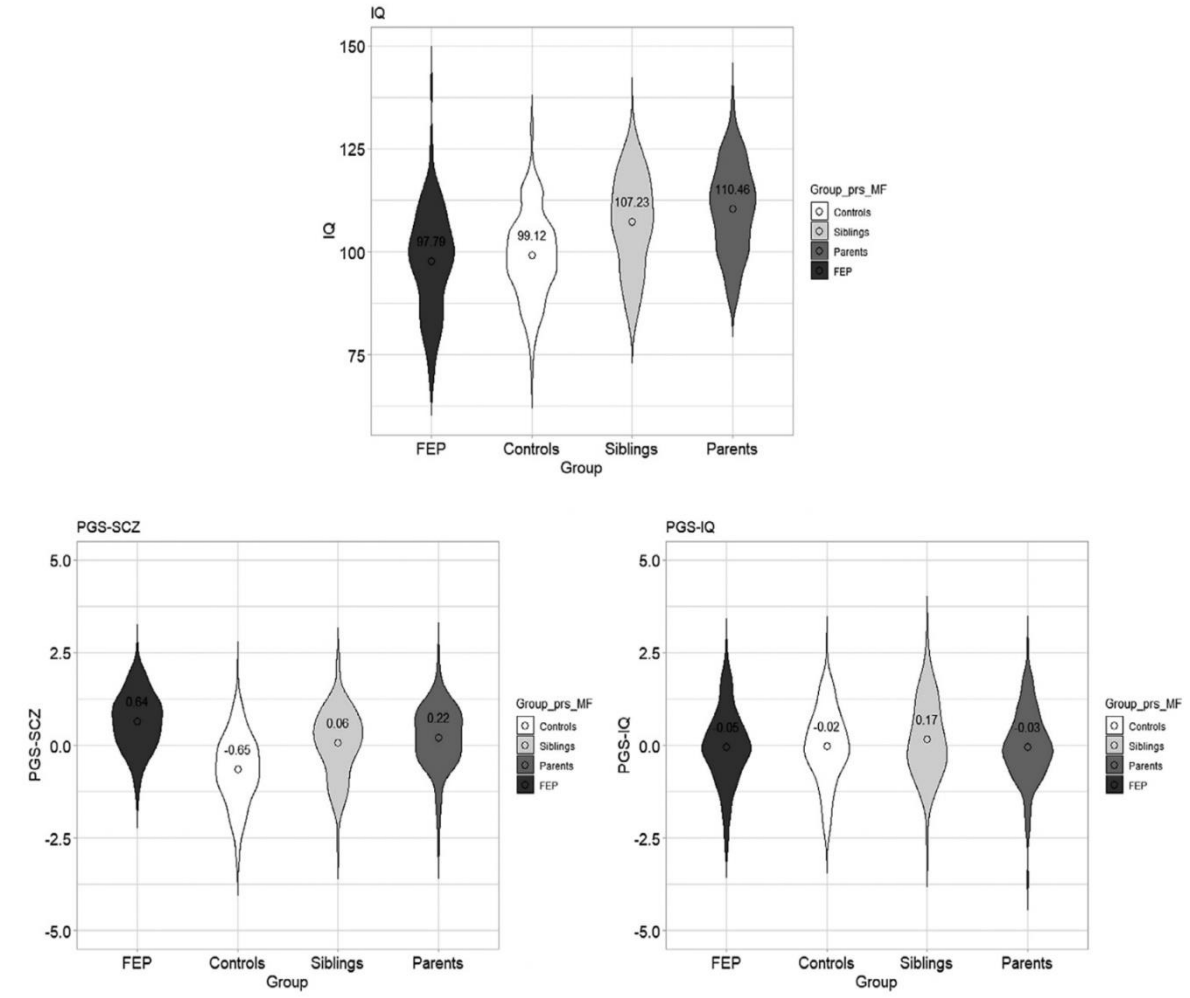

Figure 2. Violin plots of IQ, PGS-SCZ, and PGS-IQ according to the group of participants.
Note: The IQs shown in the first plot are without corrections for age and years of education. After introducing the former covariates, parents had higher IQs than FEP patients ($p = 0.024$) and controls ($p = 0.018$). Regarding PGS-SCZ, FEP patients had higher scores than all other groups ($p < 0.001$). No significant differences were found for PGS-IQ.

Table 2. The predictive effect of PGS-SCZ on IQ and deviation from family-IQ using linear mixed models

Model 1: IQ as dependent variable			
Fixed effects	Beta coefficient standardized (SE)	*T*	*FDRp*
PGS–SCZ	−0.08 (0.04)	−1.940	0.063
Years of education	0.45 (0.04)	8.570	<0.001
Age	0.39 (0.05)	10.230	<0.001
Sex	0.01 (0.04)	0.415	0.678
Model 2: Deviation from family-IQ as dependent variable			
Fixed effects	Beta coefficient standardized (SE)	*T*	*FDRp*
PGS–SCZ	−0.17 (0.04)	−3.547	<0.001
Years of education	0.16 (0.04)	3.461	<0.001
Age	0.40 (0.04)	8.089	<0.001
Sex	0.07 (0.04)	1.502	0.134

Overall model 1: *Wald* = 194.86, $p < 0.001$, $R^2 = 0.46$.
Overall model 2: *Wald* = 115.98, $p < 0.001$, $R^2 = 0.26$.

Table 3. The predictive effect of PGS-IQ on IQ and deviation from family-IQ using linear mixed models

Model 3: IQ as dependent variable			
Fixed effects	Beta coefficient standardized (SE)	*T*	*FDRp*
PGS–IQ	0.13 (0.04)	3.089	0.003
Years of education	0.34 (0.03)	8.993	<0.001
Age	0.47 (0.04)	11.237	<0.001
Sex	0.01 (0.04)	0.242	0.809
Model 4: Deviation from family-IQ as dependent variable			
Fixed effects	Beta coefficient standardized (SE)	*T*	*FDRp*
PGS–IQ	0.08 (0.04)	1.799	0.073
Years of education	0.18 (0.04)	3.738	<0.001
Age	0.44 (0.04)	9.238	<0.001
Sex	0.06 (0.04)	1.301	0.194

Overall model 1: *Wald* = 204.07, $p < 0.001$, $R^2 = 0.46$.
Overall model 2: *Wald* = 104.02, $p < 0.001$, $R^2 = 0.24$.

We found that unaffected siblings have a lower PGS-SCZ than the proband, implying a slightly reduced genetic predisposition to schizophrenia. Siblings had similar IQs to controls, and their performance aligned with their family cognitive profile. Previous research consistently shows that siblings tend to perform better than the proband in cognitive domains such as executive functions and memory (6,32,45–47). Siblings had higher educational attainment and lower cannabis use rates (Table 1), which may be protective factors that increase cognitive reserve against psychosis (48,49).

Parents in our sample were found to have higher IQs than the other participants, including the healthy controls. This finding contrasts with previous evidence showing IQ deficits among first-degree relatives of FEP patients (6,7,9,50,51). The discrepancy in results may be related to the neuropsychological measure used in our study. We estimated crystallised intelligence, which tends to increase with age (52) and is strongly influenced by education (53). As parents in our sample are the oldest, age may have contributed to their IQ advantage.

Relationship between PGS-SCZ and deviation from family-IQ

Our research shows that PGS-SCZ can predict deviation from family-IQ, but it does not have any direct relation with IQ. These findings converge with some previous studies showing no connection between genetic risk of schizophrenia and intelligence (54,55). However, others have reported a direct correlation between higher PGS-SCZ and low intelligence in individuals at high risk of psychosis (56), with schizophrenia (29), and in controls (57,58). Conflicting findings in the literature may be due to differences in neuropsychological measures and sample variation. An alternative explanation is that genetic risk for schizophrenia may influence longitudinal intellectual trajectories rather than cross-sectional IQ scores. Although the literature on FEP is limited, some insights can be drawn from studies of the general population. Germine et al. (59) described that PGS-SCZ was associated with reduced speed of emotion identification and verbal reasoning in childhood. McIntosh et al. (57) found that high PGS-SCZ was associated with greater cognitive decline. Therefore, this evidence suggests that genetic liability for schizophrenia may be related to specific cognitive domains at key life stages. These trajectories need to be explored in the FEP population, as long-term factors such as antipsychotic medication or disease progression may influence their cognitive outcomes.

Concerning intellectual family deviation, our findings indicate that an increase of one standard deviation in PGS-SCZ may lead to roughly 0.17 standard deviations of negative deviation from family-IQ. Following Kendler et al. (10), we interpret that the genetic liability for schizophrenia indirectly influences intelligence by disrupting neurodevelopment and preventing the achievement of cognitive potential. In this regard, it could be suggested that increased genetic susceptibility to schizophrenia in FEP patients may shape developmental trajectories and/or make individuals more sensitive to environmental insults (60,61), leading to the onset of psychosis. This interpretation is based on existing evidence of a common genetic susceptibility between schizophrenia and neurodevelopmental disorders (62,63), which, when combined with environmental risk factors (60,64), can increase the likelihood of impaired cognitive development from an early age.

Relationship between PGS-IQ and IQ

We confirmed a strong association between PGS-IQ and IQ. This association has been previously reported in the general population (19,22), and our study replicates it in the FEP population (25,65). As expected, polymorphic genetic factors explain a small percentage of the variance in IQ, suggesting that there is a very large amount of variability associated with other sources of genomic variability, but also with environmental factors.

As PGS-IQ showed a trend towards predicting deviation from family-IQ ($p = 0.073$), the evidence for this relationship remains unclear. Deviation from family cognition may not solely reflect the risk of schizophrenia. It is also possible that a lower genetic predisposition to intelligence contributes to this deviation. Further research on IQ in FEP, particularly investigating indirect parental genetic effects, could provide more clarity (66,67). Research has shown a robust effect of genetic nurture on education, influenced by parental education and socioeconomic status (68,69). This pathway could be homologous to IQ, although this needs to be verified in future studies.

Strengths and limitations

The strength of this study lies in the use of neuropsychological and genetic data from FEP patients and their unaffected first-degree relatives. However, some limitations should also be acknowledged. First, the modest sample size of the study, especially when analysing subgroups, and the incomplete families with only sibling pairs, limits the study of genetic transmission. In this regard, beyond larger samples future studies would also benefit from including both first-degree relatives of controls and affected and non-affected first-degree relatives of patients. Second, IQ estimation focuses on crystallised intelligence, and the results may not generalise to other types of intelligence such as fluid intelligence. Third, the inclusion of participants of European ancestry may limit generalisation to diverse populations. Finally, potential biases may also arise from voluntary participation and the exclusion of relatives with a history of psychiatric diagnosis, which may result in a sample with preserved cognitive function. Further studies involving two or more people with psychosis in the same family may be relevant for studying populations at high risk of schizophrenia.

Conclusions

Based on a family-based design in a FEP population, we confirmed that the polygenic risk for schizophrenia is increased in the probands, while first-degree relatives score intermediate between patients and controls. This validates the polygenic background as a discernible marker of genetic risk variation within families. Additionally, our results indicated that the genetic load for schizophrenia significantly predicts the deviation from the family-IQ, explaining that FEP patients underperformed in the IQ test

compared to their relatives. The genetic risk for schizophrenia may modulate cognition by shaping developmental trajectories and making individuals more sensitive to environmental insults, therefore, preventing individuals from reaching the familial cognitive potential. Further research is needed to determine the potential contribution of genetic liability for intelligence to the unrealised cognitive potential of FEP patients.

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Conflict of interest

The authors declare no conflicts of interest.

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Global discussion

The aim of this thesis was to investigate the relationship between IQ and SSDs. Using a multi-method approach, the phenotypic and genotypic factors that may contribute to the association between these two traits were analysed in a sample of individuals who have experienced FEP, their first-degree relatives, and a group of healthy controls. The neuropsychological performance of the participants was analysed in three studies, one with a longitudinal case-control design and two with a family cross-sectional design. The potential genetic association between IQ and SSDs was studied in a systematic review to identify the specific genetic variants underlying their common genetic architecture. The final study estimated the participants' genetic load for schizophrenia and tested its influence on IQ.

1. Phenotypic relationship between IQ and SSDs

1.1. Longitudinal course of IQ over 10 years in FEP patients and controls

A previous study in the PAFIP cohort showed that FEP patients had a higher prevalence of low IQ (28.8%) compared to healthy controls (14.6%) (Ayesa-Arriola et al., 2018), consistent with other studies (Kahn, 2020; G. M. Khandaker et al., 2011). Following this line of research, the first step for this dissertation was to analyse whether the intellectual performance of FEP patients remained stable or changed from baseline to 10-year follow-up.

Cluster analysis revealed greater heterogeneity in the intellectual patterns of FEP patients compared with controls. After subgrouping based on IQ trajectories, FEP patients fell into five distinct clusters, whereas controls fell into three clusters. This finding is consistent with previous research highlighting the different neurocognitive trajectories following the onset of psychosis (Fett et al., 2020; Hedman et al., 2013; Ohi et al., 2021; Zanelli et al., 2019). The heterogeneity in IQ trajectories may be related to the diversity of clinical presentations within the SSD category, as some diagnoses, such as brief psychotic disorder, are associated with better neurocognitive outcomes than schizophrenia (Ayesa-Arriola, Rodríguez-Sánchez, et al., 2016a). Further exploration of specific diagnosis is needed in future studies with larger samples, as the analyses on the PAFIP cohort did not yield significant results.

Interestingly, none of the groups, including FEP patients and controls, showed IQ decline. This result is in line with a previous systematic review that suggested that individuals experiencing a FEP may have pre-existing cognitive deficits that remain stable after the onset of psychosis (Bozikas & Andreou, 2011). However, this finding contradicts other studies that have reported a long-term decline in IQ in FEP

patients (Fett et al., 2020; Fujino et al., 2017; Ohi, Takai, et al., 2021; Zanelli et al., 2019). The observed discrepancies might be due to methodological differences. The selection of participants (outpatients vs. inpatients) and the length of follow-up could influence the results between studies, as these factors affect neurocognitive functioning at different stages of the disorder.

An important finding was that both FEP patients and controls can improve IQ in the long term, but FEP patients show greater gains. Jepsen et al. (2010) suggested that although FEP patients are able to assimilate new intellectual content and thereby increase their IQ scores, their rate of cognitive acquisition is generally slower than that of their healthy counterparts. The larger increase in FEP patients may indicate that they were performing below their own cognitive potential at baseline, probably due to neurodevelopmental disruptions, and therefore had a larger window for improvement in the long term.

This first study also highlighted that long-term cessation of cannabis use could contribute to improving cognitive outcomes in FEP patients, in line with previous evidence (Setién-Suero et al., 2019). Future research should address possible moderating factors such as consumption patterns (Schoeler et al., 2016), sex (Ayesa-Arriola et al., 2020; Setién-Suero et al., 2017), age (Barnes et al., 2006), and genetic variations (Van Winkel et al., 2011).

1.2. Neuropsychological performance of first-degree relatives compared to FEP patients and controls

The second study examined neurocognitive performance in the same cohort of FEP patients, including their first-degree relatives and the group of healthy controls. The analysis revealed no statistically significant differences in IQ between the participant groups. However, parents and siblings showed a trend towards higher IQ scores compared to both FEP patients and controls. This finding differs from the original hypothesis, which predicted lower IQ in relatives compared to controls.

The slight IQ advantage observed in parents and siblings may indicate a higher cognitive reserve that could help protect against psychosis (Ayesa-Arriola et al., 2021; Magdaleno Herrero et al., 2021). However, this finding contrasts with other evidence showing that first-degree relatives of FEP patients underperform controls on IQ tests (Barrantes-Vidal et al., 2007; Cella et al., 2015; McIntosh et al., 2005; van Os et al., 2017). These differences may be explained by methodological limitations. The sample size of this study may be insufficient to detect small effect sizes with adequate statistical power. In

addition, the voluntary nature of participation raises the possibility that the FEP patients and relatives included in this study represent a subpopulation with superior neurocognitive performance. Future family-based studies and large-scale meta-analyses are warranted to strengthen the current evidence.

Analysis of specific neurocognitive domains revealed common deficits in executive function and attention in FEP patients, their parents, and siblings. Thus, these neurocognitive functions are potential endophenotypes that require further investigation, in line with existing evidence (Bhatia et al., 2009; Cornblatt & Keilp, 1994; Laurent et al., 1999; Pawełczyk et al., 2018). Significant differences in sex distribution were observed between groups, with more males among FEP patients and more females among relatives, indicating potential differential roles in caregiving and cognitive outcomes. Siblings had completed more years of education, suggesting a protective effect against psychosis risk (Lemvigh et al., 2020; Quiñones et al., 2009). The lower educational attainment of FEP patients might be linked to prodromal symptoms or impaired intellectual ability before illness onset.

1.3. Familiality of IQ

The third study examined familial aggregation of intelligence, called IQ-familiality. This concept refers to the phenotypic similarity in IQ observed between family members, likely due to a combination of shared genetic and environmental influences. The results suggested a low to moderate familiarity of IQ in FEP, meaning that about 26% of an individual's IQ variance is explained by common familial factors, including environment and genetics. This finding corresponds with previous evidence describing familial contribution to IQ in individuals with SSDs (Andric et al., 2016; de Zwarte et al., 2019b; Goldberg et al., 2012; Weiser et al., 2021).

Additionally, this study aimed to recognize different patterns of IQ familial resemblance among FEP patients and test whether these were associated to differential clinical or functional outcomes. While no significant differences were found in clinical or functional outcomes, there was a robust association between IQ familial resemblance and both neurocognitive performance and premorbid adjustment.

When FEP patients were classified based on their intrafamily resemblance scores for IQ, a positive correlation was found: patients with greater similarity to the average IQ of their family, tended to have higher IQs themselves. Conversely, a negative correlation was observed, with patients with low resemblance to familial IQ also having lower IQs. These findings are consistent with research by Kendler et al. (2016a), suggesting that deviation from familial cognitive aptitude may be a risk factor for

schizophrenia, possibly due to underlying qualitative developmental impairments. The observed association between low intrafamily resemblance and low IQ in FEP patients may be related to other characteristics, such as lower educational attainment, higher rates of unemployment, and poorer overall functional outcomes in the community.

Premorbid adjustment during childhood and adolescence was significantly related to deviations from family IQ. FEP patients with both low IQ and low familial resemblance exhibited poorer social adjustment in their early years and were more frequently diagnosed with schizophrenia. The results suggest the presence of a potential subgroup within the FEP population. This subgroup is characterized by a deviation from their family's neurocognitive profile, poorer early social adjustment, and a higher probability of developing a chronic psychotic condition. For FEP patients with high familial IQ resemblance, their phenotypic similarity may be attributed to a shared, robust genetic basis. Nonetheless, studying familiality alone does not provide insight into the precise causes of trait resemblance within families. Therefore, it is essential to conduct research involving genetic data to explore more accurately the specific factors underlying familiality of intelligence.

2. Genetic relationship between IQ and SSDs

2.1. Common genetic variants associated with IQ and SSDs

The systematic review aimed to identify the candidate genes that may be common to the genetic architecture of both IQ and SSD. Fifty-five studies were included, the majority with a candidate gene design (89.9%) and the minority with a GWAS strategy. The SNPs most frequently investigated in candidate gene studies were located at *COMT*, *DTNBP1*, *BDNF*, and *TCF4*. These genes have traditionally been associated with schizophrenia risk because of their role in the dopaminergic pathway (*COMT*) (Craddock et al., 2006), synaptic function and neurotransmitter release (*DTNBP1*) (Waddington et al., 2020), synaptic plasticity (*BDNF*) (Gratacòs et al., 2007) and neurodevelopment (*TCF4*) (Gao et al., 2020). However, the results of these candidate gene studies were inconsistent. Also, the GWAS did not support significant associations between genetic variants in these genes and IQ and SSDs (LeBlanc et al., 2012; Whitton et al., 2016).

Instead, emerging candidate genes such as *NRN1, ZNF804A*, *CHD7* and *GATAD2A* offer promising avenues for research into the relationship between IQ and SSD. *NRN1*, which is involved in synaptic

maturation and plasticity, shows associations with fluid intelligence in SSD patients, suggesting a potential marker for risk of cognitive deficit (Chandler et al., 2010). Similarly, *ZNF804A* polymorphisms show associations with IQ variation in SSD populations, suggesting its relevance in psychosis susceptibility (Walters et al., 2010). *CHD7* and *GATAD2A*, involved in chromatin remodelling and gene expression regulation, show associations with lower IQ in SSD patients, highlighting the role of epigenetic regulation in cognitive dysfunction (Whitton et al., 2016).

The systematic review of the existing literature has confirmed the polygenic nature of the genetic overlap between IQ and SSDs. This means that numerous genes, many previously unidentified, contribute to the genetic architecture of both IQ and SSDs, each exerting a subtle influence. Based on these findings, the following study used a methodological approach that can capture the polygenic architecture of both IQ and SSDs in the participant population.

2.2. Indirect influence of polygenic scores for schizophrenia on IQ

The fifth study estimated polygenic scores for schizophrenia and IQ (PGS-SCZ and PGS-IQ, respectively) in the sample of FEP patients, their relatives, and controls. PGSs were computed based on the largest GWAS to date for IQ (Savage et al., 2018) and schizophrenia (Trubetskoy et al., 2022). Analyses showed that the PGS-SCZ was effective in identifying familial genetic risk for psychosis. FEP patients had significantly higher PGS-SCZ scores than their first-degree relatives. The latter group showed intermediate scores between probands and controls. These findings suggest the utility of the PGS-SCZ as a research tool to assess varying degrees of genetic predisposition to psychosis in at-risk individuals.

There were no significant differences in PGS-IQ between the groups. This suggests that FEP patients share a comparable genetic predisposition to intellectual outcomes with their parents and siblings. Therefore, the observed lower IQ profile in FEP patients may not be due to a reduced genetic contribution to neurocognition. Alternative explanations could include epigenetic modifications and/or environmental factors affecting neurodevelopment (Guloksuz et al., 2019; Schmitt et al., 2023).

In addition, this study sought to investigate the potential of PGS-SCZ to predict IQ, thereby exploring the hypothesis that genetic risk for psychosis might influence intellectual outcomes within the FEP group and their families. The analysis showed no significant association between PGS-SCZ and IQ. However, one notable finding emerged: PGS-SCZ significantly predicted individual deviations of FEP patients

from family-IQ. This deviation score was defined as the difference between an individual's observed IQ and the mean IQ of their siblings and parents (family-IQ). For example, a patient with an IQ of 100 whose family-IQ was around 105 would have a negative deviation from their family neurocognitive potential. On average, FEP patients exhibited a negative deviation from their family-IQ of 6.84 points, suggesting that affected individuals generally did not reach their full potential. A one standard deviation increase in PGS-SCZ was associated with approximately 0.17 standard deviations from family-IQ. This finding is consistent with the model proposed by Kendler et al. (2016a), suggesting that genetic risk for schizophrenia may indirectly affect intelligence through its effect on neurodevelopment. Specifically, this effect could prevent the full realisation of an individual's cognitive potential.

Increased genetic susceptibility to schizophrenia in individuals with FEP may influence developmental trajectories and/or increase sensitivity to environmental stressors, culminating in the onset of psychosis (Guloksuz et al., 2019; Martin et al., 2014). This interpretation builds on existing evidence of shared genetic susceptibility between schizophrenia and neurodevelopmental disorders (Owen & O'Donovan, 2017; Singh et al., 2017), which, in combination with environmental risk factors (Schmitt et al., 2023), may increase the likelihood of impaired cognitive development from an early stage.

3. Practical implications

Cognitive deficit is a common characteristic of SSDs that significantly affects a patient's daily life and overall well-being. The FEP is a crucial period in understanding the early stages of SSD and identifying potential intervention targets. Identifying neurocognitive endophenotypes within SSD can help in prevention, early detection, adequate diagnosis and intervention, and personalized treatment. By focusing on neurocognitive endophenotypes, such as IQ, clinicians can effectively reduce the impact of cognitive deficit on functional outcomes, leading to better long-term outcomes for individuals with SSDs.

The selection of IQ as candidate endophenotype of SSDs holds several advantages. IQ is an observable and quantitative measure that allows accurate comparisons between subjects. Standardized neuropsychological tests can be used to estimate IQ in different populations and age groups in a short amount of time. If IQ was validated as an endophenotype of SSDs, it could be used to estimate the risk of developing psychosis. This means that neuropsychological assessments could be promoted among populations at risk of developing SSDs, such as individuals with a high genetic

load for schizophrenia, adolescents with neurodevelopmental disorders, or people with high substance consumption. Together with the analysis of other endophenotypes, biomarkers and premorbid indicators, prevention strategies could be implemented to avoid the appearance of psychosis. In people who have already experienced the onset of psychosis, neuropsychological assessment can help to clarify the patient's neurocognitive profile at an early stage of the illness. This information, together with other clinical and functional indicators, would help to establish personalized treatment, improve the diagnosis and prognosis, and reduce the impact of the illness.

Investigating the relationship between IQ and SSDs could significantly improve our understanding of the origins of the disorder. Endophenotypes offer a deep insight into the biological and genetic underpinnings of schizophrenia. By identifying precise, quantifiable traits associated with the disease, researchers can more effectively unravel its causes and underlying mechanisms. For example, genetic polymorphisms found to overlap between IQ and SSDs play a crucial role in basic neuronal functions such as synaptic structure, differentiation, and signalling. In addition, identifying specific endophenotypes can lead to the discovery of biomarkers that can be used for early diagnosis, patient stratification, and monitoring treatment progress.

The implications of our findings on IQ-familiality hold great promise for future practical applications. By assessing the cognitive abilities of first-degree relatives through neuropsychological testing, the cognitive potential of individuals with FEP can be estimated in a simple and cost-effective strategy. This approach could enable personalized interventions based on cognitive profiles. For example, FEP patients with high familial cognitive potential might be ideal candidates for cognitive remediation interventions aimed at improving cognitive outcomes from the onset of psychosis.

The results of this dissertation indicate the usefulness of polygenic scores in predicting IQ and schizophrenia. The diagnostic use of polygenic scores still needs to be validated. However, this research highlights their potential as a valuable research tool. PGS-SZ effectively discriminate between different levels of genetic susceptibility to schizophrenia in first-degree relatives of affected individuals. Consequently, this approach shows promise for quantifying the polygenic risk of SSDs in individuals. In addition, PGS-IQ predicted IQ in the FEP population similarly to the general population. Therefore, they may be relevant to the study of genetic factors associated with neurocognition.

4. Future research on the field

Continued research is imperative to elucidate the underlying mechanisms responsible for cognitive deficits in SSDs and to identify innovative therapeutic targets aimed at enhancing cognitive outcomes and the quality of life for those affected. IQ and SSDs are complex traits that arise from an intricate interplay between genetic and environmental factors. Beyond genetic risk factors, investigating the role of epigenetic modifications is crucial in understanding the pathogenesis underlying cognitive abilities and psychosis.

The idea of genetic nurture presents an interesting research field. This concept emphasizes how the genetic makeup of parents and close relatives can indirectly impact an individual's characteristics through the environment they create, rather than solely through direct genetic inheritance (Trejo & Domingue, 2018). This understanding highlights how the nurturing environment, influenced by the genetic predispositions of the parents, plays a crucial role in the development of cognitive abilities. Environmental and nurturing factors are critical in shaping intelligence, encompassing access to education, the quality of early childhood experiences, socio-economic status, family environment, nutrition, and exposure to intellectually stimulating experiences (Cawley et al., 2023; Wang et al., 2021). Children raised in environments that are intellectually enriching, with ample educational resources and supportive caregiving, generally exhibit higher intellectual functioning compared to their counterparts from less advantaged or neglected settings (Wang et al., 2021). Comprehending these complex interactions is crucial for unravelling the aetiology of IQ and SSDs and could inform early intervention and preventative strategies.

Environmental factors continue to impact intelligence throughout childhood and adolescence and can contribute to neurocognitive deficits in SSDs. Childhood trauma (van Os et al., 2017) and cannabis use (Adorjan & Papiol, 2019; Martin et al., 2014) may account for the observed variations in cognitive performance between siblings and FEP patients. Studies focusing on unaffected siblings of individuals with SSDs are particularly promising for identifying exposure to risk factors that precipitate psychosis, starting from a similar genetic background. Additionally, increasing research on the offspring of individuals with SSDs allows for the investigation of the direct transmission of risk alleles and the influence of epigenetic and environmental factors (Axelrud et al., 2023; de Zwarte et al., 2019b; Rasic et al., 2014).

To gain a more comprehensive understanding of neurocognitive deficits in SSD, research should include additional endophenotypes, such as executive function and attention. Furthermore, validation of these endophenotypes can be greatly enhanced by investigating their neurobiological correlates through studies of brain structure and function (de Zwarte et al., 2019b).

5. Strengths and limitations

This thesis analysed the complex relationship between IQ and SSDs. A major strength was the long-term perspective provided by a longitudinal study of a sample of FEP patients and controls. By following participants over a decade, results contribute to a deeper understanding of how cognitive performance might develop in individuals with SSDs. Analyses controlled for relevant covariates, such as education level, age and sex, to avoid bias. Assessing individuals at FEP provides the advantage of accessing their outcomes in an early stage, avoiding the confusing effects of chronicity.

Three empirical studies have been conducted using a family design. This design included parents and siblings of FEP individuals, allowing group comparisons and exploration of IQ-familiality. The study of unaffected relatives of FEP patients served as a proxy measure for the potential cognitive abilities of the patients. In addition, the use of comprehensive neuropsychological assessments provided a detailed characterisation of different cognitive domains, highlighting the potential importance of investigating other higher-level cognitive processes.

The investigation of genetic factors initially involved a systematic review of the current literature on the genetic basis of both SSD and IQ. This review used a rigorous methodology and included all available evidence without restrictions on publication date. As a result, the literature review can be considered comprehensive and accurate in its representation of the existing knowledge base on this topic. A further strength of this research is the inclusion of genetic data from participants. DNA samples provided by the individuals allowed the estimation of their genetic susceptibility to both IQ and SSDs.

However, several limitations need to be considered. A recurring limitation in our studies was the sample size, especially when looking at specific subgroups. This may limit the generalisability of our findings to a larger population. In addition, this genetic research focused on participants with European ancestry, which may limit its applicability to more diverse populations.

The distribution of families in the studies was irregular. Some families were very participatory, providing data on the FEP patient, both parents and all siblings. However, many incomplete families were also included, where only one parent or sibling agreed to participate. Gender differences in participation were identified, with more participation from mothers and sisters of FEP patients. Another aspect to consider is the voluntary nature of participation. The people who agreed to participate in this research may represent a sub-sample of people with better neuropsychological performance compared to the overall FEP population. No data are available for first-degree relatives of healthy controls. A design that includes healthy families would have significant recruitment difficulties but could be informative for studying the heritability of neurocognition in the general population.

Limitations of the data collection methods have been identified. IQ was estimated using a measure of crystallised intelligence. Therefore, the findings and interpretations must be limited to this domain of intelligence, as other types of intellectual ability (e.g. fluid intelligence) may show a different pattern in FEP patients and their first-degree relatives. A challenge in considering IQ as an endophenotype for SSD is its lack of specificity. Low IQ is not exclusively associated with schizophrenia but with a range of conditions such as autism spectrum disorders or attention deficit-hyperactivity disorder. Therefore, future studies could focus on characterizing the differential intellectual profile between these disorders.

The use of the polygenic score approach had the major advantage of capturing the effect of thousands of SNPs associated with IQ and SSD. However, this method does not consider other sources of rare variant polymorphisms, such as deletions or insertions. Rare variants should be further analysed because of their association with neurocognitive deficits. Besides, only a small proportion of the heritability of IQ and SSD is attributable to robustly identified loci. Further studies with large samples are needed to gain a more precise view of the genetic architecture of these endophenotypes.

Conclusions

This dissertation contains five studies that extracted specific conclusions:

1. Individuals with FEP have a higher prevalence of low crystallised IQ compared with healthy controls, which remains stable or improves over the 10-year follow-up period, with no observed decline.

    1.1. FEP patients can improve in measures of crystallised intelligence in the long term, confirming their ability to learn and acquire new information after the onset of psychosis. However, their learning process may be different from that of healthy controls.

    1.2. There is a subgroup of FEP patients, characterized by poor premorbid adjustment and low premorbid IQ, who can achieve significant improvements in the long term and who may particularly benefit from cognitive enhancement early during the disorder.

2. Unaffected parents and siblings of FEP patients tend to have a higher IQ than the proband and healthy controls, which may be a protective factor against psychosis.

    2.1. First-degree relatives of FEP patients tend to underperform controls in executive functions and attention and are therefore suitable endophenotypes of psychosis.

3. IQ is familial to a low to moderate degree in the FEP population. Approximately 25.9% of the variance in IQ is explained by common familial factors.

    3.1. FEP patients with low IQ who do not reach their familial cognitive potential show adjustment difficulties since childhood, probably influenced by environmental factors.

4. Thousands of genetic polymorphisms are common to intelligence and schizophrenia. These polymorphisms are found in genes involved in brain development, neuronal proliferation, and synaptic plasticity.

    4.1. The *COMT*, *BDNF* and *DTNBP1* genes have not been confirmed as significantly associated to SSD and IQ by genome wide association studies.

    4.2. Other genes have been targeted to understand the molecular basis of the intellectual deficit in schizophrenia, including *NRN1*, *ZNF804A, CHD7* and *GATAD2A*.

5. Polygenic scores for schizophrenia can distinguish between different levels of genetic risk for the disorder in affected individuals, their healthy first-degree relatives, and healthy controls.

5.1. Polygenic risk for schizophrenia is indirectly related to intelligence, as it can significantly predict the negative deviation of FEP patients from their family IQ. Thus, underachieving family cognitive potential may be a risk factor for psychosis.

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Annexes

HOJA DE INFORMACIÓN PARA EL PARTICIPANTE

Ud. ha sido invitado a participar en este estudio:

TÍTULO DEL ESTUDIO: Estudio del funcionamiento neuropsicológico y variantes genéticas asociadas en familiares de pacientes con trastornos del espectro de la esquizofrenia.

ACRÓNIMO: PAFIP-FAMILIAS

INVESTIGADOR PRINCIPAL: Rosa Ayesa Arriola

CENTRO: Hospital Universitario Marqués de Valdecilla.

Nuestra intención es proporcionarle información adecuada y suficiente para que pueda evaluar y juzgar si quiere o no participar en el estudio. Para ello, es conveniente leer con atención esta hoja informativa y preguntar cualquier duda que le surja relativa al estudio. Además puede consultar con cualquier persona que considere oportuno.

Para un adecuado avance en la investigación de las diferentes enfermedades, en ciertos casos es necesaria la recogida de información a largo plazo para estudiar la evolución de la enfermedad. También es necesario utilizar todas las fuentes de información disponibles para alcanzar el máximo grado de conocimiento sobre los factores que determinan la evolución de la misma. Así se justifica la utilización de datos provenientes de muestras biológicas (sangre) y pruebas neuropsicológicas de los participantes, con el fin de obtener conocimientos que permitan desarrollar nuevas estrategias diagnósticas y preventivas, así como obtener nuevos y mejores tratamientos. Por ello solicitamos su consentimiento para participar en el estudio que se describe más abajo, que ha sido aprobado por el Comité Ético de Investigación Clínica de Cantabria y respeta la normativa vigente.

La participación en esta investigación implica la donación de una muestra de sangre que se utilizará en el estudio con el fin de encontrar variantes genéticas relacionadas con la inteligencia que expliquen el déficit cognitivo presente en la

esquizofrenia, y que posteriormente podrá formar parte de una colección del Biobanco Valdecilla. Las muestras conservadas en el Biobanco podrán ser utilizadas tanto en el desarrollo del estudio mencionado como en futuras investigaciones relacionadas con esta patología u otras asociadas.

Participación voluntaria

La participación en este estudio, así como la donación de muestras, es totalmente voluntaria y la decisión de no participar no afectará a la relación de su familiar con el equipo de médicos que le atienden ni implicará perjuicio alguno en su tratamiento.

¿Qué supone participar en este estudio?

La participación en el estudio supone que se compromete con el investigador al cumplimiento de las instrucciones del protocolo del estudio.

¿Qué beneficios puedo obtener participando en este estudio?

Es posible que no obtenga ningún beneficio directo por su participación en este estudio.

En lo referente a la donación de sus muestras, dicha donación tiene un carácter altruista y el único beneficio esperado es el avance en el conocimiento científico relativo a esta enfermedad, aunque podría suponer beneficios futuros para su familiar y otros pacientes.

COMPENSACIÓN ECONÓMICA

El investigador principal ha indicado que recibirá una compensación económica (transferencia bancaria por un valor de **50€**) por su participación en el estudio y ha declarado que no existe ningún conflicto de intereses.

DESCRIPCIÓN GENERAL DEL ESTUDIO

Objetivo principal: El objetivo es establecer las diferencias ENTRE EL FUNCIONAMIENTO COGNITIVO familiar como un fenotipo cuantitativo para investigar el papel de las variantes genéticas en los déficit cognitivo observados en pacientes con trastornos del espectro de la esquizofrenia.

Metodología y duración del estudio: Se trata de un estudio naturalístico observacional y transversal. Se incluirán progenitores y hermanos de pacientes que previamente participaron en el programa de atención a las fases iniciales de la psicosis (PAFIP). Se reclutarán sujetos durante 3 años (hasta diciembre de 2020).

Datos: Se recogerá información socio-demográfica y se realizará una extracción de sangre y una evaluación neurosicológica. Se ofrecerá también realizar una Resonancia Magnética.

PROCEDIMIENTO DE INFROMACIÓN Y DONACIÓN DE MUESTRAS

Con la firma de este Consentimiento Informado el participante autoriza la obtención de información y procesamiento de su muestra, así como la gestión de los datos referidos a su salud que sean relevantes para la investigación científica, y que implicará el siguiente proceso:

Entrevista (15 minutos).

Evaluación neuropsicológica (1 hora y 15 minutos). Los test cognitivos serán realizados por un psicólogo en un día que le sea conveniente a usted. Se trata de pruebas sencillas, de fácil aplicación y realización en las que debe estar lo más concentrado posible. No se trata de ninguna prueba de inteligencia. A través de estos test obtenemos diferentes puntuaciones de distintos aspectos cognitivos como pueden ser la memoria, la atención, la concentración, la velocidad de procesamiento, la planificación o el lenguaje. Sus puntuaciones las compararemos con las de los pacientes para poder llevar a cabo diferentes análisis de nuestro estudio.

Algunas personas se sienten cansadas antes de acabar la aplicación de las pruebas, si esto es así, háganoslo saber y podemos finalizar la prueba en cualquier otro momento.

Extracción de sangre que se realizará en el Hospital Marqués de Valdecilla, donde se obtendrá una muestra de **30 ml de sangre** mediante venopunción.

La donación de sangre apenas tiene efectos secundarios; lo más frecuente es la aparición de pequeños hematomas en la zona de punción que desaparecen transcurridos 1 o 2 días. En caso de ser necesario, o no disponerse de suficiente volumen de muestra en alguno de los controles, se utilizará sangre o sus derivados provenientes de remanentes de la actividad asistencial.

Una vez obtenida la muestra, se codificará y se procesará en el Biobanco Valdecilla y los productos obtenidos de la misma, junto a los datos asociados que se utilizarán en el desarrollo del mencionado estudio.

De las muestras de sangre se obtendrá plasma, suero, ADN, ARN y células mononucleares. Con el plasma y el suero se harán estudios de presencia de proteínas relacionadas con el neurodesarrollo y con factores metabólicos. El ADN se utilizará para estudiar las variantes genéticas asociadas a la respuesta a fármacos y a la aparición de efectos secundarios (por ej. aumento de peso, síntomas motores, alteraciones de función sexual…), y el ARN para estudiar cambios en la expresión de genes asociados a estos procesos. Además se guardarán células congeladas para realizar futuros estudios de biología celular.

Durante el estudio las muestras estarán almacenadas en congeladores a -80ºC en el Biobanco Valdecilla, ubicado en la planta 0 del Edificio de la Fundación Instituto de Investigación Marqués de Valdecilla.

Una vez finalizado el estudio que da origen a la colección, si Ud. lo autoriza, las muestras quedarán custodiadas por el Biobanco Valdecilla. Las muestras almacenadas en el Biobanco serán recodificadas a fin de garantizar la protección de la identidad del donante.

Finalidad de las muestras depositadas en el Biobanco Valdecilla.

El Biobanco Valdecilla es una entidad sin ánimo de lucro cuyo objetivo es gestionar colecciones de muestras biológicas humanas (sangre, ADN, células, plasma, orina, tejido, etc.) y ponerlas, junto a sus datos asociados, a disposición de los investigadores a fin de ser utilizadas en investigación biomédica. De esta manera, los científicos pueden disponer de una gran cantidad de muestras de una misma patología de donde obtener conocimientos para desarrollar nuevas estrategias terapéuticas y tratamientos aplicables a los pacientes.

¿Qué implica depositar las muestras en el Biobanco Valdecilla?

Autorizar que las muestras queden custodiadas por el Biobanco Valdecilla implica que los productos obtenidos de las mismas (ADN, ARN, suero, plasma, células, etc.) **podrán ser utilizados posteriormente** en otros estudios de investigación biomédica realizados por investigadores de este u otros centros, nacionales o extranjeros, siempre que cuenten con la aprobación del Comité Científico Externo y el Comité de Ética del Biobanco Valdecilla. En el caso de que su muestra sea solicitada para otros proyectos, el Biobanco enviará al investigador solicitante una fracción de la misma con los datos clínicos más relevantes. Antes del envío, el Biobanco desvinculará su identidad de la muestra cedida mediante un proceso de **re-codificación**, de manera que los investigadores no podrán relacionar la muestra con su identidad. El Biobanco Valdecilla se compromete a no comercializar, en ningún caso, las muestras ni los datos personales obtenidos a partir de las muestras. No obstante, la información generada de los estudios realizados sobre su muestra podría ser fuente de beneficios comerciales. En tal caso están previstos mecanismos para que estos beneficios reviertan en la salud de la población, aunque no de forma individual en el donante.

CONFIDENCIALIDAD

Tanto el Investigador principal del estudio como el Biobanco Valdecilla, en caso de que sus muestras sean allí depositadas, son responsables de manejo de los datos de carácter personal conforme a lo dispuesto en la Ley Orgánica de Protección de Datos de Carácter Personal, 15/1999.

Los datos recogidos para el estudio estarán identificados mediante un código de forma que no sea posible la identificación del participante. Sólo el investigador y personas autorizadas relacionadas con el estudio tendrán acceso a dicho código.

Sus datos no podrán ser relacionados con el participante, incluso aunque los resultados del estudio sean publicados.

Para todo lo no previsto en este documento, se aplicará la legislación vigente (Ley de Investigación Biomédica 14/2007), y cualquier otra que resultara aplicable.

ACCESO A RESULTADOS DE LA INVESTIGACIÓN

Aunque el participante podrá conocer los estudios de investigación en que han sido utilizados sus datos y muestras, no será posible comunicarle ningún resultado personal obtenido del estudio de las mismas. No obstante puede solicitar al investigador los resultados globales de la investigación realizada con sus datos y muestras.

En caso de que la muestra sea utilizada para realizar estudios genéticos de los cuales puedan obtenerse resultados genéticamente relevantes, Ud. tiene derecho a conocer dichos resultados, siempre que lo desee y así lo solicite. Esto solo será posible en muestras que no hayan sido anonimizadas.

REVOCACIÓN DEL CONSENTIMIENTO

El participante tiene derecho a revocar su consentimiento y a retirarse del estudio en cualquier momento y sin dar explicaciones. El cese de su participación en el estudio no afectará a la relación con su médico ni a sus futuros cuidados médicos. Igualmente el participante tiene derecho a solicitar al Investigador Principal **Dr. Rosa Ayesa Arriola** o al Responsable de Fichero del Biobanco Valdecilla, en cualquier momento, y sin necesidad de especificar el motivo, la destrucción o anonimización de sus muestras y la eliminación de la información relacionada con las mismas.

CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO: Estudio del funcionamiento neuropsicológico y variantes genéticas asociadas en familiares de pacientes con trastornos del espectro de la esquizofrenia.

ACRÓNIMO: PAFIP-FAMILIAS

INVESTIGADOR PRINCIPAL: Rosa Ayesa Arriola

CENTRO: Hospital Universitario Marqués de Valdecilla. Programa de Primeros Episodios Psicóticos de Cantabria (PAFIP).

Declaración del paciente/ participante/donante:

Yo, _____

(Nombre y apellidos del paciente en MAYÚSCULAS)

Declaro que,

- ✓ He leído y comprendido la hoja de información que se me ha entregado sobre el estudio arriba indicado.
- ✓ He recibido suficiente información sobre el estudio.
- ✓ Comprendo el fin para el que se utilizarán mis muestras y datos personales (estudios de salud pública o estadísticos, que cumplan todos los requisitos que exigen la ley y los comités Científicos y de Ética).
- ✓ He realizado todas las preguntas que he precisado sobre el estudio.
- ✓ He hablado con el Dr/a. ..... con quien he clarificado las posibles dudas.
- ✓ Comprendo que mi participación es voluntaria.
- ✓ Comprendo que puedo retirarme del estudio, cuando quiera, sin dar explicaciones y sin que repercuta en mis cuidados médicos.
- ✓ Comprendo que la información personal y familiar que aporto será confidencial y no se mostrará a nadie sin mi consentimiento.
- ✓ Comprendo que mi participación en el estudio implica autorizar la extracción de una muestra de sangre y su utilización, y en caso de ser necesario, el uso de remanentes de las muestras obtenidas en la actividad asistencial.

AUTORIZO MI PARTICIPACIÓN en el estudio.

SÍ ☐ **NO** ☐

AUTORIZO LA REALIZACIÓN DE LA EXTRACCIÓN DE UNA MUESTRA DE SANGRE Y SU DONACION

para ser procesada en el Biobanco Valdecilla:

SÍ ☐ **NO** ☐

AUTORIZO LA REALIZACIÓN DE LA EVALUACIÓN NEUROPSICOLÓGICA:

SÍ ☐ **NO** ☐

AUTORIZO SER CONTACTADO en un futuro en caso de que se estime oportuno añadir nuevos datos a los recogidos en la actualidad.

SÍ ☐ **NO** ☐

RESTRICCIONES DEL USO DE LA MUESTRA. Especifique a continuación si no desea que se utilice su muestra y datos asociados en algún uso concreto o proyecto en particular:

Y para dejar constancia de todo ello, firmo a continuación:

Firma del paciente …….. Fecha ……

Firma representante legal (si procede)…….. Fecha …… Nombre representante legal:

Constato que he explicado las características de las condiciones de conservación y seguridad que se aplicarán a la muestra y a los datos clínicos conservados.

Firma clínico responsable…….... Fecha …… Nombre del clínico responsable: ……

APARTADO PARA LA REVOCACIÓN DEL CONSENTIMIENTO

Yo,
……
…….. retiro el consentimiento de participación en el proyecto arriba citado.

Y solicito que mis muestras sean:
DESTRUIDAS ☐

ANONIMIZADAS ☐

Firma y Fecha de la revocación: ……

Los derechos de acceso, rectificación, cancelación y oposición puede ejercitarlos ante el médico responsable de su seguimiento.