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A family-based approach to the vulnerability to psychotic disorders

Insights from social cognition combined with clinical and neurodevelopmental markers

Maria Giralt López

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insights from social cognition combined with clinical and neurodevelopmental markers

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ABBREVIATIONS AND ACRONYMS

BS	Basic symptoms
CI	Confidence interval
CNS	Central nervous system
CNV	Copy number variants
DMN	Default Mode Network
DNA	Deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,
DZ	Dizygotic
FEP	First-episode psychosis
FH	Family history
GWAS	Genome-wide association studies
HARs	Human accelerated regions
ICD-11	International Statistical Classification of Diseases and Related Health Problems, Eleventh Revision
Indels	Insertion or deletion
IQ	Intelligence quotient
MZ	Monozygotic
NSS	Neurological soft signs
NT	Neurotransmitter
OFC	Orbitofrontal cortex
OXT	Oxytocin
OXTR	Oxytocin receptor gen
PA	Premorbid adjustment
PFC	Prefrontal cortex
PLEs	Psychotic-Like Experiences
PRS	Polygenic Risk Score
SC	Social cognition
SNPs	Single nucleotide polymorphisms
SNV	Single Nucleotide Variants
SSD	Schizophrenia Spectrum Disorders
SV	Structural Variants
SZ	Schizophrenia
TDT	Transmission disequilibrium test
ToM	Theory of mind
TPJ	Temporoparietal junction
WOS	Windows of disease susceptibility

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format.

The thesis includes 3 articles.

1

Giralt-López M, Miret S, Soler J, Campanera S, Parellada M, Fañanás L, Fatjó-Vilas M (2020). The role of schizotypal traits and the *OXTR* gene in theory of mind in schizophrenia A family-based study. *European Psychiatry,* 63(1), e15, 1–8 doi10.1192/j.eurpsy.2019.17
Metrics IF (2020) 5.4, Q1, Percentile SSCI 86.5.

2

Giralt-López M, Miret S, Campanera S, Moreira M, Sotero-Moreno A, Krebs MO, Fañanás L and Fatjó-Vilas M (2024). Theory of mind in schizophrenia through a clinical liability approach a sib-pair study. Front. Psychol. 151391646. doi10.3389/fpsyg.2024.1391646
Metrics IF (2023) 2.6, Q2, Percentile SSCI 74.7

3

Giralt-López M, Miret S, Campanera S, Moreira M, Sotero-Moreno A, Hostalet N, Lázaro L, Krebs MO, Fañanás L and Fatjó-Vilas M. ToM Variability in Schizophrenia: A Neurodevelopmental Perspective through Soft Signs and Premorbid Adjustment. *Submitted*

RESUM

TÍTOL: Aproximació familiar a la vulnerabilitat als trastorns psicòtics: perspectives des de la cognició social combinada amb marcadors clínics i de neurodesenvolupament

INTRODUCCIÓ: L'esquizofrènia (SZ) és un trastorn clínicament heterogeni i amb una etiologia complexa i multifactorial, en la que hi ha implicats múltiples factors de risc genètics i ambientals que afecten les trajectòries de desenvolupament del cervell. A més dels símptomes clínics que defineixen el diagnòstic de l'SZ, la vulnerabilitat per aquest trastorns s'associa amb diferents trets fenotípics, els quals es troben tant en pacients com en persones amb una major vulnerabilitat, com els familiars dels pacients. Aquests trets, com ara trets de personalitat, símptomes breus o subsindròmics, dèficits cognitius o factors genètics específics, sense mostrar una imatge completa de l'SZ, poden indicar-ne un risc incrementat. Aquests són considerats marcadors de "tret" i no d' "estat" ja que: i) són identificables en les fases primerenques de la malaltia i també abans del debut, representant el risc "latent" de patir la malaltia; ii) estan presents, encara que en menor intensitat, en els familiars sans dels pacients, assenyalant la possible relació entre la càrrega genètica compartida amb la persona afectada i el tret.
Entre els possibles marcadors, aquesta tesi es centra l'estudi de la cognició social, concretament mitjançant l'anàlisi de la Teoria de la Ment (ToM), per la seva relació amb aspectes clau de l' SZ, com ara el neurodesenvolupament, la genètica i el pronòstic funcional del trastorn.

HIPÒTESIS: L' ús i combinació de fenotips intermedis que limiten la variabilitat genètica del trastorn (i els trets associats), milloraran la comprensió dels mecanismes biològics subjacents a SZ i facilitaran no només les estratègies terapèutiques pels pacients sinó també la identificació dels individus amb alt risc. D'aquesta hipòtesi general, se'n deriven dues d'específiques:

Hipòtesi 1. Els dèficits en ToM associats a SZ estaran relacionats amb la vulnerabilitat genètica per aquest trastorn, fet que indicarà un possible paper dels dèficits de ToM

com a fenotip intermedi o endofenotip. Aleshores, l'anàlisi dels dèficits de ToM en pacients, els seus familiars de primer grau no afectats i persones sanes no emparentades presentarà un patró de marcador de tret basat en: i) la seva presència en les fases inicials de l'SZ i en els familiars dels pacients, ii) els familiars de primer grau presentaran puntuacions intermèdies entre pacients i controls sans.

Hipòtesi 2. L'anàlisi de marcadors que assenyalin una major vulnerabilitat (clínica, del neurodesenvolupament o genètica) caracteritzarà millor la variabilitat en la cognició social, mesurada amb el rendiment en ToM. En aquest sentit, els familiars sans amb una major vulnerabilitat per l'SZ (nivells més alts d'esquizotípia, símptomes bàsics o experiències *"psychotic-like"*), antecedents familiars o indicadors d'alteració del neurodesenvolupament) mostraran un rendiment de ToM més pobre.

OBJECTIUS: Per testar les hipòtesis plantejades, hem dut a terme els següents objectius específics:

Objectiu 1. Investigar la idoneïtat de la ToM, un component de la cognició social, com a marcador endofenotípic de l'SZ mitjançant l'anàlisi del rendiment de la ToM en pacients amb trastorn de l'espectre de l'SZ, familiars sans de primer grau i controls sans.

Objectiu 2. Caracteritzar els trets clínics, del neurodesenvolupament i genètics de pacients i individus sans per analitzar la seva associació amb la variabilitat de la ToM i valorar si ens ajuden a interpretar l'heterogeneïtat en el rendiment de la ToM, tant entre grups com intragrups. Per desenvolupar aquest objectiu, hem avaluat si la ToM es veu modificada per:

- la vulnerabilitat clínica per l' SZ en familiars sans i controls
- marcadors de neurodesenvolupament alterat
- la càrrega genètica (antecedents familiars de trastorn de l'espectre psicòtic) i/o variabilitat genètica en el gen del receptor d'oxitocina (*OXTR*).

MÈTODES: Les estratègies metodològiques emprades han estat:

a) **L'ús de dissenys basats en la família** que permeten comparar diferents grups amb un gradient de càrrega genètica compartida, i valorar la transmissió i associació genotip-fenotip mitjançant l'anàlisi de marcadors específics en gens candidats.
b) **L'ús de marcadors de vulnerabilitat**, potencialment fenotips intermedis, que probablement s'associen amb un subconjunt de gens més petit, que pot revelar mecanismes biològics més específics que tot el conjunt de gens relacionats amb la malaltia.
c) **La combinació de marcadors de vulnerabilitat**, que podria millorar la detecció d'individus d'alt risc mitjançant la identificació d'un subgrup més vulnerable entre aquells genèticament predisposats a la psicosi. Així, aquesta tesi combina la ToM amb marcadors de vulnerabilitat clínica (esquizotípia, símptomes bàsics, experiències *"psychotic-like"*) i marcadors d'alteracions precoces del neurodesenvolupament, com els signes neurològics menors i l'adaptació premòrbida.

PRINCIPALS RESULTATS I CONCLUSIONS: Els principals resultats i conclusions que es deriven de la present tesi són:

I. A la nostra mostra, els pacients afectats de trastorns de l'espectre de l'SZ van mostrar un pitjor rendiment en ToM que els individus sans (familiars de primer grau i controls). Els familiars van mostrar un rendiment similar als controls.

II. Tractant d'explicar l'heterogeneïtat de la ToM, la nostra investigació mostra que els familiars de primer grau amb una major vulnerabilitat clínica a l'SZ, tal com indica l'esquizotípia, els símptomes bàsics o les experiències *"psychotic-like"*

(sobretot en les seves dimensions negatives) presenten un pitjor rendiment en ToM.

III. Tot i que els pacients mostren més evidències d'alteracions del neurodesenvolupament que els individus sans (mesurades mitjançant signes neurològics menors i ajust premòrbid), aquesta càrrega de neurodesenvolupament més elevada no està relacionada amb la ToM entre o intragrups.

IV. Les nostres dades mostren que la càrrega familiar de psicosi està associada amb un pitjor rendiment en la ToM en familiars.

V. L'anàlisi de transmissió intrafamiliar genotip-fenotip (qTDT) no va mostrar associació entre el gen *OXTR* i el rendiment en ToM. En canvi, tot i que la variabilitat del polimorfisme rs53575 al *OXTR* no s'observa relacionada amb la ToM en pacients ni familiars, entre els controls, l'esquizotípia elevada s'associa amb un pitjor rendiment de la ToM entre els portadors del genotip GG.

VI. En individus sans, especialment en familiars, certs marcadors el risc de psicosi s'associen amb la variabilitat en la ToM, ajudant a explicar l'heterogeneïtat en el seu rendiment. Concretament, en aquesta tesi, es demostra que els marcadors clínics de dimensió negativa i els antecedents familiars contribueixen a la variabilitat de la ToM, mentre que els marcadors del neurodesenvolupament no, fet que suggereix que poden sorgir de diferents vies relacionades amb el neurodesenvolupament subjacents al risc i l'origen del trastorn.

VII. Aquesta tesi dona suport a l'adequació de combinar la ToM amb altres marcadors de susceptibilitat com a estratègia per limitar la variabilitat subjacent a l'SZ, millorant-ne la comprensió i la identificació d'individus amb més risc, especialment entre familiars de persones amb la malaltia.

TABLE OF CONTENTS

1 BACKGROUND

1.1 THE ORIGIN OF THE SOCIAL BRAIN

1.1.1 THE UNIQUENESS OF HUMAN BRAIN DEVELOPMENT

The evolution of the human brain is a complex and fascinating journey that spans millions of years. The human brain has undergone significant changes in size, structure, and function, reflecting adaptations to various environmental and social challenges. These changes have contributed to the unique cognitive abilities that distinguish humans from other species and may have played a role in the emergence of certain psychiatric diseases, such as schizophrenia (SZ).

Although humans share many genetic, molecular, and cellular characteristics with other non-human primates, cognitive and behavioural distinctions between them appear immense. Only humans engage in activities like calculus and poetry, use geolocation devices, explore the universe, perform a 3D-assisted surgery or preserve information in digital databases accessible globally. However, none of these achievements are inherently programmed into the human brain, nor were they created "from scratch" by a single innovator. Instead, these advancements relied on the gradual accumulation of knowledge and skills over thousands of years, facilitated by a cognitive and cultural framework that enabled individuals to gain and share accumulated expertise and abilities (1). Such specific human cognitive skills encompass a broad range of abilities that enable individuals to perceive, understand, reason, and interact with their environment. Examples of the diverse cognitive skills that characterise human cognition are shown in Box 1. Each of these abilities contributes to the complexity and richness of human thought, emotion and behaviour, and its acquisition throughout evolution could not have occurred without changes at the level of brain structure and function.

BOX 1. HUMAN SPECIFIC COGNITIVE SKILLS

- **Language Acquisition and Communication** Humans possess complex linguistic abilities, allowing for the comprehension, production, and interpretation of spoken and written language. This includes vocabulary development, grammar comprehension, and pragmatic language skills for effective communication.
- **Memory** Human memory involves the encoding, storage, and retrieval of information. This includes short-term memory for immediate recall, long-term memory for retaining information over time, and various memory strategies such as rehearsal and mnemonic techniques.
- **Attention** Cognitive attention mechanisms allow individuals to selectively focus on relevant stimuli while ignoring distractions. This includes sustained attention for maintaining focus over time, selective attention for prioritizing specific information, and divided attention for multitasking.
- **Executive Functioning** Executive functions are higher-order cognitive processes that facilitate goal-directed behaviour, problem-solving, and self-regulation. This includes abilities such as planning, organization, inhibition of impulsive responses, cognitive flexibility, and working memory.
- **Spatial Reasoning** Humans have the capacity to perceive, interpret, and manipulate spatial relationships. This includes skills such as mental rotation, spatial visualization, navigation, and map reading.
- **Critical Thinking** Critical thinking involves the ability to analyse, evaluate, and interpret information to make reasoned judgments and decisions. This includes skills such as logical reasoning, problem-solving, hypothesis testing, and evidence-based thinking.
- **Creativity** Humans can generate novel ideas, solutions, and expressions through divergent thinking, associative thinking, and insight. Creativity involves the ability to think flexibly, make unusual connections, and approach problems from unconventional angles.
- **Emotional Regulation** Emotional regulation encompasses the ability to recognize, understand, and manage one's own emotions as well as the emotions of others. This includes skills such as emotional awareness, empathy, coping strategies, and emotion regulation techniques.
- **Theory of Mind** Theory of mind refers to the ability to attribute mental states—such as beliefs, intentions, and emotions—to oneself and others, and to understand that others may have different perspectives. This is crucial for social cognition, empathy, and understanding social interactions (see section 1.1.2).

The evolutionary trajectory of the human brain demonstrates a consistent trend towards increased brain size relative to body size, known as encephalisation, as we progressed from early primates to hominids and ultimately to *Homo Sapiens*. Furthermore, the human brain has gained complexity in its folding and cortical thickness patterns, related to an increased cortex surface area, facilitating cortical expansion (Fig. 1)(2).

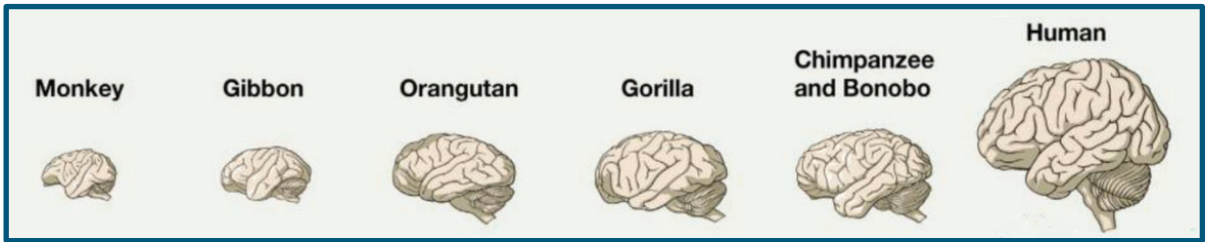


FIGURE 1. Evolutionary trajectory of the human brain. Over 30 million years, the human brain has become progressively more extensive and has gained complexity in folding. Adapted from Sousa et al., 2017 (3).

While our superior general intelligence compared to other primates may be due to an increase in both relative and absolute neuron counts, especially in the neocortex, our unique abilities likely arise from structural rewiring and molecular reorganization of specific neural circuits and cell types.

Notably, humans have a variety of neural stem and progenitor cell subtypes with enhanced proliferative abilities, facilitating the enlargement of the brain, particularly the neocortex. An evolutionary approach has focused on approximately 2700 genomic loci that are highly conserved across vertebrate evolution but show notable differences in humans; these regions are known as "human accelerated regions" (HARs); interestingly, about 10% appear to act as developmental enhancers in the brain (4). Hence, it appears that our mental capabilities, encompassing advanced or abstract cognitive functions, cannot be solely attributed to the enlargement of our brains but also to the time and space regulation of the molecular and cellular mechanisms underlying the development and function of the cortical brain circuits (3,5).

Because of the complex nature of the human brain, which has developed throughout human evolution, its development proceeds slower than that of other primate brains. As a result, changes in the brain happen not only during fetal development but extend over more than twenty years to culminate in a fully mature human brain, a timeframe exceeding the entire lifespan of certain non-human primates (6). Consequently, humans experience an extended period of childhood and adolescence and a notably lengthy gestational period. Compared to other primates, this extended developmental timeline and prolonged dependency, enable longer critical periods and greater influence of environmental factors on the development of cognitive, emotional, and social capacities. Consequently, the individual's brain development trajectories must also be considered.

More specifically, brain development begins during the third-fourth gestational week with the differentiation of the neural progenitor cells and persists at least until late adolescence, arguably throughout the lifespan (Fig.2). Building this most complex and highly organised organ involves the generation of a wide variety of specialised neural and non-neural cell types that must be produced in the correct quantity, accurately positioned, and timed appropriately.

As part of this developmental complex period, several specific processes like neural tube formation, neural patterning, and neural progenitor cell differentiation occur in embryonic and early fetal periods, followed by neuron production, migration, and differentiation in later fetal and early postnatal periods. Postnatally, the remodelling of synaptic contacts and circuitries and myelination takes place. By early adulthood, cortical circuits are refined through the pruning of excitatory synapses, a proliferation of inhibitory circuits, and the remodelling of pyramidal neurons (7,8).

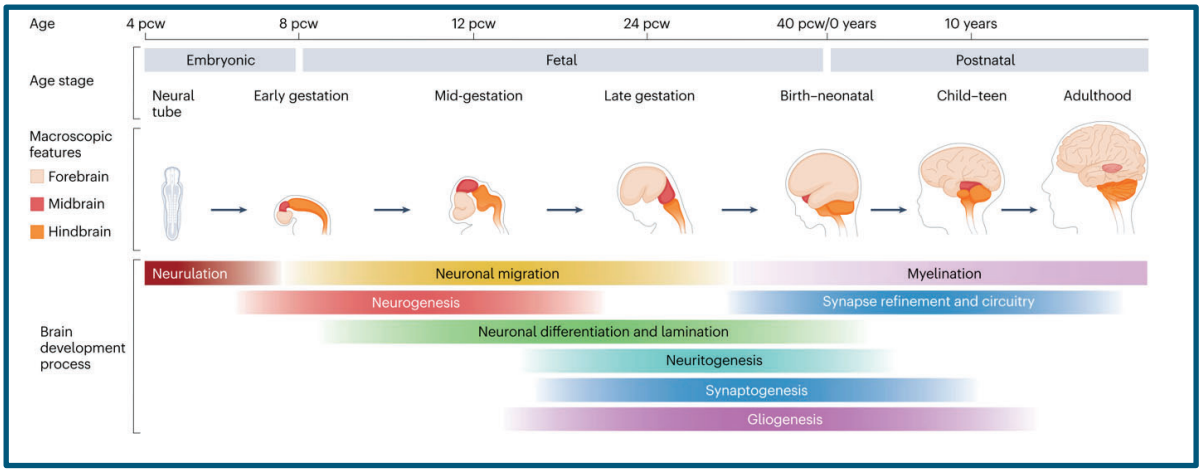


FIGURE 2. Developmental processes occur in phases. An overview of the critical processes and their timing in human brain development includes neurulation and proliferation of neural epithelial cells, neurogenesis driven by neural stem cells, migration of neural precursor cells to their target locations, neuronal differentiation and maturation for lamination, development of neurites and synapses, and gliogenesis. Additionally, certain processes that mainly occur in the postnatal period, such as ongoing synaptic pruning and oligodendrocyte myelination, are highlighted. Age timeline and brain size are not depicted to scale. Adapted from Zhou Y. 2024 (9).

In humans, the fact that brain development is not complete until near the age of 25 refers mainly to the prefrontal cortex, characterised by growth in early childhood, a decrease in adolescence, and then a slight increase and stabilisation in adulthood. This brain region has been implicated in executive functions, language, emotional processing and sociality, possibly making humans unique (10). Together, these skills would have been crucial for our hominid ancestors to deal with complex social groups and unpredictable, dangerous environments.

The prefrontal cortex is also affected by several conditions and disorders; its late maturation makes it particularly susceptible to disruption. Some have also hypothesised that the brain regions most recently developed or changed during human evolution, including the prefrontal association cortex, are predominantly the site of disorders. As an example, the dorsolateral prefrontal cortex, an especially late-developing region, exhibits abnormalities in both autism and SZ (10).

Understanding these developmental processes, from health to disease contexts, requires a view of the complex interplay of cellular and molecular mechanisms and the genetic blueprints that guide them. These genetic instructions steer the construction of an organ capable of sophisticated higher-level functions, including cognition, memory, emotion, language, and behaviour (11,12). In addition, over time, through evolution, genomes accumulate changes (genetic variability) that result in differences among individuals within a population (as interindividual variability). Common and rare variants are two primary forms of genetic variability (Box 2), which can influence the expression of phenotypes (traits) and are intrinsically related to the variability associated with the adaptability and survival of the species. However, these variations can also influence the dysregulation along human brain developmental trajectories and impact disease susceptibility.

BOX 2. COMMON AND RARE GENETIC VARIANTS

	Common Genetic Variants	**Rare Genetic Variants**
Definition	Also known as polymorphisms, occur frequently in the population. A variant is typically considered common if it is found in more than 1% of the population.	Rare genetic variants are less frequent in the population, typically occurring in less than 1% of individuals.
Impact	Small effect individually but can have significant combined effects on traits or disease risk.	More significant effect on individuals who carry them. They can be responsible for rare genetic disorders or can contribute to the risk of common diseases in a more substantial way than common variants.
Examples	**Single Nucleotide Polymorphisms (SNPs)** The most common type of genetic variation, involving a change of a single nucleotide (A, T, C, or G) in the DNA sequence.	**Single Nucleotide Variants (SNVs)** Like SNPs but occur less frequently. **Structural Variants** Larger changes in the structure of chromosomes, such as duplications, deletions, inversions, or translocations of large segments of DNA.

In summary, the human brain is considered unique due to its more extensive and complex neocortex, which opened the way to a spectacular development of cognitive and mental skills (13) while making possible certain psychiatric diseases. Therefore, for a complete understanding of the organ and the abilities sustained by its function, it is essential the integration of multilevel data involving brain formation and maturation with the role of genetic and environmental factors that shape such a dynamic process.

1.1.2 SOCIAL COGNITION

As inherently social beings, humans require interaction with others for survival. Their ability to thrive in these interactions highly depends on social communication, which relies on language and its components, as well as gaze, facial expressions, and body gestures. Sensory processes modulated by attention and memory processes provide raw data from which social meaning is constructed across three cognition domains, cold cognition, hot cognition and social cognition (Fig. 3).

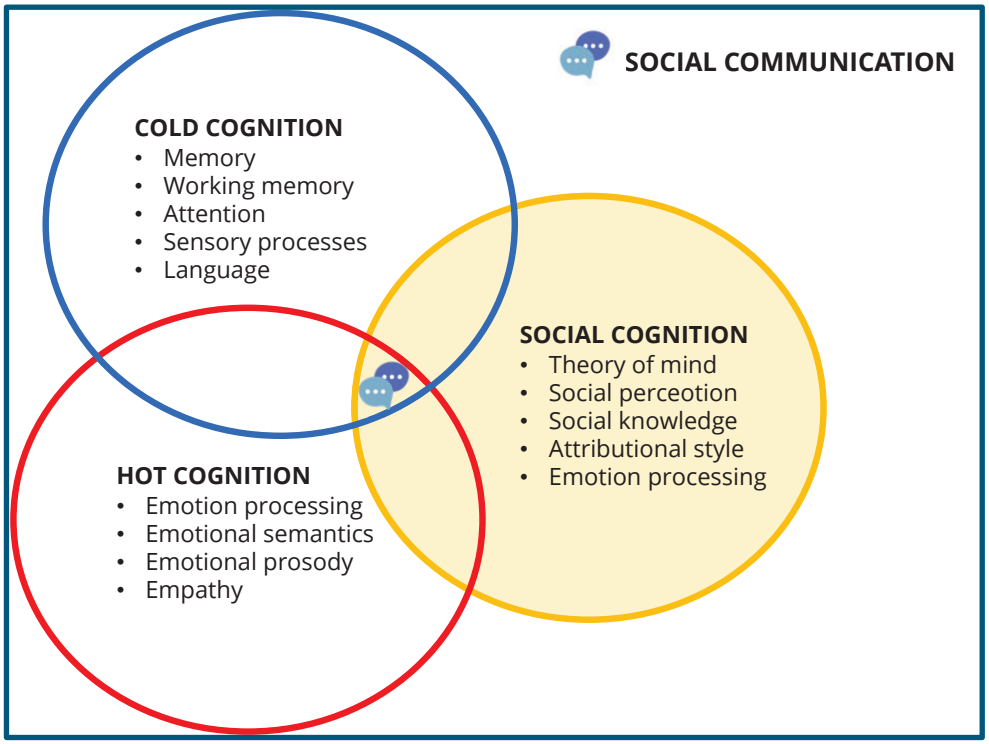


FIGURE 3. A model of interdependencies between "cold cognition," "hot cognition," and "social cognition." The building blocks of social communication belong to all three domains. Adapted from Niznikiewicz, 2013 (14).

Social cognition (SC) refers to a wide range of skills that allow people to perceive, interpret and process social stimuli, guiding social interactions. It develops throughout childhood and adolescence, and the appropriate brain maturation plays an essential role in its performance. It is a multi-dimensional construct that comprises functions such as emotional processing, social perception and knowledge, theory of mind (ToM) and attributional bias (15) (see Box 3).

BOX 3. SOCIAL COGNITION DIMENSIONS

Theory of mind	Ability to infer mental states, such as beliefs, intentions, desires, and emotions, in other people.
Social perception	Ability to identify social roles, societal rules, and social context.
Social knowledge	Awareness of the roles, rules, and goals that characterize social situations and guide social interactions. Social knowledge is viewed as an initial step and prerequisite for adequate social competence.
Attributional bias	Attributions are causal statements, i.e., statements that either include or imply the word "because." and reflect how people typically infer the causes of positive and negative events.
Emotional processing	Emotional processing refers broadly to perceiving and using emotions. One influential model of emotional processing defines emotional intelligence as a set of 4 components, including identifying, facilitating, understanding, and managing emotions.

The current thesis has focused on the ToM (also known as mentalising) among all these SC dimensions. It is the ability to represent and attribute mental states such as knowledge, beliefs, expectations, intentions, and emotions to oneself and others. It can be used to understand and predict one's own and other's behaviour (16).

In various research disciplines such as developmental psychology, social neuroscience, and studies on conditions characterised by social deficits like autism, ToM is frequently conceptualised as a multifaceted construct comprising several subcomponents. One model differentiates between the cognitive and affective ToM (17) the "cognitive", for inferring the mental state of the others (their perceptions, intentions, pretences, thoughts, and beliefs); and the "affective or empathic", for recognising and sharing the feelings of another person. The affective ToM requires emotional self-regulation for control of shared explicit emotions, inhibiting or facilitating the expression of empathic reactions, thus allowing the individual to show a more socially appropriate and

acceptable attitude toward other people in daily life functioning. Another two-component model differentiates between the “social-perceptual” and “social-cognitive” components of ToM (18). Social-perceptual tasks involve inferring the mental states of others based on non-verbal cues such as facial expressions, eye movements, and body language. In contrast, social-cognitive tasks necessitate explicit verbal reasoning about the emotional and mental states of others.

ToM is essential for children later on, as it enables them to deal with the differing perspectives and intentions of themselves and others, setting the bases for understanding conversational norms like maintaining topic continuity and respecting turn-taking. This understanding is crucial for the discursive, particularly argumentative, use of language (e.g., in conversations) and one's social functioning outcome. Accordingly, ToM is fundamental to the adaptive success of humans because it enhances social cohesion, communication, conflict resolution, strategic thinking, cultural evolution, and adaptation to environmental changes. These factors work together to ensure the survival and prosperity of human societies, making ToM a crucial element in humans' evolutionary prosperity (survival, reproduction and offspring success).

In the ontogenetic development of ToM (Fig.4), the first step is the mental construction of the object as existing outside and independent of the subject and the recognition of himself as separated from the others, which are conceived as distinct individuals. At the same time, the child perceives similarities in himself and others, thus recognising himself and others as intentional beings. This is a precondition for the child, further on (after nine months of age), to engage himself in joint attention activities with others, establishing a triadic relationship with the other individual (adult) and the object of their attention, and coordinating their interactions, for example, the child sees a toy and sees that his mother also sees it.

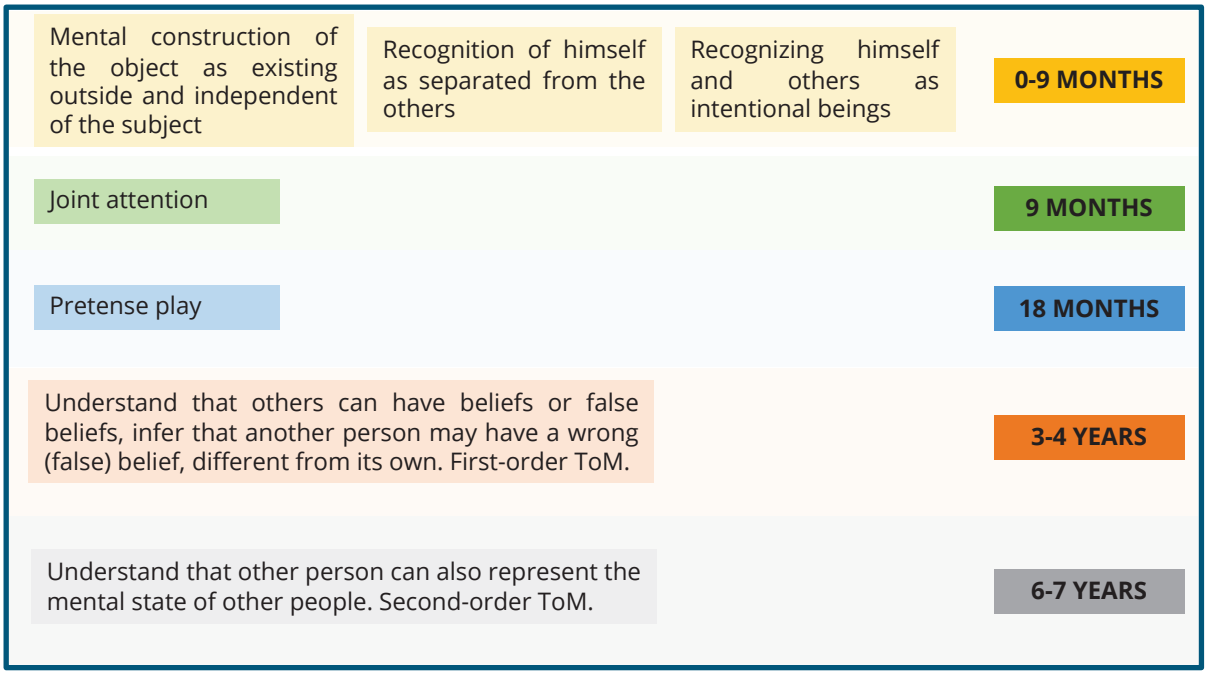
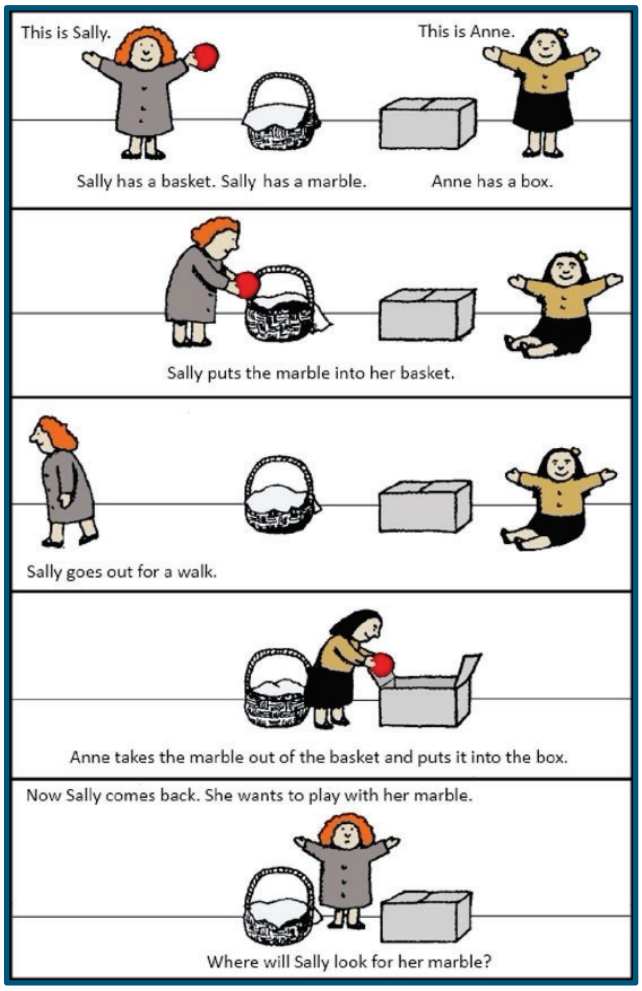


FIGURE 5. Ontogenetic development of ToM.

The next stage in the development of ToM (after 18 months of age) is pretence play, which requires the ability to uncouple simulation from reality, for example, when the child holds a banana in hand near its ear, pretending it is a telephone. Then, between 3 and 4 years of age, the child can understand that others can have beliefs or false beliefs; the child can infer that another person may have a wrong (false) belief different from his/her own. For example, in Sally and Anne's story (Fig. 5) "A child is shown a scene with two doll protagonists, Sally and Anne, with a basket and a box, respectively. Sally first places a marble into her basket. Then Sally leaves the scene, and in her absence, Anne moves the marble and puts it in her box. Then Sally returns, and the child is asked "Where will Sally look for her marble?" (19). This is called "first-order ToM."

Later, between 6- and 7 years of age, the child begins to understand that the other person can also represent other people's mental state. In this stage, the child can make inferences not only on the belief a person has about an event in the world but also on the belief this person has about the belief of another person concerning this world event. This is the "second-order ToM" (20).

FIGURE 5. Sally and Anne story Adapted from the original Sally–Anne cartoon used in the test by Baron-Cohen, Leslie and Frith (1985) (19) To pass this test, participants must correctly answer the Belief *Question* by stating that Sally believes the marble is in her basket. This answer continues with Sally's perspective but not the participant's own. If the participant cannot take an alternative perspective, they will indicate that Sally has cause to believe, as the participant does, that the marble has moved. Passing the test is thus seen as the manifestation of a participant's understanding that Sally has her own beliefs that may not correlate with reality.



Continuing with the Sally and Anne task, we can further explore the second-order ToM (21) "A child is shown a scene with two doll protagonists, Sally and Anne, with a basket and a box, respectively. Sally first places a marble into her basket. Then Sally leaves the scene, and in her absence, Anne moves the marble and puts it in her box. However, although Anne does not realise this, Sally is peeking through the keyhole and sees what Anne is doing. Then Sally returns, and the child is asked "Where does Anne think that Sally will look for her marble?" In this second-order task, the child is asked to determine what Anne believes about Sally's belief concerning the marble's location (a second-order belief). In the more straightforward first-order task, the child is just asked about Sally's belief about the location of the marble (a first-order belief).

Other high-order ToM abilities involve advanced cognitive skills such as inferring hidden intentions through indirect speech, what means understanding when someone implies a meaning without explicitly stating it and requires an ability to recognize hints and interpret what is meant beyond the literal words. Also, grasping false beliefs (recognizing that another person can hold beliefs that differ from reality) is considered advanced ToM (22,23). From an evolutionary perspective, it's important to note, that while our closest primate relatives possess fundamental aspects of ToM, (i.e.) recognizing goals, intentions, and perceptions) the ability to grasp that others may have false beliefs or beliefs that do not align with reality seems to be uniquely human (24).

Returning to a developmental approach, ToM performance continues to improve throughout childhood and adolescence into adulthood. Cognitive and affective ToM abilities increase significantly in adolescence, and a developmental step can be seen in middle adolescence.

Many authors have explored the effect of factors such as sex, age, or other cognitive dimensions on ToM. Compared to affective ToM (also called cognitive empathy), in which adult women perform better than men in most studies, studies examining sex differences in cognitive ToM have produced mixed results (25). However, concerning sex differences in the neural basis of cognitive ToM, during a ToM task relative to the baseline women have shown greater activation of the left medial prefrontal cortex (mPFC) and temporoparietal junction (TPJ) and more significant deactivation in the ventromedial prefrontal cortex (vmPFC)/orbitofrontal cortex (OFC) bilaterally (26). Such differences have also been attributed to the lasting effects of play behaviour in female children, potentially enhancing verbal communication skills (27). On the other hand, some studies suggest ToM ability declines with age. Still, the latest findings support a model in which age-related decline in ToM ability is primarily caused by compromised executive functions, not ToM competence, suggesting that underlying ToM mechanisms might still be intact in the healthy elderly (28,29). In this regard, the analysis of the interplay between social and cold cognition has reported that, across adolescence, attention and affective intelligence are associated with cognitive and affective ToM, and

specifically cognitive ToM is additionally predicted by working memory, language comprehension, and figural intelligence (27). Also, evidence shows substantial improvement across adolescence in both social-perceptual and social-cognitive components. These findings highlight the distinction between the components of ToM and emphasize the importance of adolescence in the development of ToM skills (30).

1.1.3 NEUROBIOLOGY OF SOCIAL COGNITION

BRAIN CORRELATES OF SOCIAL COGNITION

The cerebral organisation of social processes is not perfectly established. Still, as SC develops throughout childhood and adolescence, the appropriate maturation of the brain may play a key role in its acquisition and performance. Some brain regions and networks have specifically been linked to processing social information (31) although the "social brain" network varies depending on task demand (Fig. 6a and 6b) (32).

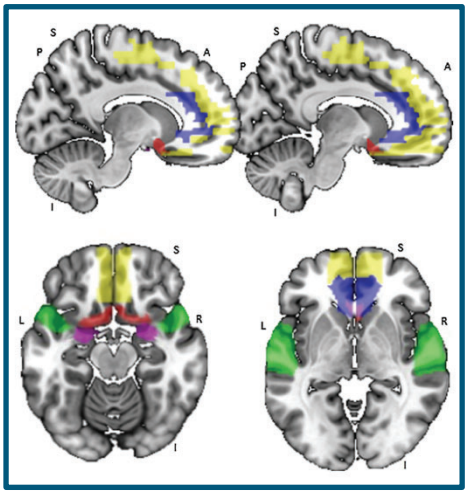


FIGURE 6a. Areas involved in the recognition and response to social-affective stimuli. Adapted from Kozhuharova et al., 2020 (296). The **amygdala** is responsible for recognising emotional expressions and evaluating stimuli. The **ventral striatum** is associated with recognising stimuli with learned reward values. The **medial prefrontal cortex** supports the ventral striatum and is further involved with interpreting nonverbal social information and the contextual interpretation of complex social information. The **anterior cingulate cortex** is associated with like/dislike judgements of social cues, and emotional information is integrated into this to motivate behaviour. The **superior temporal gyrus** is essential for recognising nonverbal social cues.

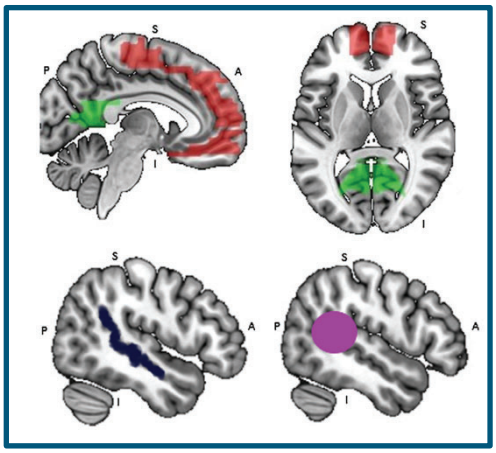


FIGURE 6b. Areas involved in higher-level mental inference. Adapted from Kozhuharova et al., 2020 (296). The **medial prefrontal cortex** is the most reliably activated structure across studies. This region is associated with thinking about the internal states of others, inferring the current beliefs of others and evaluating their long-term traits. The **posterior cingulate cortex** is associated with generating knowledge of our minds and those of others. The **temporal-parietal junction region** is associated with imaging the perspectives of others and attributing beliefs and internal states to others. The **superior temporal sulcus** and the **temporal poles** around it are associated with representing nonverbal cues (that are relevant to deciphering the intentions of others) and with representing emotional knowledge.

When we analyse in detail the areas shown in Figures 6a and 6b, we realise that there is an overlap, especially between those areas involved in higher-level mental inference (Fig. 6b) and the dorsomedial subsystem of the Default Mode Network (DMN) (33). The DMN was first defined as those brain regions whose activity increased during resting-state while showing decreased activity during outward-attention-related tasks (34). The DMN is also involved in self-related cognitive functions such as rumination, introspection, self-reflective thoughts, and autobiographical memory. Recently, however, it has been shown that the dorsomedial subsystem structures of the DMN are activated by particularly higher-order tasks, such as attributing mental states to others (ToM) (35,36).

NEUROCHEMICAL CORRELATES OF SOCIAL COGNITION

Neurotransmitters (NTs) amplify, transmit, and convert cell signals, influencing various cognitive and emotional processes or behaviours. Each NT system (ex., serotoninergic, dopaminergic, glutamatergic, GABAergic, oxytocinergic) is characterised by specific

chemical messengers and their corresponding receptor and plays a unique role in maintaining neural communication and regulating brain activity. Understanding these neurotransmitter systems' distinct yet interconnected roles provides insight into their collective influence on mental health, behaviour, and cognitive functions (37).

As regards to the neurochemical underpinnings of ToM, the most extensively studied NT to date is oxytocin (OXT). OXT is a neuropeptide consisting of nine amino acids (38,39) and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released into the periphery via the posterior pituitary (Fig. 7). In the central nervous system (CNS), OXT is released from both synapses and axons, allowing it to exert effects throughout the CNS. Cells originating in the paraventricular nucleus of the hypothalamus have specific pathways that efficiently deliver OXT to other structures in the brain, including the amygdala, bed nucleus of the stria terminalis, lateral septum, hippocampus, and nucleus accumbens (40).

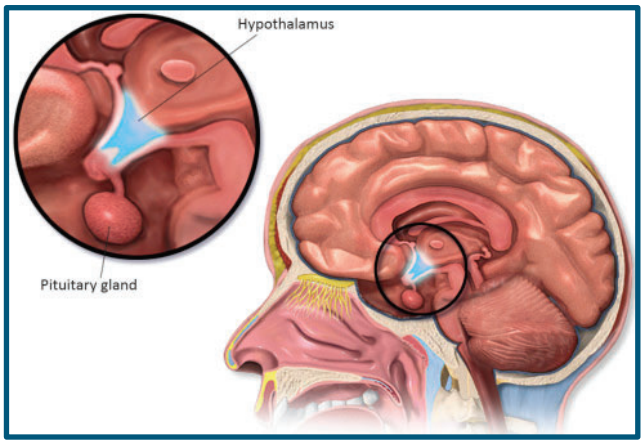


FIGURE 7. The hypothalamus and posterior pituitary. Oxytocin is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus. It is released into the periphery via the posterior pituitary and is released throughout the brain from both synapses and axons, allowing it to exert effects throughout the CNS. Adapted from Bowen et al. 2016 (40).

While OXT is involved in numerous "non-social" behaviours, including learning, anxiety, feeding, and pain perception, its roles in various social behaviours have gained significant attention recently. OXT is crucial in social memory and attachment, sexual and maternal behaviours, human bonding and trust. Many, if not most, of OXT's functions, from social interactions (such as affiliation and aggression) and sexual behaviour to childbirth, lactation, and maternal care, can be seen as explicitly aiding in species propagation (Fig. 8). (41–43).

On the one hand, several functional neuroimaging studies have shown that OXT has significant modulatory effects on the “social brain”, which refers to the brain systems that govern SC, social behaviour and affect regulation (44). For example, acute OXT administration in healthy subjects has been shown to modulate amygdala activity and other regions (e.g. prefrontal areas, superior temporal sulcus, and fusiform gyrus) and enhance the functional connectivity of the amygdala with other brain regions (45,46).

FIGURE 8. OXT involvement in social behaviours. OXT may affect behaviours and physiology during the cycle of life to facilitate the propagation of the species. Adapted from (Lee et al., 2009).(41)

On the other hand, some studies in healthy subjects have shown the enhancing effect of intranasal OXT administration on SC (47) and specifically on ToM (48) and that this is an age-independent effect (49).

Accordingly, it has been suggested that OXT signalling pathways (and their interaction with other NT systems) participate in shaping both the anatomy and functional physiology of the human nervous system, leading to the idea that its variability may contribute to individual differences in social behaviour and cognition by modulating the neural circuits involved in processing socio-affective information (50,51). Notably, the behavioural effects of OXT depend on the distribution and expression of its receptor, the oxytocin receptor receptor (OXTR), which is widespread throughout the brain and body in a sex- and species-specific manner (52). OXTRs are present in numerous limbic and reward-related regions of the human brain, mainly in (but not restricted to) the amygdala, the hippocampus and the nucleus accumbens) and also in cortical regions (such as the anterior cingulate cortex) (53). Dynamic changes in the expression of the OXTR and different downstream processes in specific regions after activation offer a source for individual variability in the activity of the endogenous OXT system (54).

Also, the OXTR gene (*OXTR*) codes the receptor and its polymorphic variability as well methylation as a result of epigenetic events provide further individual variability in the activity of the OXT system that contributes to individual differences in social behaviour and cognition (55–57). General population-based studies have highlighted the influence of this gene on many facets of SC, including ToM. The most intensively examined SNP in *OXTR* is rs53576, and a recent meta-analysis showed that individuals with a more significant number of G alleles present better empathic ability (58). Interestingly, Rodrigues et al. (2009) linked the lower empathy exhibited by A allele carriers of this SNP with a higher physiological stress reactivity than GG individuals (59). Furthermore, *OXTR* polymorphic variants (rs53576 and others) have been associated with the risk for SZ and other neurodevelopmental disorders (60), as reviewed in Bartholomeusz (2015) (46). Neuroimaging studies have provided evidence to support the rs53576 association with

brain structure and activity, mainly in healthy subjects. For instance, Tost et al. (2010) described that A allele carriers of rs53576 show the lowest amygdala activation and increased coupling of the hypothalamus and the amygdala when processing social information (61). Data also suggest that rs53576 influences striatal dopamine availability and modulates the interactions between the oxytocinergic and dopaminergic systems. In a study based on emission computed tomography, striatal dopamine transporter availability in G carriers (AG/GG) was lower than in the AA group, and G carriers showed a negative correlation between dopamine transporter availability and OXT level (62).

Then, despite rs53576 being a silent polymorphism and that the pathophysiological significance of its association with brain phenotypes remains to be elucidated, accumulated evidence suggests that this SNP could be a marker of the role of the *OXTR* in the neural mechanism that links the differences in the oxytocinergic system to individual differences in SC. A recent review (see Table 1) explores the multifaceted role of the neuropeptide OXT in human behaviour and its connection to the *OXTR* and studies the impact of OXT on social support-seeking behaviour, brain structure/functionalities, and development of brain disorders focusing on a specific genetic variation, rs53576 (63). To further investigate this receptor, Manuscript 1 of this thesis focuses on studying its variability and potential association with ToM abilities from a family-based approach, using a sample of patients with SZ, their first-degree relatives, and control subjects.

TABLE 1. Effects of genotype variation of SNP rs53576 within *OXTR* on social behaviour, brain structure/functionalities, and development of brain disorders (adapted from Hasan, 2024). Abbreviations A, Adenine; G, guanine; SNP, single-nucleotide polymorphism.

rs53576 genotypes	AA	AG/GG
Social behaviour	• Reduced trust • Greater self-reported stress • Unchanged cortisol level when seeking emotional support • Reduced responsiveness to social support • Lack of empathy • Lower level of sensitive responsiveness toward own children • Increased concern about negative perception of own's company	• Higher trust • Higher tendency to seek emotional support • Reduced secretion of cortisol when seeking emotional support • Seeking social support decreases anxiety • better empathic capacity.
Brain structure and functionalities	• Lower amount of grey matter in the hypothalamus • During processing facial emotion, lower activation in the amygdala and higher functional coupling between the amygdala and hypothalamus	• Higher amount of grey matter in the hypothalamus • During processing facial emotion, higher activation in the amygdala and lower functional coupling between the amygdala and hypothalamus • Lower striatal dopamine transporter availability
Brain disorders	• Linked to the development of autism • Linked to the development of social anxiety disorder • Linked to the development of schizophrenia	• Effects of positive social behaviour and perception reverted if raised in adverse environment

1.2 THE NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

1.2.1 THE NEURODEVELOPMENTAL THEORY FOR SCHIZOPHRENIA

The inception of a neurodevelopmental perspective on psychosis is attributed to the Scottish psychiatrist Thomas Clouston, who first proposed this concept in 1891 (64). Still, this idea was soon displaced by Kreapelin's conceptualization of "dementia praecox", or early dementia (65). While "dementia praecox" provided the intellectual background for many years, and SZ was viewed as a progressive disorder with many characteristics similar to those of neurodegenerative diseases, Kraepelin and Bleuler observed abnormal neurological and behavioural signs in the childhood histories of adult patients (66).

Indeed, in the late 1970s, neuroimaging technologies demonstrated that people with chronic SZ had lateral ventricular enlargement, the first unequivocal neurobiological marker of the illness (67). Later, in 1982, Murray reported that monozygotic (MZ) twins with SZ had larger cerebral ventricles than their MZ healthy cotwins. This implied that the larger ventricles were environmental in origin, and they noted that the affected twins had been exposed to more severe perinatal hazards (68).

By the end of the 1980s, almost forty years ago, the modern neurodevelopmental hypothesis was first formulated. Weinberger suggested that a prenatal event could disrupt the normal progression of brain development. This insult to the fetal brain structures from early in life may remain latent until the critical periods of normal maturation and neuronal pruning, which "call" into operation the damaged structures, particularly the dorsolateral prefrontal cortex, resulting in prodromal and, subsequently, diagnostic symptoms of the disorder (69).

Almost concomitantly, in the United Kingdom, Lewis and Murray inspired by previous research, proposed a neurodevelopmental model for SZ (70) and focused on the role of obstetric complications as a possible risk factor underpinning the neurodevelopmental theory. They confirmed the role of pre- and perinatal complications in a significant number of studies (of discordant as opposed to concordant MZ twins as well as in singleton patients with SZ), postulating them as a possible risk factor underpinning the neurodevelopmental theory (71). This significant discovery stimulated substantial epidemiological research to elucidate the nature of early childhood exposures.

In the following decades, many researchers have provided variants of this theory that share two fundamental principles. There is a tacit knowledge that genetic influences are involved, and there is a reasonable consensus that the essential window for exposure occurs during the pre- and perinatal period (72–74). While previous versions of the neurodevelopmental hypothesis proposed a disruption in brain development that began in early life, more contemporary versions have proposed that events close to the onset of the illness (late insults) may also be required to “precipitate” psychosis. (75,76). In other words, SZ may require more than one "hit." The "2-hit" model conceptualized by Keshavan operates within the framework of the neurodevelopmental theory, suggesting that disruptions during two crucial developmental stages (early brain development and adolescence), intersect to generate the symptoms linked with SZ. In this model, insults experienced during early development (such as perinatal complications) could disrupt neural networks, contributing to the premorbid indicators observed in individuals who later develop SZ. Also, the altered brain would be more vulnerable to the effect of later environmental stress factors (such as child adversity, urbanicity, cannabis exposure…), increasing the risk of developing SZ later in life. During adolescence, an excessive pruning of synapses and reduced plasticity may underlie the onset of symptoms (77,78).

In summary (Fig. 9), the neurodevelopmental model proposes that the illness is the culmination of aberrant neurodevelopmental processes that begin years before the onset of the illness due to a complex interaction of many susceptibility genes and

environmental variables. Nevertheless, neither genes nor input can predict the outcome. An individual may be genetically predisposed to be more vulnerable to the effects of specific environmental conditions, and some insults may result in epigenetic changes that affect the expression of some critical genes for neurodevelopment.

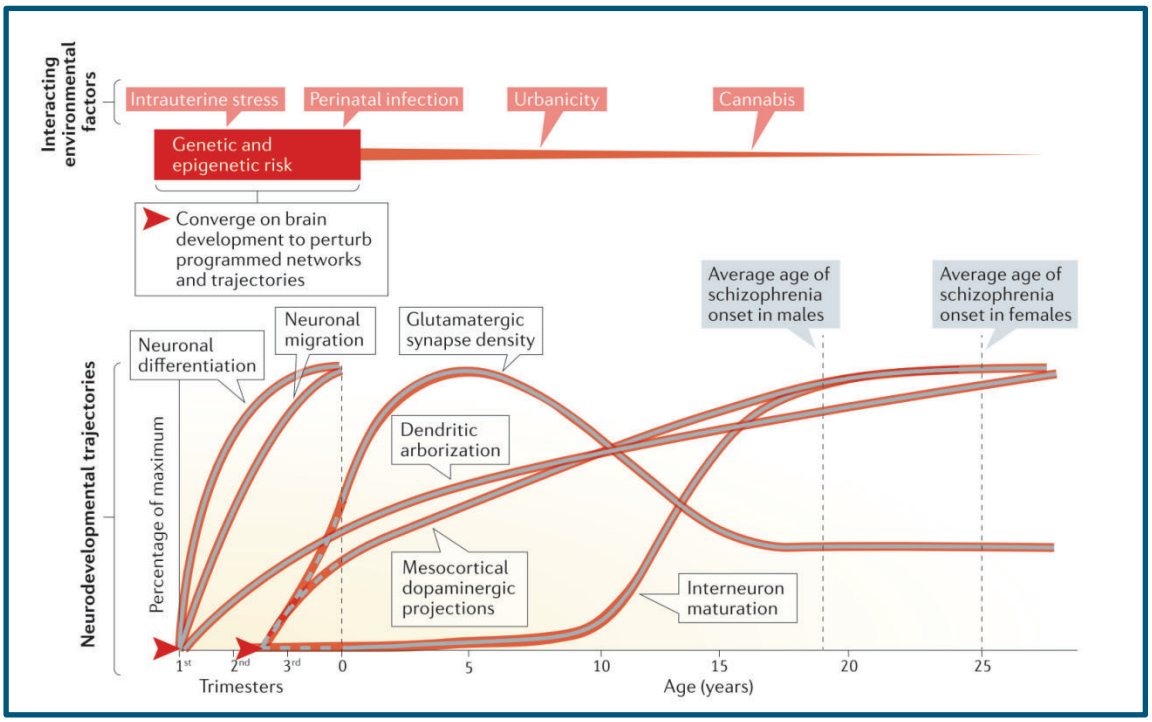


FIGURE 9. THE NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA. Schizophrenia, the combination of different genetic variants and epigenetic changes influenced by perinatal environmental risk factors, might perturb different processes, leading to an altered neurodevelopmental trajectory. That predisposes dysfunctional neural circuits that mature late in adolescence (mainly prefrontal cortex circuits). Consequently, the altered brain would be more vulnerable to the effect of later environmental stress factors (such as urbanicity and cannabis exposure), increasing the risk of developing schizophrenia later in life. Adapted from Birnbaum and Weinberger (2017) (74).

1.2.2 THE SUPPORTING DATA FOR THE NEURODEVELOPMENTAL HYPOTHESIS

Multiple sources of evidence from different research fields support the neurodevelopmental hypothesis of SZ. Together, these findings provide strong support for the involvement of neurodevelopment in SZ and may also provide an essential basis for the early detection of persons at high risk for developing it.

EPIDEMIOLOGICAL EVIDENCE

From an epidemiologic approach, several prenatal and perinatal risk factors that may influence the early stages of brain development have been linked to SZ. These include exposures to conditions such as infection, malnutrition, and obstetric and birth complications, as reviewed by Davies (79).

BRAIN-RELATED EVIDENCE

Neuropathology has supported the neurodevelopmental hypothesis. SZ is associated with findings suggestive of altered early brain development, such as loss of normal cerebral asymmetry, lack of prominent gliosis or related markers of adult-onset neuropathology, subtle alterations in cytoarchitecture (smaller neurons, shorter dendrites, increased density of neurons in the subcortical white matter) and altered expression of markers of genes/proteins implicated in brain development (80).

Neuroimaging has also provided evidence for early (pre- and perinatal) neurodevelopmental anomalies (reduced volume of temporal lobe structures, ventricular enlargement, reduced cortical folding, and loss of normal asymmetry), evidence for progressive grey-matter loss involving medial temporal and prefrontal regions around the time of transition to illness and evidence of late (post-pubertal) neurodevelopmental changes during the early stages of psychosis, involving an acceleration of normal brain maturational processes, associated with significant loss of grey matter in dorsal prefrontal regions (81,82). Post-illness onset degenerative

processes may also be involved. Moreover, neuroimage studies of high-risk subjects for psychosis suggest that those individual that will later develop psychosis show more structural and functional brain abnormalities as compared to non-converters and controls (83). Also, siblings of patients with SZ, considered subjects at genetic -risk of developing the disease, have shown similar patterns of altered task-related deactivation in the medial frontal cortex as their siblings with the disease, which suggests that default mode network dysfunction may function as a trait marker for SZ (84).

From a genetic perspective, genes related to early brain development (e.g. Disrupted in Schizophrenia 1 (*DISC1*), Dysbindin (*DTNBP1*) and Neuregulin 1 (*NRG1*)) have been associated with SZ (85). Also, the latest Genome-wide association study (GWAS) in SZ has allowed the identification of genes related to neurodevelopmental processes, such as synaptic organization, differentiation, and transmission, which are relevant to the pathophysiology of the disorder (86–88). Interestingly, many of these genes are highly expressed during fetal development, suggesting a link between SZ and the early phases of brain development (89). In this vein, several analyses have been carried out on genes proximal to SZ risk variants, suggesting enrichment pathways related to neurodevelopmental processes (90). Interestingly, a study analysed developmental time-course gene expression data from human pluripotent stem cells, associated with diseases, to identify windows of disease susceptibility (WOS) during development. SZ, like autism, was linked to WOS during the upper layer generation stage (approx. gestational weeks 18-32). In contrast, only autism was also associated with earlier WOS, corresponding to neural differentiation and cortical specification (91).

NEURODEVELOPMENTAL MILESTONES AND COGNITIVE EVIDENCE

Clinical data has also added relevant evidence. Some children who later develop SZ have early developmental, educational and social challenges (92) and childhood neuromotor dysfunction precedes the onset of SZ (93–95). Extensive cohort studies reveal that developmental delays can be detected as early as the first year of life in infants who later develop schizophrenia (SZ). These delays often include milestones such as smiling, lifting

the head, sitting up, crawling, and walking (96). Additionally, speech challenges, lower educational achievement up to age 15, and social anxiety during adolescence are have been described, observed (97). Also, a meta-analysis of motor and cognitive functioning in children later diagnosed with SZ spectrum disorders revealed significant motor function and lower intelligence quotient (IQ) between ages 13 and 16 but without deficits in general academic achievement. A later birth cohort study found similar results, describing attentional, executive and motor impairments at age 13 in those who later fulfilled diagnostic criteria for the schizophreniform disorder, suggesting that these impairments may be early emerging neuropsychological impairments in SZ-related disorders (98). After these first studies, decades of empirical research led to a consensus that children and adolescents exhibit premorbid cognitive impairments before the onset of SZ, both general (i.e., IQ) and specific (i.e., processing speed) impairments. Consistent with premorbid impairments, first-degree relatives also show cognitive impairments, and psychosis in a first-degree relative increases the severity of childhood premorbid impairment in SZ (99,100). Despite the consistency of research regarding premorbid cognitive impairments in SZ, there is less consensus regarding their exact nature and course (101).

NEURODEVELOPMENTAL INDIRECT MARKERS

Aside from the more obvious clinical and cognitive descriptions aforementioned, early indirect markers of altered neurodevelopment have been associated with SZ, such as neurological soft signs (NSS), dermatoglyphics and minor physical abnormalities.

The prevalence of NSS is higher in people with SZ than in the general population (102), in prodromic (103), and in both early and late stages of the disease (104). Interestingly, NSS are more common in first-degree relatives of people with SZ than in controls, thus arguing in favour of a trait perspective (105,106). Additionally, NSS have demonstrated moderate correlations in twin studies and between individuals with SZ and their first-degree relatives, which indicates both heritability and familial patterns, positioning NSS as a potential endophenotype for SZ (107,108). For all the reasons mentioned above, a

key strategy in our research (see Manuscript 3) has been to incorporate NSS as a marker of neurodevelopment, to help us to better understand the variability of ToM.

Similarly, an increased prevalence of minor physical abnormalities has been observed in individuals with SZ (109), particularly in the craniofacial region (110), as well as in their unaffected first-degree relatives, albeit to a lesser degree than in patients (111,112). More recently, new approaches based on new methodologies allowing the assessment of much subtle dysmorphologies (i.e. geometric morphometrics), have reported more precise facial shape differences between patients with SZ and healthy subjects (113).

Other morphologic traits that could indirectly assess these subtle developmental abnormalities are dermatoglyphic abnormalities (114). Studies on dermatoglyphics in SZ patients have identified both quantitative and qualitative differences in ridge counts and patterns compared to healthy individuals, including simplified configurations and increased bilateral asymmetry (114–117). The frequency of the ectodermic derivates abnormalities seem to be influenced by genetic risk factors, as they appear to be higher in patients and relatives than in controls, while first-degree relatives did not differ from patients (115,118).

An umbrella review highlighted dermatoglyphics as a significant risk factor for SZ (119), and another study shows how fingerprints could serve as early predictors of psychosis with about 70% accuracy using deep learning algorithms (120). Interestingly, dermatoglyphic anomalies seem to correlate with the schizotypy familial aggregation pattern (121), which further supports the hypothesis about the genetic influence on this risk marker. Although specific genetic factors influencing dermatoglyphics remain largely unknown, a recent GWAS has identified 18 fingerprint-associated loci with nearby genes strongly enriched for general limb development pathways (122). In the same lines, a recent study has reported the influence of the cannabinoid receptor 1 gene (*CNR1*), a key player within the comprehensive and homeostatic balancing system that is the endocannabinoid system, in the complexity of the finer dermatoglyphic pattern (123).

1.2.3 GENETIC AND ENVIRONMENTAL RISK FACTORS FOR SCHIZOPHRENIA

GENETIC RISK FACTORS

Two main factors support the importance of the influence of genetics in SZ.

First, having affected relatives (family history, FH) remains the most powerful indicator of individual SZ risk. Also, the disorder's high heritability suggests a strong genetic component (Box 4). Sullivan et al. (2003) meta-analytic results (124) from 12 published twin studies of SZ from independent samples in Europe and the United States estimate the heritability of SZ at 81% (95% CI, 73%–90%), whereas shared environmental influences were estimated to be 11% (95% CI, 3%–19%).

BOX 4. HERITABILITY (h^2)

- It refers to how much of the variability of the trait in the population is attributable to between-individual genetic variation (it does not indicate what proportion of a feature is determined by genes and what proportion is determined by the environment).
- Heritable traits can include characteristics such as height and intelligence and disorders like schizophrenia and autism spectrum disorder.
- An estimate of the heritability of a trait is specific to one population in one environment, and it can change over time as circumstances change.
- By comparing a trait in identical twins versus fraternal twins, researchers can estimate its heritability.
- Heritability estimates range from zero to one. A heritability close to zero indicates that almost all the variability in a trait among people is due to environmental factors, with very little influence from genetic differences. Characteristics such as religion, language spoken, and political preference have zero heritability because they are not under genetic control. A heritability close to one indicates that almost all the variability in a trait comes from genetic differences, with minimal contribution from environmental factors.
- Most complex traits in people (i.e., intelligence or multifactorial diseases) have a heritability somewhere in the middle, suggesting that their variability is due to a combination of genetic and environmental factors.
- The heritability of a trait does not provide information about which genes or environmental influences are involved or how important they are in determining the trait.

Interestingly, a study reports that 27% of SZ cases in the population can be attributed to a family history of mental disorders and suicide, while the population-attributable risk

associated with a family history specifically limited to a SZ diagnosis accounted for 6.0% (125).

Family aggregation, twin and adoption studies

In determining the involvement of hereditary factors predisposing to common diseases, studies of familial aggregation, twin and adoption studies are essential. Through these studies, it is possible to quantify the relative role of genes and environment in complex traits and diseases. Then, once the role of genetic factors is established, molecular studies become the subsequent step in the pursuit of specific genetic markers. This approach provides a more direct method for identifying and locating the genes and, consequently, the mechanisms involved in the aetiology of these disorders.

One method to estimate the contribution of genetic factors in a multifactorial trait or disease is to analyse its familial aggregation. In other words, to compare concordance for the disease in relatives of different degrees. Concerning SZ, family aggregation studies demonstrated, early in the 20th century, that the rate of SZ was higher in relatives of patients with SZ than in the general population. In particular, twin studies documented that the concordance rate was higher in MZ twins than in dizygotic (DZ) twins. As MZ twins (assumed to share 100% of DNA) and DZ twins (sharing 50% of DNA on average) share the environment they are raised in, higher concordance rates in MZ over DZ twins most likely result from genetic similarity.

In short, it could be said that the risk of developing SZ depends on the amount of genetic variability that family members and their affected relatives share (126,127) (Fig.10). Estimates of concordance rates for SZ, based on European twin studies from 1963 to 1987, show higher rates for MZ (48%) than for DZ twins (17%) (126). From the second half of the 20th century, studies of twins and adoption continued to support the relevance of genetic factors in the origin of SZ.

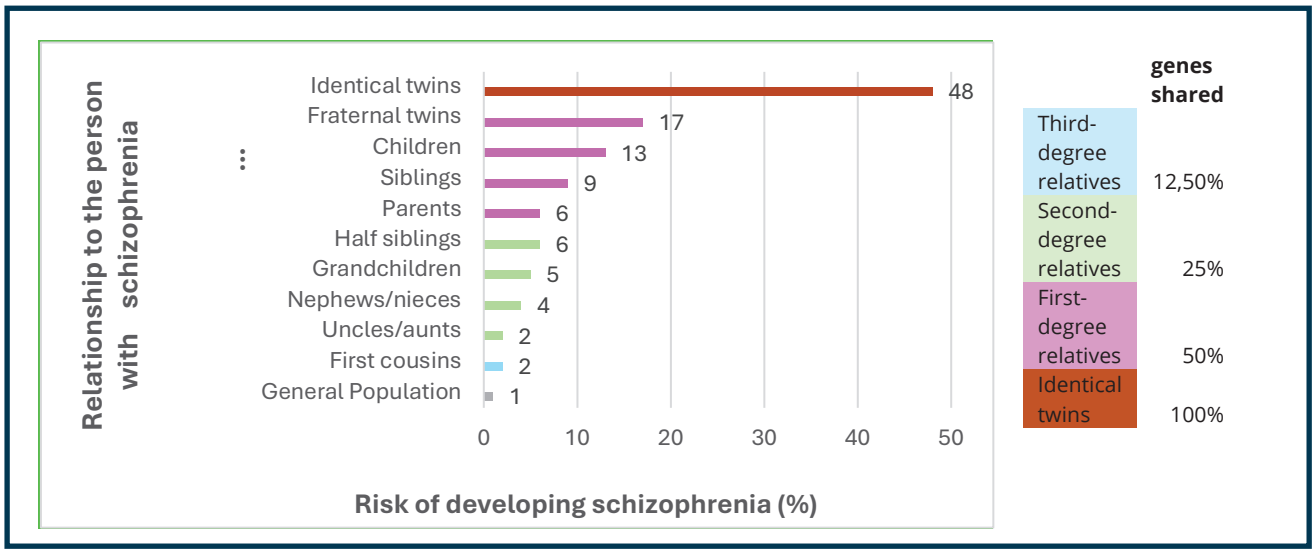


FIGURE 10. RECURRENCE RISKS FOR SCHIZOPHRENIA. Histogram of recurrence risks for SZ in different classes of relatives. Adapted from Gottesman, 1991 (119).

A Taiwanese population study found that having an affected co-twin, first-degree, or second-degree relative significantly increases the risk of SZ with an adjusted RR of 37.86, 6.3, and 2.44, respectively. Also, compared with the general population, individuals with two or more affected first-degree relative had a RR of 14.66 for SZ. The study also showed that genetic factors account for 47.3% of the phenotypic variance in SZ, with shared environmental factors contributing 15.5% and non-shared environmental factors contributing 37.2% (128). Conversely, a population-based study of Swedish families revealed a higher risk for first-degree relatives, with a relative risk (RR) exceeding 9. The study also estimated a more significant genetic contribution to SZ liability (64%) and a contribution of 4.5% for shared childhood environmental effects and 31.1% for non-shared environmental effects (129).

More recently, a meta-analysis from 19 studies of SZ in relatives, with a total sample of 4875 at-risk relatives and 5070 control relatives of different ethnic origins, estimates for SZ risk were OR = 7.69 (95% CI 5.11-11.56) for first-degree relatives of one proband with SZ compared to healthy control probands, increasing to OR = 11.11 (95% CI = 1.45-85.02) for first-degree relatives with two probands with SZ (130,131) . Also, it is remarkable that discordant MZ twins showed a similar risk of SZ spectrum disorders in the children of the affected and unaffected MZ twin, presumably indicating that unaffected MZ twins

carry silent (non-expressed) susceptibility genes for SZ and the capacity of a SZ genetic load or diathesis to be unexpressed unless it is released by some environmental, including nonfamilial, stressors. By contrast, for children of discordant DZ twins, the risk was higher in the children of the affected DZ twin compared to those of the unaffected DZ twin (132).

Henriksen et al., 2017, reviewed evidence from adoption studies. While shizophrenia spectrum disorders (SSD) are more frequent in adopted-away children of mothers with SZ than in their control adoptees, a cross-fostering study found that children of healthy parents adopted by a family where one of the parents later developed SZ did not have an increased risk of developing SZ . Other studies found that children of mothers with SZ had the same risk of developing the disorder independent of whether they were raised by their biological mothers or by adopting parents with no history of mental illness. Importantly, a Finish adoption study and the High-Risk Danish study found an increased risk of SZ in children of mothers with SZ who were exposed to unstable parenting or raised in public childcare institutions (133).

Molecular studies

Association studies are currently one of the best strategies for identifying genes responsible for genetically complex and polygenic diseases, in which there is no known inheritance model and several genes with minor effects are involved. Then, in SZ, genetic association studies face the challenge of identifying genetic variants, each of which is neither necessary nor sufficient to cause the disease individually; thus, they predispose to its development.

One of the main types of genetic association studies is the case-control approach, which compares the frequency of genetic variants in samples of affected (patients) and unaffected and unrelated individuals (controls). A variant of classical association studies designed according to a case-control model is family-based association studies, in which the parents of the cases are used as controls. This method eliminates the possible problems of population stratification. Since all individuals within a family pedigree share

a common genetic background and are typically more homogeneous in their exposure to environments linked to the disorder, they provide a more controlled context for studying genetic associations (134,135).This approach studies how alleles are passed from parents to affected children. They only consider the heterozygous parents of the affected individual since this is the only way to determine precisely which alleles have been transmitted to the affected individual and which have not. To estimate the association between the analysed marker and the disease, the transmission imbalance is calculated using the transmission disequilibrium test (TDT) (136), based on the comparison of the transmitted and non-transmitted alleles using a statistical test for paired samples. Specifically, it assesses whether the proportion of alleles transmitted from heterozygous parents to affected offspring deviates from the 50% we expect according to the Mendelian inheritance laws, assuming no linkage. In other words, the TDT estimates in the family samples if all alleles are transmitted with the same frequency from parents to affected children or if there is a differential transmission of the alleles or risk variants to the offspring affected by the disease.

Association studies have mainly been carried out by analysing polymorphic (or common) genetic variants, meaning that their differences in DNA sequence prevail in about 1% of the population (see Box2). Single nucleotide polymorphisms (SNPs) are the most studied markers among these. SNPs are changes at a single position in a DNA (a single nucleotide A (adenine), C (cytosine), T (thymine) or G (guanine) in the genome sequence. As the Human Genome Project indicates, these changes make up about 90% of DNA sequence variation. These changes usually have small (almost negligible) effects on gene function or expression (137). However, apart from polymorphisms, we also know that rare or low-frequency genetic variants, also called mutations, are also involved in genome variability.

Finally, according to the type of approach, studies can be differentiated in candidate-gene or GWAS. A candidate gene is related to a specific disease, either because it is located in a region of a chromosome suspected of being involved in a disease (proposed from linkage studies) or because the protein it encodes has one(s) function(s) related to

the pathophysiology of the disease. Technical advances in the past few years have made it possible to go from the analysis of single candidate genes towards genetic association studies based on whole genome approaches that allow the analysis of thousands of genetic variants all along the human genome without requiring functional knowledge of each variant (hypothesis-free approaches) and thereby allow for the discovery of potentially novel genes. These studies employ microarrays or chips, which allow rapid scanning of each individual for 300,000 – 1,000,000 Single nucleotide polymorphisms (SNPs) together with large samples to find markers associated with a particular trait or disease.

A decade of GWAS indicates that combining multiple genetic variants (single base changes A, T, C, or G) can influence complex polygenic traits, each with minor additive effects. This gives the Polygenic Risk Score (PRS), which represents the sum of the trait-associated genetic variants (SNPs) carried by an individual, weighted by the estimated effect size of the variant (these effect sizes are estimated from a GWAS for the specific trait). The total score can summarize an individual's common genetic predisposition for a specific trait (Fig. 11) but doesn't inform about the genetic architecture, the gene-environment, or the gene-behaviour relationship (138).

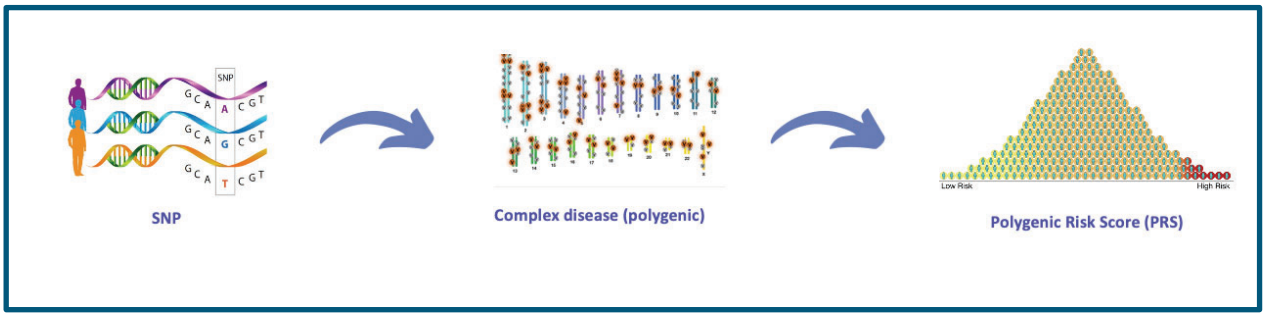


FIGURE 11. POLYGENIC RISC SCORE. A polygenic risk score (PRS) estimates an individual's genetic liability to a trait or disease, calculated according to GWAS data about multiple single nucleotide polymorphisms associated with the trait or disorder.

The multiple findings accumulated by genetic association studies concerning SZ have been reviewed and summarised by different authors (139–141). More than 1000 candidate genes have been tested (see http//www.szgene.org). Even so, despite the usefulness of the candidate-gen approach for delimiting effects in more specific

functions and the identification of some genes with minor effect alleles (142), the overall results from the candidate gene studies have been limited by the polygenic background of the disorder. For this reason, it should be noted that the candidate gene and whole genome approaches are complementary.

ENVIRONMENTAL RISK FACTORS

While it is well-established that SZ is a highly heritable disorder, and considerable progress has been made in identifying their shared and distinct genetic risk factors, the 15–40% of risk derived from environmental sources is less definitively known. Environmental factors that have been repeatedly investigated and often associated with SZ include sociodemographic, perinatal, and later adversities (see Table 2). (73)

Table 2. Summary of the most relevant Environmental Factors Associated with the Risk of Schizophrenia.

Risk Factor	Odds Ratio (95% CI)[a]
Obstetric complications	1.84 (1.25-2.70)
Winter birth in the Northern Hemisphere	1.04 (1.02-1.06)
Childhood trauma	2.87 (2.07-3.98)
Urban living	2.19 (1.55-3.09)
Migration (first generation)	2.10 (1.72-2.56)
Severe cannabis use	5.17 (3.64-7.36)

[a]Odds Ratio taken from Radua et al. (119)

Sociodemographic factors

- *Winter/spring season of birth in the Northern hemisphere* The season of birth effect in SZ is one of the most replicated features in SZ epidemiology, with most Northern Hemisphere studies finding a 5 to 15 per cent excess in the winter and early spring (143,144).

-*Urbanicity* Meta-analyses show consistent association in a dose-response manner with the urban environment (145). There is probably a general stress processing factor, diagnostically nonspecific, as mood and anxiety disorders are also elevated.

-*Ethnic Minority/immigrant status* Minority group position is associated with psychotic symptoms across different cultures, and the effects are probably mediated by chronic social adversity. This is one of the best-documented and most substantial environmental risk factors. For instance, the strongest association has been described for Black-Caribbean ethnicity in England (OR 4.87, 95% CI 3.96-6.00)(146).

Perinatal factors

Pregnancy and early postpartum insults are implicated in the etiopathogenesis of psychotic disorders.

-*Infection* Clinical, epidemiological, and translational studies link prenatal infection and SZ. Prenatal exposure to rubella, toxoplasma, and herpes simplex virus type 2 are known causes of developmental disorders, including intellectual disability, learning disabilities and sensorineural dysfunction. Also, studies consistently find an association between Toxoplasma Gondii infection and SZ (OR 1.82). Still, evidence suggests an association with other infections, such as with lower evidence of Chlamydia psittaci, Chlamydia pneumonia and other retrovirus or herpes virus (119).

- *Famine* A follow-up of previous work on the Dutch Hunger Winter revealed that individuals in utero during this famine showed an increased risk of brain abnormalities, SZ, and depression (20).

-*Obstetrical Complications (Table 3)* Obstetric complications can disrupt the expected trajectory of brain development, contributing to neurodevelopmental abnormalities and providing a mechanism to explain the increased risk of SZ (71). For example, immune responses triggered by maternal infections or hypoxia during birth may increase neuroinflammation, which has been linked to the development of SZ(147). Many studies find some relationship between obstetric complications and later onset of SZ (148).

Obstetrical events may be causal in themselves or reflect other causal processes. In a recent metanalysis, Davis et al. (79) updated the consistency and magnitude of their associations with psychosis.

TABLE 3 Meta-analytic association between obstetric factors and psychotic disorders. Adapted from Davies (2020)

Obstetrical Complications	OR	P value
Toxoplasma infection	1.30	0.022
Herpes Simplex type 2 infection	1.30	0.0002
Maternal stress NOS	2.40	0.019
Famine or nutritional deficit	1.40	0.0002
Maternal hypertension	1.40	0.0058
Hypoxia	1.63	0.014
Rupture membranes	1.86	0.0033
Premature rupture membranes	2.29	0.0013
Polyhydramnios	3.05	0.025
Definite obstetric complications NOS (Lewys Murray OC Scale)	1.83	0.0042
Birthweights of less than 2000 g	1.84	<0.0001
Birthweights of less than 2500 g	1.53	<0.0001
Birthweights 2500-2999 g	1.23	<0.0001
Winter to spring birth in the Northern Hemisphere	1.05	<0.0001
Small for gestational age	1.40	<0.0001
Premature birth <37	1.35	0.0016
Congenital malformations	2.35	0.0093

-*Parental factors (Table 4) Some* parental factors have also been associated with SZ.

TABLE 4 Meta-analytic association between parental and familial factors and psychotic disorders. Adapted from Davies, 2020

Parental Factors	OR	P value
Maternal age younger than 20 years	1.17	0.0004
Maternal age 30-34 years	1.05	<0.0001
Paternal age younger than 20 years	1.31	<0.0001
Paternal age older than 35 years	1.28	0.012
Any maternal psychopathology	4.60	<0.0001
Any paternal psychopathology	2.73	<0.0001
Maternal psychosis	7.61	<0.0001
Maternal affective disorder	2.26	0.029
Three or more pregnancies	1.30	<0.0001

Later risk factors

-*Childhood trauma* Increasing evidence shows a significant relationship between early childhood trauma and risk of psychosis, OR 2.87 (2.07-3.98) (Radua et al., 2018). Sexual abuse may be of particular importance (149,150).

-*Adult life events* recent models of psychosis implicate other stressful events in its aetiology. Some evidence has reported exposure to adult life events, such as migration (73) or social status, e.g. occupying a social minority position or experiencing social exclusion, promotes the development of SZ (126,145). Meta-analysis yielded an increased risk of 3.19-5.34 (119,151)

-Severe *Cannabis Use* Literature indicates that psychotic illness arises more frequently in cannabis users than non-users, OR 5.17 (3.64-7.36) (152). Also, cannabis use is associated with a dose-dependent risk of developing a psychotic illness, and cannabis

users have an earlier onset of psychotic illness than non-users (153). Moreover, GWAS meta-analysis of cannabis use disorder showed that cannabis use disorder was positively genetically correlated with SZ (154). This is extremely interesting, as cannabis has long been suspected to be the most closely related modifiable environmental risk factor in SZ; however, this finding suggests that genetics conferring vulnerability to both disorders mediate this association. This is an example of how difficult it is to separate environmental, genetic, and clinical risk factors.

1.2.4 GENE-ENVIRONMENT-TIME INTERACTION

With everything explained above, we can understand that, on the one hand, there are infinite combinations of genetic variants that confer a specific risk for each individual. However, this risk will be compounded by the possibility of exposure to a wide range of environmental influences, the impact of which will be determined by the type of exposure and dose and the moment of exposure during brain development (Fig. 12). Therefore, we could summarize that different pathophysiological mechanisms with specific etiological factors could be subsumed under the broad concept of SZ, showing a high phenotype variability among individuals with the same condition. This phenotype variability highlights the complexity of SZ as a disorder, making diagnosis, prognosis, and treatment approaches more challenging due to the range of possible presentations in patients.

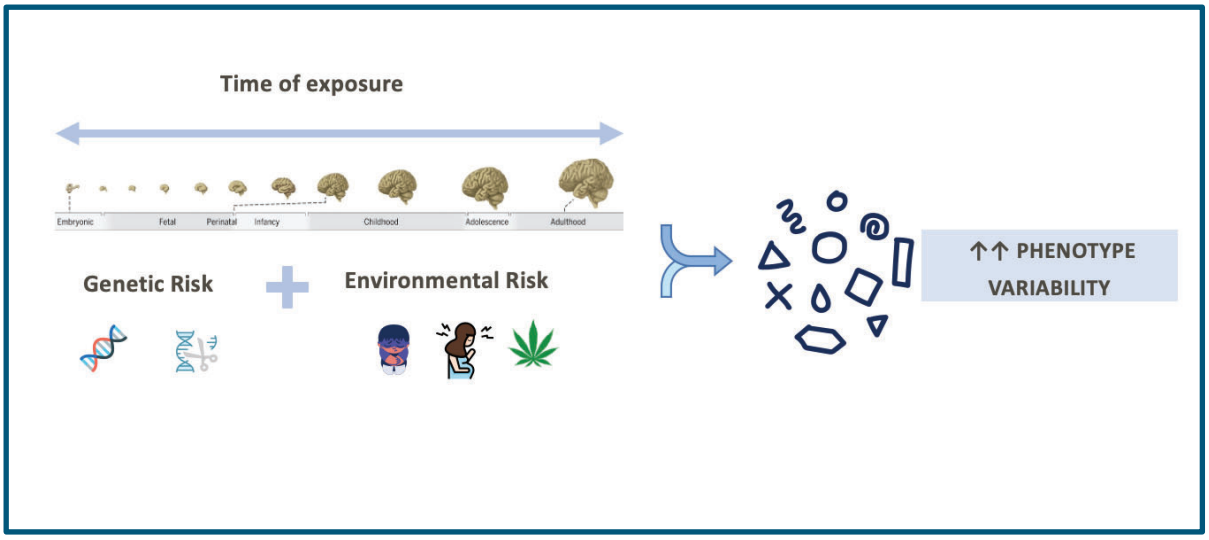


FIGURE 12. GENE-ENVIRONMENT-TIME INTERACTION IN SCHIZOPHRENIA. The interaction between these three components is complex and dynamic. An individual may inherit a genetic predisposition to SZ. Still, his/her risk of developing the disease may increase or decrease depending on their exposure to environmental factors and the timing of these events.

In summary, the gene-environment-time interaction in SZ underscores the importance of considering multiple factors in the development and expression of the disease. It should be noted that this interplay involves elements such as i) sensitivity to environmental factors mediated by genetic variability, ii) the probability of exposure to certain environmental factors mediated by genetic factors, iii) the impact of environmental factors regulated by epigenetic mechanisms. All these elements justify the need for an integrated approach to understand and address the disease effectively.

1.3 THE COMPLEX AND HETEROGENOUS EXPRESSION OF SCHIZOPHRENIA

1.3.1 SCHIZOPHRENIA COMPLEXITY

When we refer to the complexity of SZ, we are addressing it on multiple levels, not just in terms of its heterogeneity causes but in terms of its causes and underlying pathophysiological mechanisms. This complexity makes it a challenging disorder to define and one that lacks clear diagnostic markers or highly effective treatments, which is particularly worrying considering the epidemiological characteristics and impact of the disease.

Moreover, SZ is a severe psychiatric disorder with a lifetime prevalence of around 0.5-1%, affecting 23 million people worldwide. Incidence per 100,000 people per year is roughly 15 in men and 10 in women. These estimates were based on reasonably conservative diagnostic criteria (155,156). Because SZ typically begins as people approach or enter adulthood and persists indefinitely, it is one of the leading causes of disability worldwide. The high degree of disability, prevalence, chronicity and financial costs place an enormous burden on patients, their families, and society. The SZ burden, as estimated by Global Burden Disease study in 2019, is attributed to a disability-associated load (i.e., 20th position in the global ranking of the Years Lived with Disability) and despite its low prevalence in comparison to other conditions, is in the top twenty most disabling disorders among 369 diseases and injuries globally in 2019 (157). The disorder is also associated with reduced life expectancy someone with SZ has a mean life expectancy of about 15 years shorter than the general population and a 5% to 10% lifetime risk of death by suicide (158).

The two most formidable challenges for all the above mentioned are understanding the disorder's causes and pathogenesis and developing new, effective, and acceptable treatments.

1.3.2 SCHIZOPHRENIA CLINICAL PRESENTATION

SZ is a primary psychotic disorder (Box 5), characterised by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganisation in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behaviour are under the control of an external force), cognition (e.g., impaired attention, verbal memory, and SC), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behaviour (e.g., behaviour that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organisation of behaviour). Also, psychomotor disturbances, including catatonia, may be present.

Therefore, SZ is defined as a syndrome and its diagnosis is based on a constellation of clinical symptoms and not on a common pathomechanism, as is the case for ischemic stroke or cardiac infarction. Diagnosis is made clinically based on history and mental state examination; no diagnostic tests or biomarkers are available. From 2022, the two used diagnostic systems are ICD-11 (159) and DSM-V (160).

BOX5. PRIMARY PSYCHOTIC DISORDERS

Brief Descriptions of Diagnostic Categories in the ICD-11 Schizophrenia or Other Primary Psychotic Disorders Subchapter

Schizophrenia	Characterised by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganisation in the form of thought), perception (e.g., hallucinations), self- experience (e.g., the experience that one's thoughts or behaviour are under the control of an external force), cognition (e.g., impaired attention), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behaviour (e.g., bizarre behaviour). Symptoms must be present for at least one month.
Schizoaffective disorder	Episodic disorder in which the diagnostic requirements of schizophrenia and a manic, mixed, or moderate or severe depressive episode are met within the same episode of illness.
Schizotypal disorder	Characterised by an enduring pattern (i.e., at least several years) of eccentricities in behaviour, appearance and speech, accompanied by cognitive and perceptual distortions, unusual beliefs, and discomfort with interpersonal relationships.
Acute and transient psychotic disorder	Characterised by an acute onset of psychotic symptoms that emerge without a prodrome and reach their maximal severity within two weeks.
Delusional disorder	Characterised by the development of a delusion or a set of related delusions that persist for at least three months (usually much longer), which occur in the absence of a depressive, maniac, or mixed mood episode. Other characteristic symptoms of schizophrenia are not present.

Both diagnostic systems provide a catalogue of symptoms and demand that a certain number of this pool must be present over a given period of time for a diagnosis to be made (Table 5).

A diagnosis of SZ requires the presence of at least two of five or seven (DSM-V or ICD-11, respectively) symptom categories, including at least one 'core' symptom. ICD-11 presents two differences in the diagnostic criteria of SZ with DSM-5. Although ICD-11

and DSM-5 require that psychotic symptoms last at least one month to diagnose SZ, DSM-5 also requires the presence of these symptoms, prodromal or residual symptoms during six months. In SZ, the symptoms are typically chronic, impair daily life, and result in a significant decline in functioning. However, while impaired function is a diagnostic criterion of SZ in DSM-5, it is not considered in ICD-11.

TABLE 5. Diagnostic Criteria for Schizophrenia According to DSM-V and ICD-11

DSM-V	ICD-11
Two (or more) of the following, each present for a significant portion of time during 1 month (or less if successfully treated). At least one of these should include 1–3. 1. Delusions 2. Hallucinations 3. Disorganised speech 4. Grossly disorganised or catatonic behaviour 5. Negative symptoms (i.e., diminished emotional expression or avolition)	At least two of the following (one must be from 1 to 4.) present for a significant portion of time during a 1-month. 1. Persistent delusions 2. Persistent hallucinations 3. Disorganised thinking 4. Experiences of influence, passivity, or control 5. Negative symptoms 6. Grossly disorganised behaviour 7. Psychomotor disturbances
The symptoms are not a manifestation of another health condition (e.g., a brain tumour) and are not due to the effect of a substance or medication on the OXT(e.g., corticosteroids), including withdrawal (e.g., alcohol withdrawal).	

Because of the characteristics of the diagnostic criteria of both classification systems, two patients can be diagnosed with SZ even though they do not share a single symptom at the time of examination. According to these classifications, a patient presenting with delusions and hallucinations can be diagnosed with SZ, as can a patient presenting with disorganised speech and negative symptoms. Although both hypothetical patients arguably differ in their clinical presentations, they are given the same diagnosis. In other words, SZ can manifest with different clinical phenotypes; therefore, the diagnostic terminology is far from the biological basis, makes it challenging to identify the etiological bases of the disease, which is another example of its complexity.

Changes in the definition of SZ in DSM-5 and, recently, ICD-11 seek to address these shortcomings and incorporate the new information about the nature of the disorder accumulated over the past two decades. Specific changes in its definition include replacing the subtypes (paranoid, hebephrenic, catatonic, etc.) with a set of symptom ratings, which could be applied across the whole group of primary psychotic disorders (Box 5), thereby adding dimensional information to a categorical classificatory approach. Also, cross-sectional and longitudinal course specifiers should be added. These changes should improve the diagnosis and characterisation of individuals with SZ, facilitate measurement-based treatment, and concurrently provide a more helpful base for research that will elucidate its nature and permit a more precise future delineation of the 'schizophrenias' (161). The proposed ICD-11 symptom specifiers rating scale includes six domains Positive Symptoms, Negative Symptoms, Depressive Symptoms, Manic Symptoms, Psychomotor Symptoms and Cognitive Symptoms (Fig. 13). It should be noted, within the framework of this thesis, that neither of the two classifications (DSM-5 or ICD-11) includes SC within the specifier scales for symptomatic manifestations in the cognitive domain of primary psychotic disorders.

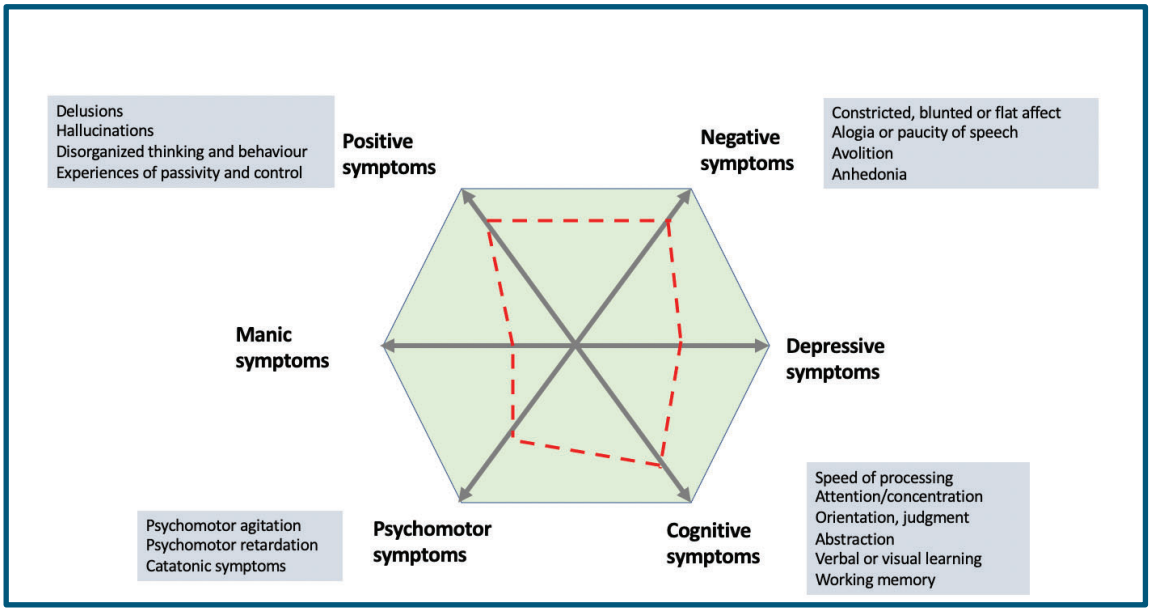


FIGURE 13. Primary psychotic disorders symptom domains. Modified from (van Os & Kapur, 2009) (153).

Moving on to the dimensional approach to psychopathology, it suggests that psychosis exists on a continuum with usual experience, varying across multiple, independent yet related symptom dimensions (163). Two main perspectives have emerged the "quasi-dimensional" model, which views disease as degrees of symptom expression, and the "fully dimensional" model, which takes normality as its baseline. The latter proposes that psychotic symptoms like delusions and hallucinations can appear in non-clinical populations without necessarily indicating a disorder. Thus, while the clinical disorder prevalence is low, symptom prevalence is higher. Thus, the boundaries between SZ and mental health are marked by the severity, frequency, and impact of symptoms on functioning (164).

SZ, like most psychiatric diagnoses, remains a syndromic concept and can be considered part of a spectrum of psychotic disorders rather than a distinct entity. Thus, beyond its limits with normality, SZ shares a continuum of symptoms with other psychotic disorders, and the boundaries between these conditions are fluid, making differential diagnosis complex (158). According to DSM-V, the primary differential diagnoses are affective psychoses (bipolar disorder with psychotic features and major depressive disorder with psychotic features), other closely related non-affective psychoses (schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), psychotic disorders induced by alcohol or other substances, and psychotic disorders caused by a general medical illness. Differential diagnosis considers the duration of illness, the nature and pattern of associated substance abuse, the co-occurrence of depression or mania, and the presence of somatic illness.

In brief, individuals diagnosed with SZ vary greatly in predominant symptoms, response to treatment, course, and outcome. However, attempts to resolve this heterogeneity into valid subtypes have repeatedly failed. The term “psychosis spectrum disorder” is sometimes used to refer to a range of conditions that include SZ, schizoaffective disorder, and brief psychotic episodes. The fact that SZ and related disorders present with diverse symptoms, course and outcomes can be partially explained by a variable

psychosis proneness or schizotaxia. Individuals on this proneness spectrum may exhibit a range of manifestations, from personality traits (schizotypy), subclinical (basic symptoms) or transient symptoms (PLEs), depending on their position on the spectrum of vulnerability and other factors related to environment.

1.3.3 SOCIAL COGNITION IN SCHIZOPHRENIA FOCUS ON ToM

ToM deficits are increasingly observed in individuals with SZ (165). While some studies have interpreted ToM deficits as a state marker associated with symptoms in the active phase of the disease (166), the majority have reported ToM impairment to be a trait marker, present in first-episode psychosis (FEP) (167), during remission (168) and found to be stable after a longitudinal three-year follow-up design (169).

Interestingly, similar impairments have been found in at-risk individuals. Such effects have been reported in people at clinically high risk (such as unmedicated prodromal individuals), indicating that these issues may arise before the onset of psychosis (167). Also, in unaffected relatives of patients with SZ (familial high risk), with meta-analytic data showing their decreased performance compared to healthy controls. The impairment level in relatives lies between the levels seen in probands and healthy non-relatives (170). However, more recent studies still reveal significant heterogeneity, and some fail to demonstrate the expected intermediate position of the relatives' group (168,171–174).

Evidence suggests that some aspects of SC have a genetic component, with heritability estimates ranging from 28-37% for emotion recognition (175) and around 67% for ToM (176). As a result, SC is being recognized as a quantifiable vulnerability marker for SZ.
In this regard, SC assessment involves evaluating an individual’s ability to process and respond to social information, including how they perceive, interpret, and generate responses in social situations. It is a crucial aspect of understanding social interactions and is particularly important in conditions like SZ, autism, and other neuropsychiatric

disorders where social cognitive impairments are common. Unfortunately, there has been a lack of consensus regarding which measures of SC best capture each functioning domain. There are several standardized tests and observational tools designed to assess these domains.

The Social Cognition Psychometric Evaluation (SCOPE) study aims to identify and improve the best existing measures of SC so they can be suitably applied in large-scale treatment studies (Box 6). Findings from the initial validation study (177) suggested that Bell-Lysaker Emotion Recognition Task (BLERT) and Hinting task (HT) showed the most robust psychometric properties across all evaluation criteria and thus recommended for use in clinical trials. The Penn Emotion Recognition Task (ER-40), the Reading the Mind in the Eyes Test (Eyes Task) and the Awareness of Social Inferences Test (TASIT) showed weaker psychometric properties and The Ambiguous Intentions Hostility Questionnaire (AIHQ), Relationships Across Domains (RAD), and Trustworthiness Task showed poorer psychometric properties that suggested caution for their use in clinical trials. It's important to note that the SCOPE study included a mostly middle-aged, chronic sample of patients with SZ. To address this limitation, another study built upon the SCOPE study examined the psychometric properties of the eight candidate measures in individuals in the early course of psychosis. Among these measures, only the HT displayed sufficient psychometric properties to be recommended for use in clinical research with first-episode psychosis (178).

Box 6. DESCRIPTION OF FINAL MEASURES OF THE SOCIAL COGNITION PSYCHOMETRIC EVALUATION (SCOPE)

Hinting Task	The HT examines the ability of individuals to infer the true intent of indirect speech. The task includes 10 short passages presenting an interaction between 2 characters that are read aloud by the experimenter. Each passage ends with one of the characters dropping a hint, and participants are asked what the character truly meant. If the first response provided is inaccurate, a second hint is delivered, and participants may earn partial credit for that passage. Total scores range from 0 to 20.
Bell Lysaker Emotion Recognition Task (BLERT)	The BLERT measures the ability to correctly identify 7 emotional states happiness, sadness, fear, disgust, surprise, anger, or no emotion. Participants view 21 ten-second video clips of a male actor, which provide dynamic facial, vocal-tonal, and upper body movement cues. After viewing each video, participants identify the expressed emotion.
Reading the Mind in the Eyes Test	The Eyes task measures the capacity to discriminate the mental state of others from expressions in the eye region of the face. Participants view 36 photos of the eye region of different faces and choose the most accurate descriptor word for the thought/feeling that is portrayed. Four possible options are presented with each photo, and a glossary of mental state terms is provided for reference.
Penn Emotion Recognition Test	The ER-40 assesses facial affect recognition ability. It includes 40 color photographs of static faces expressing 4 basic emotions (ie, happiness, sadness, anger, or fear) and neutral expressions. For each emotion category, 4 high-intensity and 4 low-intensity expressions are included. Participants view 1 image at a time and choose the correct emotion label for each face.
The Awareness of Social Inferences Test, Part III	The TASIT is comprised of videotaped vignettes of everyday social interactions, and Part III, the Social Inference-Enriched test, assesses detection of lies and sarcasm. Participants watch each vignette and answer 4 standard questions per vignette that probe understanding of the intentions, beliefs, and meanings of the speakers and their exchanges.
Relationships Across Domains, abbreviated version	The RAD measures competence in relationship perception. The abbreviated RAD is comprised of 15 vignettes involving different male-female dyads that represent one of 4 relational models (communal sharing, authority ranking, equality matching, and market pricing). Participants read each vignette and answer 3 yes/no questions about whether a future behavior is likely to happen given the described relationship.
Ambiguous Intentions and Hostility Questionnaire, abbreviated version	Designed to evaluate hostile social cognitive biases. Participants read 5 hypothetical, negative situations with causes that are ambiguous), imagine the scenario happening to them, and record a reason why the scenario occurred. Independent raters later code this initial response to compute a hostility index. Also, the participant is asked to write down how they would respond to the situation, which is later coded by 2 independent raters to compute an aggression index.
Trustworthiness Task, abbreviated version	Participants rate 42 faces for trustworthiness. Faces are presented in grey scale and represent ethnically diverse males and females. The task assesses participants' ability to make complex social judgments by comparing the participant ratings to normative

1.4 APPROACHES TO UNDERSTANDING THE COMPLEXITY AND HETEROGENEITY SCHIZOPHRENIA

Based on the above-mentioned, the multi-level complexity of SZ is hard to question. As we have seen, the genetic-environment-time interaction already explains a wide range of possible phenotypic presentations for SZ that may vary throughout the illness and due to response to treatment, that can be very variable.

In this sense, one of the challenges of research on the neurobiological bases of SZ is to find strategies to analyse and reduce the biological variability or heterogeneity. In the context of this thesis, we will highlight two strategies that allow us to advance this goal i) the use of intermediate phenotypes, ii) The use of family-based studies.

1.4.1 THE USE OF INTERMEDIATE PHENOTYPES.

A common strategy involves the analysis of intermediate phenotypes that are likely associated with a smaller subset of genes, which can reveal more specific biological mechanisms compared to examining the entire set of genes related to the disease.

Endophenotypes are a specific type of intermediate phenotype (e.g., quantitatively measurable cognitive, neurophysiological, or biochemical trait) that lies between the disease and its genetic basis and must fulfil specific criteria can be considered an endophenotype (see Box. 7). The endophenotype approach has become an essential strategy in genetic studies of complex neuropsychiatric disorders, such as SZ.

Their main advantage is that they are generally less heterogeneous than the disorder itself and offer a neurobiological framework to identify genetic risk variants underlying brain dysfunction pathways in SZ (179).

BOX 7. CRITERIA FOR A MARKER TO BE CONSIDERED AN ENDOPHENOTYPE

1) it is present in probands with the disorder;
2) it is heritable;
3) it is state-independent (that is, it does not occur only during clinical episodes);
4) within families, endophenotype and illness co-segregate
5) it is observed in unaffected family members at a higher rate than in the general population.

A feature that fulfils these criteria can be considered an endophenotype and therefore it is assumed to be is associated with a genetic load of vulnerability for the disease in question. Accordingly, social cognition seems of interest as a putative endophenotype; however, further studies are needed to validate it, especially on the family related criteria.

The most validated SZ endophenotypes include prepulse inhibition (a measure of sensorimotor gating), mismatch negativity (a measure of an index of preattentive sensory processing), oculomotor antisaccade (a measure of inhibitory failure), letter-number sequencing (as a measure of working memory), and continuous performance tests (as a measure of attention) (180). Also, other candidate endophenotypes, including emotion processing as a measure of SC, have been proposed (181). Moreover, recent findings from large consortia suggest the potential role of genes, in several of these endophenotypes, particularly in those related to glutamate and axonal dysfunction pathway (182).

This thesis aims to explore whether ToM deficits could function as a potential endophenotypic marker of SZ and to contribute to analysing of its varied expression in populations with familial risk, as outlined in point 3.3.

A convergent research approach that combines various vulnerability markers could improve the identification of high-risk individuals by identifying a more susceptible subgroup among those genetically predisposed to psychosis, particularly those with significant neurodevelopmental alterations such as social cognitive deficits. This approach can also clarify the variability or inconsistent findings regarding ToM deficits within the relatives' group. This thesis will concentrate on three clinical vulnerability markers (schizotypy, basic symptoms, psychotic-like traits), two neurodevelopmental

(NSS and Premorbid Adjustment (PA)), the family load for schizophrenia and one specific genetic factor.

SCHIZOTYPY

The term schizotypy, first coined by Rado (183), was used by Meehl (184) to refer to a set of personality traits encompassing behaviours, cognitions and emotions and resembling the signs and symptoms of SZ in the general population. It encompasses perceptual impairments, unusual views or ideas, a loss of normal emotional, physical and social functions and odd behaviour and speech, among other traits (185). On the other hand, due to presumably shared neurodevelopmental pathways with patients with SZ, schizotypy overlaps with SZ across multiple clinical, cognitive and neurobiological domains (186,187). As SZ, schizotypy is a multi-dimensional construct which consists of at least three factors that correspond to positive, negative and disorganized symptom dimensions in psychotic disorders (188).

Schizotypal traits can be taken to represent a proneness toward developing SZ, and this is consistent with the association of the polygenic risk for SZ was associated with some subdimensions of schizotypy, such as delusional experiences and reduced social interest (189).

Evidence of genetic overlap between SZ and schizotypy is supported by family studies, which reveal that first-degree relatives of individuals with SZ exhibit higher levels of schizotypy (190,191) especially in the negative dimension (192). Another study suggests that schizotypy is a clinical liability marker that could be useful in the identification of families with a higher genetic loading for SZ (121).

Notably, a metanalysis shows that ToM abnormalities were significantly related to both positive and negative schizotypy, suggesting that ToM abnormalities might be vulnerability markers for psychosis (187) and the results of Irani et al. (193) suggested that the distinction between relatives of patients and controls on schizotypal traits best explained their between-group difference on a mentalizing task.

BASIC SYMPTOMS

The Basic Symptoms (BS) consists of subtle, subclinical complaints of volition, affect, thinking and language (speech), body perception, memory, motor action, central vegetative functions, control of automatic cognitive processes, and stress tolerance. They represent the earliest symptoms the patient experiences subjectively and can appear a long time before the outbreak of SZ (194). In this regard, a meta-analysis showed the role of BS as a risk predictor by concluding that the mean risk of transition to psychosis established from BS criteria is 48.5% (195). Moreover, an increasing gradient of some BS was observed from non-clinical to SSD individuals, with unaffected siblings in the intermediate position (196). Also, the offspring of a parent with mood and psychotic disorders had significantly higher BS scores than the control offspring (197), placing BS as a marker of familial risk of psychopathology.

PSYCHOTIC-LIKE EXPERIENCES (PLEs).

PLEs are subtle, subclinical hallucinations and delusions which present in the general population with a prevalence of around 6% (198,199). An extensive study reported a shared genetic liability between psychotic-like experiences and several psychiatric disorders (200), and another has related their presence to an increase in the risk for transition to psychotic and (to a lesser degree) non-psychotic disorder at an annual rate of 0.6% (201). Some studies have shown that non-affected siblings of patients with SZ show higher PLEs scores than controls (202,203), but another study found inconsistent results (204).

THE *OXTR* GEN

Following the candidate gene approach, if we focus on the role of OXT and its involvement in the OXT modulatory effects on the "social brain", studies have focused

on oxytocinergic gene variants (*OXT*, *OXTR*). Evidence shows significant associations of *OXTR* SNPs rs53576 (A > G) and rs237885 (T > G) with a diagnosis of SZ (205). Furthermore, *OXTR* polymorphic variants (rs53576 and others), have been associated with the risk for SZ and other neurodevelopmental disorders (reviewed in (46)).
Mice with knockouts of either *OXT* (206) or *OXTR* have deficits in social recognition, and OXT supplementation to the preoptic region rescues these deficits (207).

1.4.2 THE USE OF FAMILY-BASED STUDIES.

Another strategy to address SZ and its vulnerability heterogeneity is the family-based approach. Family-based studies are appropriate for studying a trait or disease, mainly when the deficit is observed in healthy family members at a higher rate than controls. While recruiting large samples of well-characterized families can be challenging, these studies offer a significant advantage over case-control studies of controlling for certain confounding factors, as family members share genetic background and are usually more similar in terms of environmental influences. Different types of family-based designs exist, and in the context of studying developmental disorders, designs that use siblings as the control group (rather than other relatives like parents or children) have the added benefit of better controlling for environmental factors, as siblings are more likely to be exposed to the same environmental conditions simultaneously. This approach also helps control for age-related variables and allows the definition of new indexes, such as familiality or familial aggregation (clustering of certain traits, behaviours, or disorders within a given family), which gives an idea of the phenotypic resemblance among family members (121,208).

In summary, the interaction of multiple genetic and environmental risk factors gives rise to neurodevelopmental vulnerabilities for the development of SZ spectrum disorders (69,70), which can be manifested as clinical vulnerability markers. These are those phenotypic traits, such as personality traits, brief or subsyndromal symptoms, specific cognitive impairments or specific genetic factors that, without showing a complete

picture of the SZ, can indicate an increased risk or "latent" SZ. Therefore, this thesis, through a family-based convergent approach around ToM, aims to contribute to the understanding of psychosis heterogeneity, its biological underpinnings and to enhance the identification of high-risk individuals.

2 HYPOTHESIS

SZ is a severe psychiatric disorder characterized by diverse liability pathways that result in a heterogeneous phenotypic presentation, which complicates diagnosis, prognosis, and treatment. Such complex phenotypes are modelled by the dialogue between the unique individual genetic make-up and envirome, with effects shaped by type, intensity, and timing of exposure during brain development. This gene-environment interplay guides the neurodevelopmental trajectories, and subtle deviances impact different outcomes, even before the onset of the disease. These differences in the trajectories and outcomes can manifest as clinical markers, encompassing traits such as personality characteristics, subclinical symptoms, cognitive impairments, and specific genetic factors. While these markers do not comprehend the full spectrum of SZ, they may signal an increased or "latent" risk, making them identifiable in individuals at risk for the disorder.

In order to constrain the phenotypic variability and facilitate the understanding of the underlying mechanisms as well as to improve the identification of individuals at high risk, the strategies followed in this thesis have been

a) **The use of family-based designs** (including families with at least one patient with a psychotic disorder). Family-based studies are appropriate for studying a trait or disease, mainly when the deficit is observed in healthy family members at a higher rate than controls. Different types of family-based designs exist, and in the context of studying neurodevelopmental disorders, using siblings as control subjects offers the advantage of better accounting for environmental factors and age-related differences, as siblings are often exposed to similar environmental conditions at the same time.
b) **The use of endophenotypes** A common strategy involves including intermediate phenotypes in analyses that are likely associated with a smaller subset of genes, which can reveal more specific biological mechanisms than the entire set of genes related to the disease. Among markers of vulnerability, SC, measured through ToM, stands out as a promising candidate endophenotype for SZ as it has a genetic basis, exhibits relatively stable impairments across the lifespan,

appears in unaffected first-degree relatives, and is closely linked to functional outcomes.

c) **The combination of vulnerability markers**, that could improve the identification of high-risk individuals by identifying a more susceptible subgroup among those genetically predisposed to psychosis. For this purpose, this thesis combines ToM with other clinical vulnerability markers, such as basic symptoms, psychotic-like experiences (PLEs), and levels of schizotypy, to identify individuals who exhibit a profile potentially predisposing them to the disorder. Also, understanding ToM as a fundamentally neurodevelopmental skill, this thesis integrates ToM with markers of early neurodevelopmental alterations, like NSS and PA, to explore how early neurological development is related to SC abilities.

Accordingly, and in line with the current approaches that try to disentangle the heterogeneity of psychotic disorders, the general hypothesis of this thesis holds that the knowledge of the biological mechanisms underlying SZ will benefit from the use and combination of intermediate phenotypes that constraint the genetic variability underlying the disorder (and the associated traits), thus facilitating its comprehension and improving the identification of individuals at high risk. This thesis focuses specifically on analysing ToM, a trait of particular importance due to its connection with key aspects of SZ, including neurodevelopment, genetics, SC and the overall functional outcome of the disorder.

From this general hypothesis, two specific hypotheses have been derived

Hypothesis 1. The ToM deficits associated with SZ will be linked to the genetic vulnerability for the disorder. Then, the analysis of ToM deficits across patients, their first-degree relatives and healthy unrelated subjects will reveal a trait marker pattern based on i) their presence in the initial phases of SZ, and in the patients' relatives, ii) first-degree relatives demonstrating intermediate scores between patients and healthy

controls. Such a pattern will be concordant with a potential role of ToM deficits as an intermediate phenotype.

Hypothesis 2. The analysis of markers of enhanced vulnerability (clinical, neurodevelopmental and genetic) will better characterise the variability in SC measured with the ToM. In this sense, healthy relatives with higher vulnerability for SZ (higher levels of schizotypy, basic symptoms or psychic-like experiences, family history or indicators of neurodevelopmental deviance) will show poorer ToM performance.

3 OBJECTIVES

The general aim of the present thesis, focusing on ToM while considering other vulnerability markers, was to advance the understanding of the heterogeneity of psychosis and its biological underpinnings, potentially offering insights into risk factors, treatment targets, and prognosis indicators. It also aims to improve the identification of high-risk individuals, helping to predict the onset of the disease and design preventive interventions for more vulnerable family members. Based on this, the specific objectives were

Aim 1. To investigate the suitability of ToM, a component of SC, as an endophenotypic marker of SZ by analysing ToM performance in SSD patients, healthy first-degree relatives and healthy controls. In particular, we aimed to compare the patients and controls performance and to investigate the similarity/dissimilarity of relatives' scores in relation to patients and controls.

Aim 2. To characterize patients and healthy individuals' clinical, neurodevelopmental and genetic traits to analyse whether such traits i) are associated with ToM variability, ii) contribute to interpreting the heterogeneity in ToM performance between and within groups. To develop this aim, we set three more specific aims to assess whether ToM is modified by

2.1 Clinical liability to SZ in healthy relatives and controls (schizotypy, basic symptoms and psychotic-like experiences).

2.2 Markers of altered neurodevelopment, such as poorer PA and the severity of NSS

2.3 The genetic load (family history of psychotic spectrum disorder) and/or genetic variability at oxytocin receptor gene (OXTR).

4 MATERIAL AND METHODS, AND RESULTS

Supervisor's report on impact factor

The doctoral thesis "A family-based approach to the vulnerability to psychotic disorders insights from social cognition combined with clinical and neurodevelopmental markers" is based on the original results obtained by Maria Giralt López.

These results and the review have been published in the following international peer reviewed

Journals

Manuscript 1.

Giralt-López, M., Miret, S., Soler, J., Campanera, S., Parellada, M., Fañanás, L., Fatjó-Vilas, M. (2020).

The role of schizotypal traits and the OXTR gene in theory of mind in schizophrenia A family-based study.
European Psychiatry, 2020 Feb 14;63(1)e15.
DOI 10.1192/j.eurpsy.2019.17.

This journal, which is the official journal of the European Psychiatric Association, publishes the latest advances in the field of psychiatry, including new developments in diagnosis and treatment and advances in the biological underpinnings of mental, behavioural and cognitive function in clinical and general population samples.

According to the Journal Citation Reports (Science Edition, 2020), the impact factor of the journal at the time of publication was 5.361 classified in the first quartile (Q1) of the area of psychiatry (ranking 29/159).

Manuscript 2.

Giralt-López, M., Miret, S., Campanera, S., Moreira, M., Sotero-Moreno, A., Krebs, MO., Fañanás, L., & Fatjó-Vilas, M. (2024).

Theory of mind in schizophrenia through a clinical liability approach a sib-pair study.
Frontiers in Psychology, 2024 Dec; *15*, 1391646.
DOI 10.3389/fpsyg.2024.1391646

Frontiers in Psychology is a multidisciplinary journal that publishes advances in psychological research. Topics include, health and clinical psychology, cognitive science, consciousness research, perception science, personality and social psychology.

According to the Journal Citation Reports (Science Edition, 2023), the impact factor of the journal at the time of publication was 2.6 classified in the first quartile (Q2) of the area of psychology (ranking 56/219).

Manuscript 3.

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Theory of Mind Variability in Schizophrenia: A Neurodevelopmental Perspective through Soft Signs and Premorbid Adjustment

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MANUSCRIPT 1

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The role of schizotypal traits and the *OXTR* gene in theory of mind in schizophrenia: A family-based study

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Abstract

Background. There is consistent evidence that theory of mind (ToM) is impaired in schizophrenia (SZ); however, it remains unclear whether such deficits are trait- or state-dependent. We evaluated ToM in patients with schizophrenia spectrum disorders (SSDs), their healthy first-degree relatives, and controls to test its suitability as an endophenotypic marker. We also studied the modifying effect of markers of clinical and genetic liability to SZ (schizotypy and genetic variability in the oxytocin receptor gene: *OXTR*) on ToM in healthy individuals.

Methods. The sample included 38 stable SSD patients, 80 unaffected first-degree relatives, and 81 controls. ToM was assessed using the Hinting Task (HT) and schizotypy via the Schizotypal Personality Questionnaire-Brief (SPQ-B), which generates interpersonal (SPQ-IP), cognitive-perceptual (SPQ-CP), and disorganization (SPQ-D) scores. The polymorphism rs53576 of *OXTR* was genotyped.

Results. Patients presented poorer HT performance than relatives and controls ($p = 0.003$ and $p < 0.001$). High SPQ-IP and SPQ-CP scores correlated with poorer ToM performance in relatives ($p = 0.010$ and $p = 0.030$), but not in controls. *OXTR* was not associated with HT scores, but it showed a modifying effect within controls; high SPQ-CP was related to HT poorer performance conditional to GG genotype ($p = 0.007$).

Conclusions. ToM deficits were present in patients but not in unaffected relatives or controls. However, our data indicate the usefulness of clinical and genetic liability markers to characterize differences in ToM abilities within healthy individuals. Then, the observed link between ToM and SZ liability suggests the putative role of ToM as an endophenotypic marker. Nevertheless, new analyses in larger samples are needed.

Introduction

Schizophrenia (SZ) is a prevalent and severe psychiatric disorder with a complex etiology involving environmental and genetic factors (heritability ≅ 80%). The high degree of disability, prevalence, chronicity, and financial costs place an enormous burden on patients with SZ, their families, and society as a whole. This burden warrants efforts to identify predictors directly applicable to prevention, diagnosis, and therapy. Research into these predictors has produced growing evidence that social cognition deficits are an important predictor of outcome, even more so than neurocognition [1]. Social cognition refers to a wide range of skills that allow people to perceive, interpret and process social stimuli, and that guide social interactions. One of its multiple components is theory of mind (ToM), that is, the ability to infer mental states, such as beliefs, intentions, desires, and emotions, in other people [2].

ToM impairments are being increasingly reported in SZ [3–5]. Although some studies have interpreted ToM deficits as a state marker associated with symptoms in the active phase of the disease [6] or with the severity of negative symptoms [7], the majority have reported ToM impairment to be a trait marker, still present in remission [8,9] and found to be stable after a longitudinal 3-year follow-up design [10]. Several studies also indicate that ToM deficits are present in first-episode psychosis and in high-risk individuals (unmedicated prodromal subjects) [4,11].

Family-based study designs are suitable for establishing whether ToM is a trait feature when the defect is also seen in healthy family members (in a higher prevalence than in controls). Although large samples of well-characterized families are difficult to recruit, these studies have

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the advantage of controlling for certain confounder factors, as family members have a shared genetic background and tend to be more homogeneous with respect to exposure to environmental factors.

Meta-analytic data on social cognition in unaffected relatives of patients with SZ have reported their decreased performance when compared to healthy controls [12] and that the social cognition abilities in relatives lie somewhere between the levels seen in probands and in healthy non-relatives [4].

All of the above, in addition to the fact that some social cognitive impairment are heritable (28–37% for emotion recognition) [13], account for the interest in social cognition as a candidate endophenotype.

To explain the heterogeneous results in the relative group and to detect healthy relatives with a potentially higher genetic loading for SZ, a useful strategy would be to study the association between the endophenotypic marker and other known vulnerability markers in SZ such as schizotypy, family history, and specific genetic factors. Schizotypy is a set of personality traits that encompasses behaviors, cognitions, and emotions, and resembles the signs and symptoms of SZ in the general population. It has been associated with ToM impairment [14,15].

As regards the biological underpinnings of ToM, the most extensively studied neuropeptide to date is oxytocin (OXT). On the one hand, several functional neuroimaging studies have shown that OXT has significant modulatory effects on "social brain," which refers to the brain systems that govern social cognition, social behavior, and affect regulation [16]. For example, acute OXT administration in healthy subjects has been shown to modulate amygdala activity as well as other regions (e.g., prefrontal areas, superior temporal sulcus, and fusiform gyrus) and to enhance the functional connectivity of the amygdala with other brain regions [17,18]. Also, animal models of psychosis have shown that OXT administration reduces dopaminergic hyperactivity in the striatum and nucleus accumbens [19] in a similar manner to antipsychotic medications [20,21].

On the other hand, some studies in healthy subjects have shown the enhancing effect of intranasal OXT administration on social cognition [22] and specifically on ToM [23] and that this is an age-independent effect [24]. A meta-analysis based on neurodevelopmental disorders (SZ and autism spectrum disorders) also reported the age-independent intranasal OXT improvement effect on ToM across these disorders [23]. Accordingly, it has been suggested that both the anatomy and functional physiology of the human nervous system may be shaped by OXT signaling pathways (and their interaction with dopaminergic ones), leading to the idea that their variability may contribute to individual differences in social behavior and cognition by modulating the neural circuits involved in processing socio-affective information [25,26].

Importantly, the behavioral effects of OXT depend on the distribution and expression of its receptor (*OXTR*). OXT receptors are present in numerous limbic and reward-related regions of the human brain; mainly in (but not restricted to) the amygdala, the hippocampus and the nucleus accumbens, and also in cortical regions (such as the anterior cingulate cortex) [27]. The receptor is coded by the *OXTR* gene and its polymorphic variability may contribute to individual differences in social behavior and cognition [25].

General population-based studies have highlighted the influence of this gene on many facets of social cognition including ToM. The most intensively examined single nucleotide polymorphism (SNP) in *OXTR* is rs53576, and a recent meta-analysis showed that individuals with a greater number of G alleles present better empathic ability [28]. Interestingly, Rodrigues et al. [29] linked the lower empathy exhibited by A allele carriers of this SNP with a higher physiological stress reactivity as compared to GG individuals.

Furthermore, *OXTR* polymorphic variants (rs53576 and others) have been associated with the risk for SZ and with other neurodevelopmental disorders (reviewed in [17]).

Neuroimaging studies have provided evidence to support the rs53576 association with brain structure and activity, mainly in healthy subjects. For instance, Tost et al. [30] described that A allele carriers of rs53576 show the lowest amygdala activation and an increased coupling of the hypothalamus and the amygdala when processing social information. Data also suggest that rs53576 influences striatal dopamine availability and modulates the interactions between the oxytocinergic and dopaminergic systems. In a study based on single-photon emission-computed tomography (SPECT), striatal dopamine transporter availability in G carriers (AG/GG) was lower than in the AA group, and G carriers showed a negative correlation between dopamine transporter availability and OXT level [31]. Then, despite rs53576 is a silent polymorphism and that the pathophysiological significance of its association with brain phenotypes remains to be elucidated, accumulated evidence suggest that this SNP could be a marker of the role of the *OXTR* in the neural mechanism that links the differences in the oxytocinergic system to individual differences in social cognition.

In line with the above, our study first aimed to explore ToM in schizophrenia-spectrum disorder (SSD) patients, healthy first-degree relatives, and healthy controls to test whether ToM deficits may be a putative endophenotypic marker of SZ. We hypothesized that ToM deficits would show a trait marker pattern with first-degree relatives showing intermediate scores between patients and healthy controls. Second, to understand the ToM variability, we aimed to investigate whether ToM is modified by: (i) clinical liability to SZ in healthy individuals (schizotypy) and (ii) the OXT receptor gene (*OXTR*). We hypothesized that the polymorphism rs53576 at the *OXTR* would modify the association between schizotypy and ToM, and that the allelic variants would co-segregate with ToM performance within families.

Methods

Sample

The sample comprised 199 individuals: 38 patients with a diagnosis of a SSD, 80 healthy first-degree relatives of these patients (22 fathers, 30 mothers, and 28 siblings), and 81 unrelated controls with no psychiatric history (Table 1). All participants were of Caucasian origin. All were recruited at the Centre de Salut Mental d'Adults de Lleida and evaluated by the same clinician (S.M.), and were assessed when they were clinically stable.

Patients' DSM-IV-TR diagnoses were: SZ ($n = 32$) and psychotic disorder not otherwise specified ($n = 6$). Patients' mean age at onset was 22.12 (SD = 3.83) and the mean duration of illness was 26.40 months (SD = 24.44).

All patients were treated with antipsychotic monotherapy: 94.7% with second-generation antipsychotic (24 risperidone, 5 olanzapine, 3 amisulpride, 2 ziprasidone, 2 clozapine) and 5.3% with haloperidol.

The exclusion criteria for relatives included any psychotic spectrum disorder and any major affective disorder. Controls had no personal or family history of psychiatric disorders or treatment.

Table 1. Sample description and statistical comparisons among patients, first-degree relatives, and controls

	Patients ($n = 38$)	First-degree relatives ($n = 80$)	Controls ($n = 81$)	ANOVA F/χ^2 (p)	Post hoc significant differences
Male (%)	73.68	41.25	45.68	11.54 (0.003)	P > C, P > R
Age at interview	24.92 (3.90)	44.74 (13.43)	34.77 (12.53)	38.46 (<0.001)	R > C > P
Years of education	13.43 (3.12)	11.42 (4.83)	15.23 (3.82)	16.59 (<0.001)	C > R, P > R
IQ	90.03 (15.23)	94.97 (15.26)	107.98 (11.96)	27.67 (<0.001)	C > R, C > P
PANSS positive	10.63 (3.36)	–	–		
PANSS negative	20.37 (4.01)	–	–		
PANSS general	32.58 (7.32)	–	–		
PANSS "lack of insight"	2.50 (0.80)	–	–		

Proportion (%) or mean scores (SD). Only significant differences in post hoc comparisons are given (all p-values were <0.001).
Abbreviations: C, controls; P, patients; R, first-degree relatives.

Other exclusion criteria common to all groups were any major medical illness that could affect brain function, neurological conditions, and history of head trauma with loss of consciousness.

All participants provided written consent after being informed of the study procedures and implications. The study was performed in accordance with the guidelines of the institutions involved and approved by the local research ethics committees. All procedures were carried out in accordance with the latest version of the Declaration of Helsinki.

Assessments

The patients were diagnosed according to DSM-IV-TR criteria and interviewed by means of the Comprehensive Assessment of Symptoms and History [32].

Symptom severity and prevalence of positive or negative symptoms were assessed by means of The Positive and Negative Syndrome Scale (PANSS) [33]. It is a 30-item scale designed to obtain a measure of positive, negative, and general psychopathology symptoms in patients with SZ. The scores for these scales are arrived at by summation of ratings across component items. In addition to these measures, a Composite Scale is scored by subtracting the negative score from the positive score. This yields a bipolar index, which is essentially a difference score reflecting the degree of predominance of one syndrome (positive or negative) in relation to the other.

Based on the previously reported association between insight and social cognition [34], the PANSS item "lack of insight" was also independently used to test such association.

Social cognition, specifically ToM, was assessed by means of the Spanish version of the Hinting Task (HT) [35,36], a test that consists of 10 brief stories involving two people in a conversation. The task is to infer what a person is implying indirectly. In each item, a correct answer gives 2 points (for a total of 20 points). In case of an incorrect answer, an additional hint is given, after which a correct answer gives 1 point.

The task has good validity for patients with SZ and has proven sensitive to ToM difficulties in a number of studies to date [37].

Schizotypy assessment was carried out by means of the Schizotypal Personality Questionnaire-Brief (SPQ-B) [38]. SPQ-B is a 22-item self-report; each item presents a statement or question to the respondent, who then circles "yes" or "no." Each affirmative response counts as one point toward the total score, which ranges from 0 to 22, with higher scores indicating higher levels of self-reported schizotypy. Items were created to measure three schizotypal dimensions: cognitive-perceptual dimension (i.e., ideas of reference or odd beliefs), interpersonal dimension (i.e., suspiciousness, inappropriate, or constricted affect), and disorganization dimension (i.e., odd thinking/speech/behavior/appearance). In order to select a subgroup of carriers of higher-vulnerability SPQ subscales, raw scores were dichotomized using the SPSS visual binning method in each group to define high/low scorers for each SPQ subscale.

Intellectual quotient (IQ) was estimated using the Block Design and Vocabulary or Information WAIS-III subtests.

Family history was assessed with the Family Interview for Genetic Studies. Following broad SZ spectrum criteria [39], families were classified as having a positive family history when patients had at least one first- or second-degree relative with SZ, affective or non-affective psychosis, or schizotypal or paranoid personality disorder.

Molecular analysis

Genomic DNA was extracted from peripheral blood cells or buccal mucosa using standard methods, that is, the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain) or the BuccalAmp DNA Extraction Kit (Epicenter Biotechnologies, Madison, WI).

The *OXTR* gene on chromosome 3p25 spans ~19 kbp and contains four exons and three introns. Genotyping of the intronic SNP rs53576 in the *OXTR* gene was performed using a fluorescence-based allelic discrimination procedure (TaqMan 5′ exonuclease assays; Applied Biosystems). Standard conditions were observed. The genotyping call rate was higher than 86%. After randomly regenotyping 10% of the sample, 100% of the genotyping results were confirmed.

The SNP was in Hardy–Weinberg equilibrium. Due to the low frequency of individuals homozygous for the allele A, the genotype variable was dichotomized in GG versus A allele carriers (AA+AG).

Statistical analyses

All data were processed using SPSS 22.0 software (SPSS IBM, Armonk, NY).

Sociodemographic and clinical data were compared between groups by means of analysis of variance (ANOVA) tests or a chi-squared test when appropriate.

The effect of age, years spent in education, and IQ on HT performance for each group was tested using the Pearson correlation test. Within groups, differences on HT performance according to sex or family history were tested using Student's t-test. From all these analyses, age and sex showed a trend toward or significant effect in relatives ($p = 0.059$ and $p = 0.001$, respectively), so they were added as covariates in the subsequent analyses.

The association between HT performance and clinical characteristics (PANSS) within patients was tested with linear regressions (adjusted for age and sex).

HT performance differences between patients and their first-degree relatives were assessed by means of linear mixed models (LMMs) with total HT as the dependent variable, family member (patients/first-degree relative) as the fixed-effect factor, sex and age as fixed-effect covariates, and family as the random effect (subjects nested within families). When the analyses included nonrelated groups (patients vs. controls and relatives vs. controls), the same models were used for the comparison without including the family random effect.

The association between HT performance and schizotypy within healthy relatives and controls was tested with linear regression (adjusted for age, sex, and family history).

To test the putative effect of the *OXTR* gene as a mediator of the relationship between HT performance and schizotypy, the genotype (GG vs. A allele carriers) was added to these analyses.

In addition, a family-based association test between rs53576 and the HT scores was conducted with PLINK v1.07 by means of the quantitative transmission disequilibrium test (qTDT). Since PLINK does not allow covariates to be included in qTDT analyses, the analyses were performed in two steps. First, lineal regressions between HT scores and each schizotypy factor (covaried by age and sex) were conducted. Second, the residuals from these regressions were used to conduct the qTDT.

Results

Sample characteristics

Tables 1 and 2 show the main sociodemographic and clinical data of the sample. The proportion of males was higher in the patients group (73.7% male) than in the relatives (41.3%) or controls (45.7%) groups. Relatives had spent less time in education than patients or controls. Such a difference was mainly attributable to parents (mean years of education [SD] = 9.46 (4.05) and not to siblings (mean years of education [SD] = 14.93 (4.12)]. IQs were higher in the control sample than in the relatives or patients. A total of 21.1% of patients and 17.5% of relatives had a family history of psychotic disorders.

Within the family group, there were no significant differences in HT or SPQ-B scores between siblings and parents (data not shown); for this reason, they were considered a single group in all analyses.

According to the PANSS Composite Scale, all patients showed more prevalent negative than positive symptoms. When we tested whether ToM performance in patients is modulated by clinical severity or insight as measured with PANSS, no association was detected. Thus, these clinical variables were not considered in the following analyses.

Analysis of ToM performance in SSD patients relative to their first-degree relatives and healthy individuals

A comparison of HT performance between patients and first-degree relatives and between patients and controls showed significant group effects ($F = 8.96$, $p = 0.003$ and $F = 17.64$, $p < 0.001$, respectively). Patients presented lower scores than relatives (estimated mean difference = −2.27) and controls (estimated mean difference = −2.44). These results remained significant after including IQ as a covariate ($p = 0.007$ and $p = 0.025$, respectively). The scores of relatives and controls did not differ significantly.

Association between HT performance and schizotypy in healthy relatives and controls

We tested whether ToM performance in healthy individuals is modulated by schizotypy, a marker of liability to SSD.

A linear regression analysis (adjusted for age, sex, and family history) showed that being a high scorer for Schizotypal Personality Questionnaire-interpersonal (SPQ-IP; $\beta = -0.277$, $p = 0.010$, $R_{adj}^2 = 22.2\%$) and Schizotypal Personality Questionnaire cognitive-perceptual (SPQ-CP; $\beta = -0.243$, $p = 0.030$, $R_{adj}^2 = 20\%$) was related to poorer ToM performance in relatives. Results for SPQ-IP remained significant when the IQ was included as a covariate ($p = 0.025$). No such relationship was observed in the controls.

Association between OXTR gene (rs53576) and ToM performance

For the *OXTR* SNP, the genotype distribution is shown in Table 3.

The qTDT analysis showed no association between the *OXTR* gene and HT performance within families.

The rs53576 (GG vs. A allele carriers) did not show a significant association with HT performance but showed a modifying effect on the relationship between schizotypy and HT in controls. When including the *OXTR* variability in the model (see "Association between Hinting Task performance and schizotypy in healthy relatives and controls" section) being a high scorer for SPQ-CP turned to be related to poorer ToM performance in controls ($\beta = -0.307$, $p = 0.030$, $R_{adj}^2 = 13.8\%$). Accordingly, within GG subjects (17 SPQ-CP low scorers and 12 high scorers), the effect of SPQ-CP on HT performance was statistically significant ($\beta = -0.468$, $p = 0.007$, $R_{adj}^2 = 30.1\%$), while it was not within A carriers.

Table 2. ToM and schizotypy (SPQ-B) scores in patients (P), their first-degree relatives (R), and controls (C)

HT[a]	Patients		First-degree relatives		Controls	
	15.74 (4.07)		17.88 (2.16)		18.46 (1.64)	
	Low scorers	High scorers	Low scorers	High scorers	Low scorers	High scorers
SPQ-CP[b]	0.91 (0.81)	4.15 (1.41)	0 (0)	2.00 (1.11)	0 (0)	2.00 (1.11)
SPQ-IP[b]	2.38 (1.50)	6.55 (1.13)	1.60 (1.01)	4.96 (1.19)	1.05 (0.83)	4.03 (1.15)
SPQ-D[b]	0 (0)	2.24 (1.48)	0 (0)	1.63 (0.92)	0 (0)	1.39 (0.72)

Schizotypy scores for each dimension were dichotomized in low and high scorers. Mean scores (SD).
Abbreviations: HT, Hinting Task; SPQ-CP, Schizotypal Personality Questionnaire-cognitive-perceptual; SPQ-D, Schizotypal Personality Questionnaire-disorganization; SPQ-IP, Schizotypal Personality Questionnaire-interpersonal.
[a]Available for 39 patients, 82 relatives, and 81 controls.
[b]Available for 36 patients, 76 relatives, and 68 controls.

Table 3. Genotype frequencies for the single nucleotide polymorphism rs53576 at the *OXTR* gene and HT mean scores within each group

	Patients ($n=37$)			Relatives ($n=76$)			Controls ($n=56$)		
	GG	GA	AA	GG	GA	AA	GG	GA	AA
Genotype frequencies	21 (56.8%)	15 (40.5%)	1 (2.7%)	43 (56.6%)	31 (40.8%)	2 (2.6%)	31 (55.4%)	21 (37.5%)	4 (7.1%)
HT mean score (SD)	15.24 (4.83)	16.20 (3.03)	16.00	17.77 (2.40)	17.97 (1.96)	19.50 (0.71)	18.58 (1.61)	18.38 (1.80)	18.00 (1.63)

In relatives, the association between SPQ and HT remained significant while the genotype did not show an effect per se.

Discussion

In our study, SZ patients showed impairments in inferring the mental states of others (i.e., intentions) via indirect speech such as hints, measured with the HT, in comparison to controls. This result is consistent with previous studies that have used the same task [40–42] and others that have used different tools for assessing ToM [3,5,8,11].

To further investigate the properties of ToM as an endophenotypic marker, we looked at how healthy relatives behave in relation to patients and controls. In our study, the mean score of healthy relatives in the HT fell somewhere between the scores of the other two groups, but the differences between relatives and controls were not significant. In line with our findings, other studies that have assessed ToM aspects have also observed no differences in relatives compared to controls [43,44]. In contrast, other studies have suggested a genetic liability effect with relatives demonstrating impairments in advanced ToM ability [4,45,46]. A recent study that included several different measurements reported mixed results across tasks [9].

This heterogeneity of results could be explained by different factors including the sample sizes of studies and the different tasks used to evaluate ToM.

First-order false belief or deception tasks test the ability to understand that someone can have an inaccurate mental representation of events based on incomplete knowledge. In a second-order false belief or deception task, participants have to infer the (false) beliefs of one character about the (false) beliefs of a second character [47,48].

More complex ToM includes the comprehension of indirect speech, such as irony, metaphors, faux pas, and hints, assessed using the Strange Stories Task [49] or the HT. This is based on the notion that understanding indirect speech requires an understanding of another person's mental state.

It has been reported that ToM abilities might decline at different times over the course of SZ. This is consistent with Brüne's developmental model, which posits that ToM abilities decline in the reverse order of acquisition [5]. Therefore, deterioration is first detected in complex ToM tasks, while the decline in first-order ToM tasks is observed later. This theory is consistent with studies that have observed a deficit in second-order mentalizing questions, but not in first-order inference items, in patients experiencing a first episode of psychosis [50]. Thus, it can be deduced that tasks assessing higher-order forms of ToM could be more sensitive and especially appropriate for detecting ToM impairment in nonclinical samples such as healthy relatives. Also, there could be other factors intrinsic to the task that conditions its sensitivity to changes in social cognition abilities performance. For instance, Grainger et al. [24] detected that intranasal OXT administration improved ToM when the task had minimal contextual information, but not when the task had enriched contextual information.

Another element to consider when explaining the heterogeneity of ToM capacities in the healthy relatives' group is the variability in clinically defined liability. As regards to the selection of schizotypy, it is a clinical liability marker that has shown to be useful in the identification of families with a higher genetic loading for SZ [51]. In this respect, our study shows that high levels of positive and negative schizotypy (cognitive-perceptual and interpersonal dimensions) are related to poorer ToM performance in relatives but not in controls. Within the general population, ToM has been extensively studied in relation to schizotypy. Several studies have detected ToM impairments associated with high levels of total schizotypy [14,15]. In line with our results, other studies have failed to identify this association in controls [52,53], but some have reported that poorer social cognition is a function of specific schizotypy traits such as positive schizotypy [54,55].

Overall, the mixed findings associated with schizotypy and ToM performance in healthy controls may be due to the fact that individuals with positive and negative schizotypy display poor ToM performances for different reasons. Frith [56] asserted that individuals with positive symptoms of SZ show deficits in ToM tasks due to inaccurate representations of the intentions of others, whereas individuals with negative symptoms of SZ display ToM deficits due to a lack of experience of or interest in social interactions. It may also be that different aspects of social cognition are differentially affected by positive and negative schizotypy.

Another fact that could explain the heterogeneity is the different ways of quantifying schizotypy levels. Some studies have used a continuous variable, while others have used median splits or the top and bottom 5 or 10% in an attempt to emphasize the qualitative differences between groups. We were not able to use this method due to the limited size of our sample.

In contrast to the results for the control group, data from the subgroup of healthy relatives of SZ-spectrum patients suggest that high levels of cognitive-perceptual and interpersonal dimensions are related to poorer ToM performance. To the best of our knowledge, only three studies have tested this association in a sample of healthy relatives of SZ patients. Two found no significant correlations between ToM and schizotypy scores in the relative sample [57,58]. However, SPQ mean scores and ranges in these samples were somewhat low.

Irani et al. [59] used the Revised Eyes Test and reported a trend whereby relatives were more accurate than patients and less accurate than controls in the ToM task, although these differences only became significant when the SPQ social-interpersonal subscale scores were included. This is consistent with the hypothesis that these social-interpersonal features are the best differentiators between relatives and controls, and might be the most important schizotypal traits associated with genetic vulnerability for SZ [60]. Despite the fact that the relatives in our sample showed higher schizotypy levels than controls on the social-interpersonal subscale, differences were not significant.

In our study, schizotypy symptoms in healthy first-degree relatives seem to put individuals at an increased risk of these ToM deficits, thus suggesting that some social cognition functions might be sensitive to subthreshold psychotic symptoms. These results are similar to those reported by Johnson et al. [61], in which the relationship between schizotypy and other measures of cognition was mediated by SZ genetic risk.

Finally, regarding the role of the *OXTR* gene in ToM, our study did not report a family-based association. However, despite not having an effect per se on HT, the genotype showed a modifying effect of the association between schizotypy and HT in controls. Then, while the genotype did not change the significant relationship observed between schizotypy and HT within relatives, in controls, this association became significant when the polymorphism was included. This suggests that in controls (with less liability load than relatives) high schizotypy would be related to a poorer performance on ToM conditional to GG genotype. This result is consistent with other studies that observed the role of this polymorphism on different social cognition domains in healthy subjects [25–27], nonetheless the comparison is not straightforward as previous studies were based on different social cognition dimensions or scales and none has analyzed the role of *OXTR* gene jointly with schizotypy. In all, these results should be treated with caution, as the sample size limits the statistical power of our study and replication is needed in larger samples in order to confirm such effect.

Given the well-documented role of OXT in mammalian social behavior, and the previously mentioned effects of OXT administration on social abilities in humans, it is not surprising that *OXTR* gene variability has been studied with a range of social phenotypes [62]. In this regard, some studies have provided evidence that *OXTR* polymorphisms are associated with different dimensions of social cognition in healthy individuals [63,64] and also with the risk for SZ and poorer performance in ToM measurements in SZ, while others have failed to find such an association [17,65,66].

Focusing on the family-based approach, despite the design being particularly robust for controlling widespread confounds such as admixture and stratification [67], we are aware of only one previous study with a similar approach as ours. In that study, Wade et al. [67] reported the association of another polymorphism at intron 3 of *OXTR* (rs11131149) with social cognition in 18 months old children. Interestingly, the same authors also reported the interaction between *OXTR* and parenting behavior on 4 years old children's ToM [68], suggesting a nature–nurture interaction with regard to ToM in early development. Therefore, our results add to the variability and discrepancies observed in the limited body of literature in relation to SZ, which are likely related to several factors such as the diversity of genotypes across studies, the variation in participants' ancestry and limited sample sizes. Also, for the understanding of heterogeneity across studies, our data and other family-based studies indicate the need of considering environmental and developmental factors.

To interpret our data, it is important to consider the strengths and limitations of the study. The strengths include the use of a family-based design with a control group of healthy subjects and the availability of social cognition measurements and clinical and genetic liability markers. In addition, only a few studies have explored the association between social cognition and schizotypy, and none of these has incorporated data on genetic liability (family history and genetic variability). The design of our study and the phenotypic variability therefore contributes to the state–trait debate and helps shed light on the heterogeneity of the complex traits related to SZ liability.

On the other hand, even though the sample size is comparable to previous studies and that one of the main disadvantages of family-based designs is the challenge associated with recruiting large samples of well-characterized families, the size of our sample represents the main limitation of the study. In line with this, the family-based design is intrinsically associated with differences in sample sizes of the subgroups (more relatives than patients), which could represent a bias when conducting subgroups comparison analyses. Moreover, although ToM is an important area of social cognition, other areas, such as emotion processing and social knowledge, were not studied. Also, according to some recent data showing that antipsychotic treatment can improve social cognition performance [69,70], the non-inclusion of the treatment data in our analyses could limit the interpretation of our results. Then, if we had excluded the treatment effect, the patients' performance on ToM could be potentially worse and could show larger differences with relatives and healthy controls. Finally, although one of the most studied polymorphisms in the *OXTR* gene is rs53576, the analysis of a single SNP does not represent the whole variability gamut of *OXTR*. In addition, like many human competencies, ToM is a complex trait influenced by multiple genes, future research should screen the polymorphic variability along the *OXTR* gene and other OXT signaling pathway-related genes.

In conclusion, our study initially shows that ToM deficits are greater in patients with SSDs as compared to healthy relatives and controls; however, when clinical and genetic liability markers such as schizotypy and *OXTR* gene in healthy subjects are considered, our data indicate the putative role of ToM as a trait marker. Our study does not report the role of the polymorphism rs53576 at the *OXTR* gene on ToM abilities within families; however, new studies in larger family-based samples are needed.

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Theory of mind in schizophrenia through a clinical liability approach: a sib-pair study

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Background: Consistent findings indicate that Theory of Mind (ToM) is impaired in schizophrenia (SZ). To investigate whether such deficits are trait- or state-dependent, we investigated if ToM is modified by clinical liability markers (such as basic symptoms and psychotic-like experiences), focusing on the analysis of unaffected siblings of individuals diagnosed with SZ.

Methods: The study included a total of 65 participants: 38 patients diagnosed with a schizophrenia-spectrum disorder and 27 healthy siblings. ToM was assessed using the Hinting Task (HT), Basic symptoms with The Frankfurt Complaint Questionnaire (FCQ), Psychotic-like-experiences with the Community Assessment of Psychic Experiences (CAPE) and Family history with the Family Interview for Genetic Studies.

Results: First, a comparison of HT performance between patients and siblings (linear mixed model adjusted for age, sex and Intelligence Quotient (IQ)) showed that patients presented lower scores than siblings (p = 0.022). These differences did not remain significant after adjusting for clinical vulnerability markers. Second, within siblings, linear regression analyses (adjusted for age, sex, IQ and family history) showed that higher FCQ Depressiveness and CAPE negative scores were related to poorer ToM performance (p = 0.007 and p = 0.032, respectively).

Conclusion: Our findings suggest that clinical liability markers are valuable for delineating variations in ToM capabilities within healthy individuals. Moreover, our results indicate that ToM deficits are not solely linked to SZ but also extend to its clinical vulnerability, suggesting that ToM could serve as an endophenotypic marker. This implies that ToM could help distinguish particularly susceptible individuals from a population at risk, such as those with a genetic predisposition (siblings).

KEYWORDS

schizophrenia, theory of mind, basic symptoms, psychotic-like experiences, unaffected siblings, endophenotype

1 Introduction

Social cognition encompasses a diverse range of skills that facilitate the perception, interpretation and processing of social stimuli and enable individuals to interact with one another and function in society (Frith and Frith, 2007). Growing evidence indicates that schizophrenia (SZ) is associated with impaired social cognition, emerging as a predictor of the disorder outcome, even more than neurocognition (Fett et al., 2011; Lewandowski et al., 2020).

The neurodevelopmental model of SZ posits that the illness results from deviations of neurodevelopmental processes that commence years before symptom onset due to a complex interplay of numerous susceptibility genes and environmental factors (Birnbaum and Weinberger, 2017). While the cerebral organization of social processes remains incompletely understood, the maturation of social cognition during childhood and adolescence suggests that proper brain development may be pivotal in its acquisition and performance. These considerations jointly point towards the presence of neurodevelopmental disturbances that could influence both the risk of developing a psychotic disorder and the social cognition deficits associated with it. In this regard, some structures and neural networks implicated in SZ are also crucial for the development of social cognition skills, such as the prefrontal cortex (Weinberger, 2002; Teffer and Semendeferi, 2012; Green et al., 2015) or the default mode network (Salgado-Pineda et al., 2011; Schurz et al., 2014; Soares et al., 2023), which adds evidence to the potential overlap between the disorder and the neurobiological substrate of the social brain.

Theory of Mind (ToM) is one of the various domains of social cognition, including the ability to deduce the mental states of others, such as their beliefs, intentions, desires, and emotions (Frith and Frith, 1999). ToM impairments are reported in SZ (Brune, 2005; Bora and Pantelis, 2013; Chung et al., 2014; Mondragón-Maya et al., 2017; Giralt-López et al., 2020). Some investigations interpreted such deficits as a state marker (linked to symptomatology) (Mazza et al., 2012; Balogh et al., 2014). Conversely, other research characterizes ToM impairments as a trait marker, pointing to data indicating that it is not modulated by clinical severity or insight (Sprong et al., 2007; Ay et al., 2016; Giralt-López et al., 2020), or to the stability observed after a longitudinal three-year follow-up design (Ayesa-Arriola et al., 2014).

In line with the view as a trait marker, several studies also indicate that ToM deficits are present in first-episode psychosis (FEP) and high-risk individuals (unmedicated prodromal subjects) (Bora and Pantelis, 2013; Healey et al., 2016). Based on these data, the aforementioned deficits in ToM have been proposed as a potential endophenotype for SZ-spectrum disorders. On this subject, an essential aspect to investigate the properties of ToM as an intermediate phenotype is to examine the performance of healthy relatives compared to both patients and control groups. Meta-analytical findings on social cognition among unaffected relatives of individuals with SZ have revealed their poorer performance compared to that of healthy controls (Lavoie et al., 2013), and that the level of impairment in relatives lies somewhere between the levels seen in patients and controls (Bora and Pantelis, 2013). However, other more recent studies show heterogeneity, and some studies fail to demonstrate this intermediate position of the relatives' group (Fett and Maat, 2013; Cassetta and Goghari, 2014; Ho et al., 2015; Ay et al., 2016; Raju et al., 2019; Giralt-López et al., 2020; Abreu-Fernández et al., 2023). A helpful strategy to explain the heterogeneous results in the relatives' group and detect healthy relatives with a potentially higher load for SZ is to narrow the cohort-related confounders between patients and relatives by focusing on the sib-pairs. This way, different studies consistently report that different facets of social cognition performance in the sibling group are significantly lower than those of the control group (Ho et al., 2015; Fusar-Poli et al., 2022; Altuntaş et al., 2023).

Another strategy is to study the association between ToM and other known vulnerability markers in SZ. In this respect, we previously showed that high levels of positive and negative schizotypy are related to poorer ToM performance in relatives but not in controls (Giralt-López et al., 2020), suggesting the association of schizotypal traits with an increased risk of ToM deficits. However, previous research aiming to link social cognitive abilities with markers of familial and clinical risk for SZ, such as schizotypy and high-risk populations, has yielded inconclusive findings. These inconsistencies could be attributed to variations in the specific dimensions of social cognition assessed, as well as the diverse tasks utilized to measure the multifaceted construct of ToM. Specifically, evidence shows an association between the positive dimension of schizotypy and deficits in ToM as assessed by the Hinting Task (HT) (Gooding and Pflum, 2011). Nonetheless, no such relationship has been observed between any dimension of schizotypy and ToM when using alternative tests such as the Reading the Mind in the Eyes Test or the ToM Picture Stories Task (Gooding and Pflum, 2011; Bedwell et al., 2014; Kong et al., 2021). Moreover, at-risk populations, especially those at clinical high risk, show altered, both increased and decreased, functional activation in a range of cortical and subcortical regions during social cognition tasks, while results in familial risk populations have not driven direct conclusions (Kozhuharova et al., 2020).

Following a fully dimensional model, beyond schizotypy, other clinical markers of vulnerability have been described for SZ. For example, Basic Symptoms (BS) and Psychotic-Like Experiences (PLEs) constitute the earliest subsyndromal symptoms or cognitive impairments experienced by the patient and they are considered the most immediate symptomatic expression of the neurobiological substrate of the disease (Huber and Gross, 1989). They can be assessed concretely and consistently, providing a precise meaning of what the subject is experiencing subjectively.

The BS consist of subtle, subclinical complaints principally of volition, affect, thinking and language (speech), (body)perception, memory, motor action, central vegetative functions, control of automatic cognitive processes, and stress tolerance and represent the earliest symptoms that the patient experiences subjectively and can appear a long time before the outbreak of SZ (Huber and Gross, 1989). In this regard, a meta-analysis showed the role of BS as a risk predictor by concluding that the mean risk of transition to psychosis established from BS criteria is 48.5% (Fusar-Poli et al., 2012). Moreover, an increasing gradient of some BS was observed from non-clinical to SZ-spectrum individuals, with unaffected siblings in the intermediate position (Maggini and Raballo, 2004). Also, the offspring of parents with mood and psychotic disorders had significantly higher BS scores than control offspring (Zwicker et al., 2019), placing BS as a marker of familial risk of psychopathology. However, to our knowledge, no relationship between BS and social cognition has been established except for an association with emotion recognition processing speed in high-risk individuals (Glenthøj et al., 2020).

PLEs are subtle, subclinical hallucinations and delusions, which present in the general population with a prevalence around 6% (Linscott and van Os, 2013; McGrath et al., 2015). An extensive study reported a shared genetic liability between psychotic experiences and several

psychiatric disorders (Legge et al., 2019) and another has related their presence to an increase in the risk for transition to psychotic and (to a lesser degree) non-psychotic disorder at an annual rate of 0.6% (Kaymaz et al., 2012). Some studies have shown that non-affected siblings of patients with SZ present higher PLEs scores than controls (Johnstone et al., 2000; Fekih-Romdhane et al., 2020), but another study found negative results (Landin-Romero et al., 2016). To our knowledge, only two studies have investigated the association between social cognition and the presence of PLEs in the general population, showing its association with poorer Facial Emotion Recognition and ToM (Barragan et al., 2011; Roddy et al., 2012).

Another complementary approach pursuing the understanding of the association of ToM with vulnerability to psychosis is to examine whether ToM is influenced by the genetic burden of the disease. In this sense, family history of SZ can be considered a proxy for the genetic liability background. First, because research has consistently shown that individuals with a relative with SZ have a higher risk of developing the disorder themselves compared to the general population and that it is related to the degree of relatedness (i.e., the amount of genetic variability shared with the affected relative/s) (Gottesman, 1991; Lo et al., 2020). Molecular studies have provided convergent results by reporting that first-degree relatives of patients with psychotic disorder have higher levels of polygenic risk scores (PRS) for SZ, and showing that such genetic-based risk is associated with subthreshold psychosis phenotypes (Lin et al., 2023). Therefore, while PRS of SZ mediates the family history of SZ/psychoses (Agerbo et al., 2015), it is not a necessary or sufficient factor for developing the disorder (Mars et al., 2022), due to its multifactorial and complex patterns of inheritance.

Aims of the study

We aimed to expand our comprehension of ToM variability and its potential role as a trait marker by focusing on the unaffected siblings of individuals diagnosed with psychosis. The use of a sib-pair design is particularly relevant due to its recognized power to control for cohort and familial characteristics (Begg and Parides, 2003; Susser et al., 2010), and because healthy siblings are genetically related to affected individuals but are not exposed to potential confounders such as the pharmacological treatment (Lange et al., 2008; Glahn et al., 2019).

First, we examined differences in ToM between patients and their healthy siblings, while also exploring whether these differences persisted after considering clinical and familial risk markers for psychosis. Such clinical risk was assessed through BS and PLEs, which have proven to be effective indicators for identifying healthy individuals at risk of mental health issues compared to the broader general population (Andreou et al., 2023). Second, we explored if the ToM performance of siblings could be better understood by considering these clinical vulnerability markers and the genetic load based on the family history of psychotic disorders.

2 Materials and methods

2.1 Sample

The sample included 65 participants: 38 patients diagnosed with SZ-spectrum disorder (SSD) and 27 healthy siblings from these patients. All participants were of European origin. The sample was recruited at the Outpatient Mental Health Clinic of the Hospital Santa Maria de Lleida and assessed by the same clinician (SM). This belongs to a family-based sample already described in Giralt-López et al. (2020). In this study, with the intention of reducing the heterogeneity of the group of healthy relatives and some confounding factors (such as age or others related to cohort-effects), we have focused on studying new risk markers in the group of unaffected siblings.

The patients' siblings underwent a clinical interview, and those without current or lifetime psychotic spectrum or affective disorder diagnoses were included in the study.

Both siblings and patients fulfilled the following exclusion criteria: (i) intellectual disability or any major medical illness that could affect brain function, (ii) neurological conditions and history of head trauma with loss of consciousness.

2.2 Assessments

The patients were diagnosed according to DSM-IV-TR criteria and interviewed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). It consists of almost 1000 items, most of them with detailed clinical definitions, which are scored with a Likert-type scale with values from 0 to 5. The CASH facilitates the possibility of adopting a dimensional perspective (mania, depression, catatonia, disorganization, psychosis and negative dimensions).

Symptom severity and prevalence of positive or negative symptoms were assessed by means of The Positive and Negative Syndrome Scale (PANSS) (Peralta Martín and Cuesta Zorita, 1994). It is a 30-item scale designed to measure positive, negative and general psychopathology symptoms in patients with SZ. The scores for these scales are arrived at by summation of ratings across component items. Also, a Composite Scale is scored by subtracting the negative score from the positive score. This yields a bipolar index, which is essentially a difference score reflecting the degree of predominance of one syndrome (positive or negative) in relation to the other.

Siblings were evaluated through an interview following the Structured Clinical Interview for DSM Disorders (SCID) (First and Gibbon, 2004), with the aim of ruling out the presence of a psychotic spectrum disorder. SCID is a structured interview guide for making diagnoses according to the diagnostic criteria published in the Diagnostic and Statistical Manual for Mental Disorders (DSM) of the American Psychiatric Association.

Social cognition, specifically ToM, was assessed through the Spanish version of the Hinting Task (HT) (Corcoran et al., 1995; Gil et al., 2012), a test that consists of 10 brief stories involving two people in a conversation. The task consists of inferring what a person is implying indirectly. In each item, a correct answer gives two points (for a total of 20 points). In case of an incorrect answer, an additional hint is given, after which a correct answer gives one point. The task has good validity and has proven sensitive to ToM difficulties in a number of studies to date (Corcoran and Frith, 2003).

BS were assessed by means of the Spanish version of the Frankfurt Complaint Questionnaire (FCQ), named Inventario Psicopatológico de Frankfurt, by Peralta and Cuesta (2003). The FCQ contains 98 statements describing particular complaints, each rated from 0 to 4

(never, sometimes, usually, always), indicating either the presence or absence and frequency of the complaint.

For the analyses, the structure of factors was used. In accordance with the original validation, a solution of 4 main dimensional factors was obtained (Süllwold, 1986). F1 Central cognitive disorders (11 items), F2 Perception and motor skills (15 items), F3 Depressiveness (14 items), F4 Internal and external overstimulation (9 items). This four-factorial model has provided the best fit for the 98-items version, in both first-episode of psychosis and at-risk mental state populations. The psychometric properties of these factors have been reviewed by other authors (Cuesta et al., 1996; Jimeno Bulnes et al., 1996).

Also, most of the factorial aggrupations of the FCQ have demonstrated good or excellent reliability (Uttinger et al., 2018). Interestingly, FCQ has also shown a moderate-strong long-term test–retest reliability (Loas et al., 2011).

PLEs were assessed by means of the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002). This self-report questionnaire measures the lifetime prevalence of PLEs on a frequency scale ranging from 'never' to 'nearly always'. The positive dimension of the CAPE includes items mainly referring to subclinical expressions of positive psychotic symptoms such as hallucinations and delusions. Similarly, the negative dimension of CAPE includes items assessing subclinical expressions of negative psychotic symptoms such as alogia, avolition, anhedonia and lack of interest in social relationships. The instrument provides a total continuous score per dimension ranging from 20 to 80 in the positive dimension and 14 to 56 in the negative dimension. Self-reported dimensions of psychotic experiences assessed by means of the CAPE have shown to be stable, reliable and valid (Konings et al., 2006). Cronbach's alpha reported for CAPE has a meta-analytic mean of 0.91 (SD = 0.05), while alpha values of CAPE positive and negative factors (n = 9) had a mean of 0.84 (SD = 0.1) and 0.81 (SD = 0.10) respectively (Mark and Toulopoulou, 2016). Furthermore, this instrument has been validated in the Spanish population (Ros-Morente et al., 2011).

Nor FCQ nor CAPE contain any item assessing the social cognition domain; thus, there are no intersections.

The Intelligence Quotient (IQ) of all participants was estimated using the Block Design and Vocabulary or Information WAIS-III subtests (Wechsler, 1997).

Family history was assessed with the Family Interview for Genetic Studies (FIGS). Following broad SZ spectrum criteria (Kendler et al., 1995), families were classified by history with binary coding, as having a positive family history when patients had at least one first- or second-degree relative with SZ, affective or non-affective psychosis, or schizotypal or paranoid personality disorder. Thus, family history values are shared by all family members.

2.3 Statistical analyses

All data were processed using IBM SPSS Statistics Version 25.0 (SPSS IBM, Armonk, NY: IBM Corp).

Sociodemographic and clinical data were compared between groups using Student's t-test for independent samples or chi-squared tests when appropriate.

HT performance differences between patients and siblings were assessed by means of linear mixed models (LMM), with total HT as the dependent variable, family member (patients / sibling) as the fixed-effect factor, sex, age and IQ as fixed-effect covariates and family as a random effect factor (subjects nested within families). In the next step of the same model, clinical vulnerability markers (BS and PLEs) were added as fixed-effect covariates.

Within patients, the relationship between HT performance and clinical characteristics (PANSS and CASH) was tested with linear regressions (adjusted for age and sex).

Within siblings, the association of HT performance with BS and PLEs was tested with a stepwise linear regression model, including in the first step age, sex and IQ; adding in the second step the family history, and finally adding each of the clinical vulnerability factors.

3 Results

3.1 Sample characteristics

Patients were assessed when clinically stable and their DSM-IV-TR diagnoses were: schizophrenia (n = 32) and psychotic disorder not otherwise specified (n = 6). Patients' mean age at onset was 22.12 (SD = 3.83), and the mean duration of illness was 26.40 months (SD = 24.44). All were treated with antipsychotic monotherapy: 94.7%, with second-generation antipsychotic (24 risperidone, 5 olanzapine, 3 amisulpride, 2 ziprasidone, 2 clozapine) and 5.3% with haloperidol.

None of the siblings presented a psychotic spectrum disorder, which was ruled out by means of a structured clinical interview.

The sample's sociodemographic and clinical features are presented in Tables 1, 2. Compared to the patients, the siblings had a larger percentage of women and were older but did not show differences in years of education and IQ. As per the PANSS Composite Scale, negative symptoms were more prevalent than positive symptoms in all patients. No significant associations were found between ToM performance and PANSS or CASH scores (data not shown).

TABLE 1 Sample description and statistical comparisons between patients and siblings.

	Patients (n = 38)	Siblings (n = 27)	t/ χ^2 (p-value)
Male (%)	73.68	40.7	7.14 (0.008)
Age at interview	24.92 (3.90)	28.78 (5.12)	−3.45(0.001)
Years of education	13.43 (3.12)	14.74 (4.07)	n.s.
IQ	90.03 (15.23)	93.19 (15.58)	n.s
PANSS positive	10.63 (3.36)	–	
PANSS negative	20.37 (4.01)	–	
PANSS general	32.58 (7.32)	–	
CASH mania dimension	0.79 (0.27)	–	
CASH depression dimension	1.45 (0.76)	–	
CASH catatonia dimension	0.26 (0.50)	–	
CASH psychosis dimension	0.41 (0.64)	–	
CASH disorganization dimension	0.50 (0.76)	–	
CASH negative dimension	2.01 (0.67)	–	

Proportion (%) or mean scores (standard deviation). IQ Intelligence quotient, PANSS Positive and Negative Syndrome Scale, CASH Comprehensive Assessment of Symptoms and History (Present State).

3.2 Differences in ToM performance between individuals with psychosis and healthy siblings

A comparison of HT performance between patients and siblings (adjusted by age, sex and IQ), showed that patients presented significantly lower scores than siblings ($F = 5.56$, $p = 0.022$; estimated mean difference = −2.20). None of the covariables showed a significant effect (Supplementary Table S1).

After adjusting the previous model for the clinical vulnerability markers (BS and PLEs) the differences in HT performance between patients and siblings became not significant, indicating that the initially observed HT differences between them were attributable to the clinical vulnerability (Supplementary Tables S2–S7).

TABLE 2 Theory of Mind (HT: Hinting Task), Basic Symptoms (FCQ: The Frankfurt Complaint Questionnaire) and Psychotic-Like Experiences scores (CAPE: Community Assessment of Psychic Experiences) in patients and healthy siblings.

	Patients	Healthy siblings	t (*p*-value)
Hinting Task[a]	15.74 (4.07)	18.37 (1.47)	−4.01 (<0.001)
FCQ Central cognitive disorders[b]	9.22 (14.62)	0.83 (1.27)	3.47 (0.001)
FCQ Perception and motor skills[b]	5.84 (10.76)	0.58 (0.78)	2.96 (0.005)
FCQ Depressiveness[b]	14.19 (16.22)	2.67 (2.31)	4.23 (<0.001)
FCQ Internal and external overstimulation[b]	8.19 (9.48)	1.25 (1.48)	4.37 (<0.001)
CAPE positive[b]	25.70 (9.43)	20.71 (1.60)	3.15 (0.003)
CAPE negative[b]	25.11 (7.19)	20.63 (3.46)	3.25 (0.002)

[a]Available for 38 patients, 27 siblings.
[b]Available for 37 patients, 24 siblings.
Mean scores (standard deviation).

3.3 Association between clinical liability markers and hinting task performance in healthy siblings

3.3.1 Association of basic symptoms with hinting task performance

First, sex, age and IQ showed non-significant effects on HT performance (assessed with a linear regression model).

As a second step, when the family history (a proxy of the genetic load) was added to the model, it showed a significant effect ($\beta = -0.584$, $p = 0.003$, $R_{adj}^2 = 34.8\%$). This indicates an inverse relationship between genetic load and ToM abilities. In this model, age and IQ become significant ($p < 0.05$), but sex did not ($p = 0.08$).

As a third step, we included the FCQ Factors (Table 3). Higher scores on the Depressiveness factor (F3) were associated with worse HT performance ($\beta = -0.444$, $p = 0.007$). This model explains 54.4% of the HT variance (R_{adj}^2), which represents a significant increase in the explained variance as compared with the previous model ($\Delta R^2 = 18.2\%$).

No relationship was observed with the other FCQ factors (Supplementary Tables S8–S10).

3.3.2 Association of psychotic-like experiences with hinting task performance

Following the same approach as in the previous section, we assessed the role of the family history and the clinical liability measured with the CAPE (Table 4). We observed that higher scores on the CAPE Negative dimension were associated with worse HT performance ($\beta = -0.357$, $p = 0.032$). This model explains 47% of the HT variance (R_{adj}^2), which represents a significant increase in the explained variance as compared with the previous model ($\Delta R^2 = 12.4\%$). No relationship was observed with CAPE positive scores (Supplementary Table S11).

4 Discussion

This study aimed to improve the understanding of the ToM variability by investigating whether ToM is influenced by genetic and clinical liability markers of SZ in healthy relatives (siblings).

Previous research findings regarding social cognition in unaffected relatives of individuals with SZ have yielded inconclusive results, potentially attributed to several factors such as varying sample sizes, diverse tasks used for ToM assessment, and the characteristics of the comparison group comprising relatives. While most studies have examined first-degree relatives, limited research has specifically targeted the siblings. Therefore, the current study, based on a sib-pair approach, enriches the findings regarding the differences detected in ToM between patients and relatives reported in our previous study (Giralt-López et al., 2020), thanks to: (i) controlling for relevant cohort-effects related to ToM competence such as age and educational level (Moran et al., 2012; Cassidy et al., 2020; Velthorst et al., 2023), (ii) refining the characterization of the ToM heterogeneity by assessing the role of both clinical liability and genetic load markers on the HT performance.

When we analysed whether HT performance differed between unaffected and affected siblings, we first observed that the healthy ones presented higher scores than patients. This is in line with previous meta-analytic data, reporting that the social cognition abilities in relatives lie somewhere between the levels seen in patients and healthy non-relatives (Bora and Pantelis, 2013; Lavoie et al., 2013); although these results are not consistently replicated (Fett and Maat, 2013; Cassetta and Goghari, 2014; Ho et al., 2015; Ay et al., 2016; Raju et al., 2019; Giralt-López et al., 2020). Second, when we assessed the role of clinical liability in such a between-groups effect, we observed that HT performance differences between patients and siblings became not significant. Hence, we interpret that, when accounting for clinical markers (here, BS and PLEs), the priorly observed differences are blurred, probably reflecting a similar performance between patients and a subgroup of siblings especially vulnerable to the disease.

To interpret this finding, we have considered other possible factors, such as the potential effect of medication. In this sense, it is necessary to highlight that the evidence seems to indicate that antipsychotic medication would improve ToM (Javed and Charles, 2018; Kimoto et al., 2018), possibly by stabilizing symptoms. Therefore, while the non-inclusion of the treatment data in our analyses could limit the interpretation, we could hypothesize that if considered the patients' performance on ToM could be potentially poorer, potentially revealing greater disparities with the siblings. Also, other factors such as educational level, age and environment could influence the evaluation of ToM. In this sense, the sib-pair design is the best fitted to control for this type of cohort

TABLE 3 Results of the linear regression analysis of family history and FCQ Depressiveness factor (The Frankfurt Complaint Questionnaire, F3) on Hinting Task performance in healthy siblings.

	Standardized ß coefficient	*p*-value
Age at interview	−0.438	0.011
Sex	0.444	0.011
IQ	0.498	0.005
Family history	−0.616	0.001
FCQ depressiveness	−0.444	0.007

IQ Intellectual quotient.

TABLE 4 Results of the linear regression analysis of family history and Community Assessment of Psychic Experiences (CAPE) negative dimension on Hinting Task performance in healthy siblings.

	Standardized ß coefficient	*p*-value
Age at interview	−0.395	0.028
Sex	0.325	0.064
IQ	0.422	0.020
Family history	−0.623	0.001
CAPE negative	−0.357	0.032

IQ Intellectual quotient.

or stratification confounders since siblings are more likely to have grown up in a similar environment, have a smaller age difference (compared to parent–child designs), and are more likely to have received a similar educational style. Nevertheless, the effect of age and IQ has been considered in the models. Conversely, we did not include the educational level because of its association with IQ in our sample (increasing the risk of collinearity) and the non-different mean years of education between our groups (Table 1).

Focusing on the healthy siblings, our data showed that familial and clinical liability markers for SZ were related to ToM performance. In the first instance, the analysis of age, sex and IQ variables did not show an effect on healthy siblings HT scores. Next, when the family history was included in the model, we observed that a higher familial load was significantly related to lower ToM scores, which highlights the relationship between genetic vulnerability in the sibling group and poorer ToM skills.

Interestingly, we also report that the addition to the models of the FCQ Depressiveness Factor and the CAPE negative scores improved the explained variance of ToM, with the higher scores in both factors being significantly related to lower HT performance. Thus, our data seems to point towards the role of SZ genetic and clinical proneness in modulating the ToM in healthy individuals.

While the limited sample size of the study warrants cautiousness in the interpretation of our findings, it is remarkable that they are consistent with not only our previous study (Giralt-López et al., 2020), but also with other studies describing the association of other clinical liability markers for SZ with social cognition deficits in relatives (Irani et al., 2006) and the general population (Bora, 2020). In all, these findings add evidence of the interest in considering different vulnerability markers to characterize the underlying heterogeneity of ToM. Also, they indicate the interest of further analyses to elucidate the role of this heterogeneity as a potential explanation of the divergent results across studies evaluating social cognition within healthy or at-risk relatives. In this direction, longitudinal studies of siblings might disentangle the pattern of ToM in those who would develop or not psychosis.

Regarding the specific association of the dimensions reflecting subclinical expressions of negative symptoms (FCQ Depressiveness and CAPE negative dimension), it is partially consistent with accumulated evidence suggesting that ToM deficits are linked to negative (and disorganization) symptoms (Urbach et al., 2013; Ventura et al., 2013; Mehta et al., 2014; Bliksted et al., 2017; Yolland et al., 2020). The same specificity has been described in social cognition dimensions other than ToM, such as emotion perception or management (Charernboon and Patumanond, 2017; Yolland et al., 2020).

Moreover, the fact that all patients in our sample were in remission state and showed more prevalent negative than positive symptoms, and that ToM performance was not modulated by clinical severity (PANSS and CASH), seems to support that ToM behaves as a trait variable associated with the disease or its vulnerability more than a state variable associated with acute episodes. Nevertheless, a few studies have previously described significant associations between positive symptoms and ToM performance (Sprong et al., 2007; Mehl et al., 2010; Fretland et al., 2015; Bliksted et al., 2017). One study reported the association of poorer ToM performance with positive symptoms due to a specific error type (overmentalising instead of reduced ToM) (Fretland et al., 2015). Bliksted et al. (2017) noted that only in the presence of high levels of negative symptoms, positive symptoms were associated with deficits in social cognition. These findings lend evidence to a more complex pattern of ToM performance in SZ than only a matter of impaired versus non-impaired ToM.

As regards the characterization of ToM or other domains of social cognition concerning the genetic load for SZ (family history), as already mentioned before, some molecular-based approaches have contributed to defining the relationship between the genetic liability for SZ and social cognition (Lin et al., 2023). Estimating the individual genetic risk for SZ through the Polygenic Risk Score (PRS-SZ) has provided information on the link between the genetic risk for the disorder and the development of aspects of social cognition such as emotion identification speed (Germine et al., 2016). Also, the PRS-SZ has been associated with differences in the interregional correlations (assessed through both structural and functional neuroimaging approaches) between the core and other face-processing brain regions in healthy young adults (Lieslehto et al., 2019), and inversely associated with emotional recognition in healthy subjects but not in patients affected by SZ (Tripoli et al., 2022).

From the perspective of the genetic load assessed through familial relatedness and high-risk conditions, Tikka et al. (2020) conducted a study comparing ToM performance among patients with psychosis, a group of individuals at clinical high risk for psychosis, a cohort of siblings, and a control group. Their findings indicated that patients and both at-risk groups (familial and clinical) exhibited poorer ToM performance compared to controls, with no significant differences observed between the patient group and either of the risk groups (Tikka et al., 2020). Building upon this framework, our study contributes to the examination of ToM variability by juxtaposing patients with those at familial risk (siblings) and considering clinical liability markers.

With all the aforementioned, our data suggest that ToM deficits could be a promising indicator of those subjects within a population at risk (in this case, genetic risk due to the fact of being

siblings) who have a greater risk for psychosis and on whom monitoring measures could be applied for early detection. The considerable negative impact of cognitive impairment (neurocognition and social cognition) on different domains of real-world outcomes (Fett et al., 2011; Silberstein and Harvey, 2019), and our current lack of efficient treatment strategies emphasize the importance of identifying the underlying mechanisms of cognitive phenotypes in psychotic disorders as a crucial step towards understanding the aetiology of these disorders (Owen et al., 2016).

To contextualize our findings, it is crucial to consider the strengths and limitations of the study. The strengths include the family-based design and the use of an affected-unaffected sibling approach, and the inclusion of clinical and genetic liability markers together with social cognition data. Notably, only a limited number of studies have investigated the correlation between social cognition and BS or PLEs, with none incorporating data on genetic liability (family history). Consequently, our study design and the phenotypic variability contribute to the ongoing debate regarding state versus trait characteristics and offer insights into the complexity of traits associated with SZ liability.

On the other hand, although the sample size is comparable to that of previous studies and a common limitation of family-based designs is the difficulty in recruiting large, well-characterized families, the size of our sample remains the main limitation of the study. This issue could result in an overestimation of the effect size, and, therefore, requires caution in the interpretation of the findings as well as indicates the need for larger samples. Likewise, the sample size has prevented the analyses separately by-sex, affecting the generalization of the results. The current design could also be improved by the inclusion of a control group, which would allow testing the intermediate position of relatives between patients and controls. Additionally, while ToM is a crucial aspect of social cognition, our study did not explore other domains, such as emotion processing and social knowledge.

Finally, in terms of the translation of our results, identifying ToM deficits can facilitate the development and implementation of tailored interventions for individuals with psychosis or those in at-risk mental state. As highlighted, deficits in ToM can significantly affect social functioning, thus targeted rehabilitation in this area establishes a new avenue for intervention in psychosis and for individuals at heightened risk.

Improving ToM skills can also enhance engagement with therapy and treatment programs for psychosis because of better communication and an improved ability to understand others' viewpoints, ultimately leading to higher receptiveness to therapeutic interventions and more favorable treatment outcomes. Furthermore, the improvement in ToM abilities can empower individuals with psychosis to advocate for themselves in various social and clinical settings and to actively participate in their treatment and daily lives, thereby enhancing their overall quality of life.

5 Conclusion

Overall, our findings contribute to the ongoing discussion surrounding the potential for social cognition, specifically ToM, to serve as an endophenotypic marker of psychotic disorders.

In particular, our data indicate the usefulness of clinical liability markers in characterizing differences in ToM abilities within healthy individuals and suggest that deficits in ToM are not only associated with SZ-spectrum disorders but with clinical vulnerability for this disorder. These findings support that ToM could behave as an endophenotypic marker and contribute to discriminating especially vulnerable subjects from a population at risk, in this case, genetic risk (siblings). Nevertheless, new analyses in larger samples are needed.

Data availability statement

The dataset generated for this study is available on request to the corresponding authors.

Ethics statement

The study involving humans was approved by Ethics committee of the University of Barcelona (IRB0003099). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in the study.

Author contributions

MG-L: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. SM: Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. SC: Investigation, Writing – review & editing. MM: Investigation, Writing – review & editing. AS-M: Investigation, Writing – review & editing. MK: Conceptualization, Funding acquisition, Writing – review & editing. LF: Conceptualization, Funding acquisition, Resources, Writing – review & editing. MF-V: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a shared affiliation, though no other collaboration, with several of the authors [SM, LF, MF-V, GM] at the time of the review.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1391646/full#supplementary-material

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MANUSCRIPT 3

Theory of Mind Variability in Schizophrenia: A Neurodevelopmental Perspective through Soft Signs and Premorbid Adjustment

Giralt-López, M., Miret, S., Campanera, S., Moreira, M., Sotero-Moreno A., Hostalet N, Lázaro L., Krebs MO., Fañanás, L., & Fatjó-Vilas, M. (2024).

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Theory of Mind Variability in Schizophrenia: A Neurodevelopmental Perspective through Neurological Soft Signs and Premorbid Adjustment

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ABSTRACT

Background. Theory of Mind (ToM) is impaired in individuals with schizophrenia (SZ). Given the neurodevelopmental nature of both social cognition and SZ, variations in ToM abilities likely originate early in life. Thus, indirect markers of altered neurodevelopment, such as neurological soft signs (NSS) and premorbid adjustment (PA), may help explain these differences.
Methods. The study included 38 patients with schizophrenia-spectrum disorder (SSD), 26 healthy siblings and 47 controls. ToM was assessed using the Hinting Task (HT). NSS were evaluated with the Neurological Evaluation Scale (NES) and PA with the Premorbid Adjustment Scale (PAS), yielding Social and Academic scores. Intelligence Quotient (IQ) was estimated two subtests of the WAIS-III and Family History (FH) through the Family Interview for Genetic Studies (FIGS).
Results. First, patients presented more deficits in two subscales of the NES (motor coordination and sequencing of complex motor acts) than siblings and controls, with siblings performing intermediate in the sequencing subscale (linear mixed models, adjusted for age, sex and IQ). Patients showed worse social PA than siblings during childhood and late adolescence. Second, patients showed poorer HT performance than siblings and controls, but the neurodevelopmental markers did not modulate such differences. Third, within each group, neurodevelopmental vulnerability markers were not associated with ToM performance (linear regression analyses adjusted for age, sex, IQ and FH).
Conclusion. In our sample, while patients showed more evidence of neurodevelopmental deviances than siblings and controls, such differences did not contribute to ToM variability, suggesting that they may stem from different neurodevelopment-related pathways.

Keywords: Schizophrenia, Theory of Mind, Neurological Soft Signs, Premorbid Adjustment, unaffected siblings, endophenotype.

1. INTRODUCTION

Social cognition refers to a wide range of skills that allow people to perceive, interpret and process social stimuli, guiding social interactions. It is a multi-dimensional construct that comprises functions such as emotional processing, social perception and knowledge, theory of mind and attributional bias (Green et al., 2008). Among all these social cognition dimensions, the current article focuses on the theory of mind (ToM, also known as "mentalising"). It is defined as the ability to deduce the mental states of others, such as their beliefs, intentions, desires, and emotions (Frith & Frith, 1999).

The development of ToM skills includes, first, the mental construction of the object as existing outside and independent of the subject, the recognition of himself as separated from the others and the engagement in joint attention activities with others or the pretence play. Next, between 3 and 4 years of age, the child can infer that another person may have a belief different from its own, called "first-order ToM" (Baron-Cohen et al., 1985). Later, between 6- and 7 years old, the child begins to understand that the other person can also represent other people's mental state, known as "second-order ToM" (Damasceno, 2020). As ToM performance continues to improve throughout childhood and adolescence into adulthood (Meinhardt-Injac et al., 2020), proper brain maturation likely plays a crucial role in acquiring and performing these skills.

Although the precise cerebral organisation of social processes is not fully defined, specific brain regions and networks are associated with social information processing (Gazzaniga MS, 2019; Green et al., 2015; Magno et al., 2022). In particular, the medial prefrontal cortex (PFC) is involved in interpreting nonverbal social cues, understanding complex social contexts, inferring others' internal states and beliefs, and evaluating their traits over time, skills closely related to ToM performance (Kozhuharova et al., 2020). From an evolutionary standpoint, the PFC's involvement in social cognitive abilities such as ToM aligns with the idea that the expansion of the cerebral cortex is the substrate for human-specific higher cognitive processes (Sousa et al., 2017). It is important to note that while our closest primate relatives exhibit essential components of ToM (i.e., understanding goals, intentions, and perceptions), the ability to understand that others can hold beliefs that are incorrect or misaligned with reality appears exclusively human. (Call & Tomasello, 2008).

From a developmental view, the gradual achievement of ToM skills from infancy through childhood into adulthood aligns with the maturation of the PFC (Blakemore& Choudhury, 2006). For this reason, the PFC is viewed as a region particularly susceptible to disruption due to its long-lasting period of maturation (in humans, not complete until near the age of 25). Additionally, researchers hypothesize that brain regions, such as the PFC, which evolved most recently in humans, play a crucial role in advanced cognitive abilities, such as high-order ToM (i.e., the ability to infer hidden intentions through indirect speech or to grasp false beliefs). Interestingly, these same regions are involved in different neurodevelopmental disorders, such as schizophrenia and autism, which involve impairments in ToM (Teffer & Semendeferi, 2012).

Accordingly, ToM impairments are well-documented in schizophrenia (SZ) (Bora & Pantelis, 2013; Brune, 2005; Chung et al., 2014; Giralt-López et al., 2020; Mondragón-Maya et al., 2017). Some studies interpret these deficits as a state marker linked to symptomatology (Balogh et al., 2014; Mazza et al., 2012). Others, however, describe ToM impairments as a trait marker, noting that they are not influenced by clinical severity or insight (Ay et al., 2016; Giralt-López et al., 2020; Sprong et al., 2007) and are stable over time, as seen in prospective data (Ayesa-Arriola et al., 2014). Supporting the trait marker view, ToM deficits have also been observed in first-episode psychosis (FEP) and individuals at clinical or genetic high risk for psychosis (unmedicated prodromal subjects or first-degree relatives, respectively) (Bora & Pantelis, 2013; Healey et al., 2016). Based on these data and considering the developmental nature of ToM, it is appropriate to examine the variability in ToM impairments in patients and family members through the lens of the neurodevelopmental model of SZ. This model suggests that SZ arises from abnormal neurodevelopmental processes, starting years before the illness manifests, due to the complex interaction of genetic susceptibility and environmental factors (Birnbaum & Weinberger, 2017; Jones & Murray, 1991; Rapoport et al., 2012).

Clinical data have also shown that children who later develop SZ face earlier developmental, educational, and social challenges compared to others (Jaaro-Peled & Sawa, 2020) exhibit neuromotor dysfunction (Cunningham Owens & Johnstone, 2006; Rosso et al., 2000; Walker et al., 1994), and worse general cognitive functioning (Cannon et al., 2006; Sheffield et al., 2018) all contributing to poorer premorbid adjustment (PA) (Parellada et al., 2017). In turn, poor PA was significantly associated with prominence of negative symptoms and worse quality of life functional outcome (MacBeth & Gumley, 2008) , early age of onset, educational problems, chronicity, and neurological soft signs (NSS), becoming an essential predictor of a particularly severe form of SZ (Gupta et al., 1995).

In this sense, NSS are early indirect markers of subtle deviations from normal neurodevelopment that have been associated with SZ (Bora et al., 2018; Tsapakis et al., 2023). They are minor neurologic deficits observable by clinical examination, including deficits in sensory integration, motor coordination, sequencing of complex motor acts, eye movements, and developmental reflexes. NSS occur more frequently and pronounced in SZ than in other neuropsychiatric disorders (Bora et al., 2018), with a prevalence of over 50% compared to about 5% in healthy individuals (Rathod et al., 2020a). Also, NSS are more common in childhood and adolescent-onset SZ than in adult-onset cases (Biswas et al., 2007) and correlate with negative symptoms and cognitive dysfunction in SZ patients (Chan et al., 2015). This suggests a relationship between NSS and deficit schizophrenia in a subgroup of patients with neurodevelopmental alterations (Hoffmann et al., 2018).

NSS are present in prodromal phases before medication exposure (Kong et al., 2019), first-episode and chronic SZ (Chan, Xu, Heinrichs, Yu, & Wang, 2010a), and are more prevalent in first-degree relatives of people with SZ than in controls (Chan, Xu, Heinrichs, Yu, & Gong, 2010; Feng et al., 2020; Neelam et al., 2011). Furthermore, NSS were found to have moderate but significant heritability in a healthy twin sample and patients with SZ showed a strong correlation in NSS with their first-degree relatives (Xu et al., 2016), which supports a trait perspective and their potential endophenotypic role (Chan & Gottesman, 2008). However, evidence shows that NSS fluctuate, decreasing as psychopathological symptoms remit, though they do not return to levels seen in healthy controls, generating a state-trait debate about NSS (Bachmann & Schröder, 2018).

Considering all the points mentioned above, it can be hypothesised that the variability in ToM abilities observed after the onset of the illness likely originates early in life. Therefore, the presence or absence of indirect markers of altered neurodevelopment, such as NSS or distinct patterns of PA, might play a key role in shaping these differences. In other words, these early indicators could reflect distinct neurodevelopmental trajectories that influence how ToM abilities evolve, potentially affecting how the illness manifests and progresses in different individuals.

Some previous studies have explored the relationship between NSS and PA and ToM, but they are scarce, and none explored this relation in non-affected relatives (Herold et al., 2019; Punsoda-Puche et al., 2024; Romeo et al., 2014). Then, we aimed to deepen our understanding of ToM variability and its potential role as a trait marker by examining whether ToM performance could be better characterised by considering other markers of altered neurodevelopment, such as poorer PA and the severity of NSS in patients, siblings and controls.

2. METHODS

2.1 Sample

The sample included 121 participants: 38 patients diagnosed with recent onset schizophrenia-spectrum disorder (SSD), 26 healthy siblings from these patients and 47 controls. All participants were of European origin. The sample was recruited at the Outpatient Mental Health Clinic of the Hospital Santa Maria de Lleida and assessed when clinically stable by the same clinician (SM). It is important to note that the sample in this study partially overlaps with a dataset previously analysed by Giralt-López et al. (2020 and 2024). In this research, we integrated methodologies from our prior studies. First, we have focused specifically on siblings as the relatives' group, to reduce the heterogeneity of this group and some confounding factors (such as age or others related to the cohort effect). Second, we have included a control sample, which was recruited in Lleida and Barcelona from non-medical staff working in the hospital, their relatives and acquaintances, and independent community sources.

The key contribution and originality of this study lie in combining neurodevelopmental markers to better understand ToM variability.

Patients were diagnosed according to DSM-IV-TR criteria and interviewed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Siblings were evaluated through a clinical interview and the Structured Clinical Interview for DSM Disorders (SCID) (First & Gibbon, 2004), and only those who had no history of current or lifetime psychotic spectrum disorders or mood disorders were included in the study. The control group did not have a personal or family history of psychiatric disorders or any prior treatments for such conditions. Other common exclusion criteria for all groups were intellectual disability, any severe medical conditions that could impair brain function, neurological disorders, or previous head injuries with loss of consciousness.

2.2 Assessments

Social cognition, specifically ToM, was assessed through the Spanish version of the Hinting Task (HT) (Corcoran et al., 1995; Gil et al., 2012), a test comprising ten brief stories involving two people in a conversation. The task consists of inferring what a person is implying indirectly. In each item, a correct answer gives two points (for a total of 20 points). An additional hint is given in case of an incorrect answer, after which a correct answer gives one point. The HT assesses second-order ToM because it evaluates the ability to interpret indirect communication, which requires understanding the speaker's belief about how their hint will be perceived by the listener. The task has good validity and has proven sensitive to ToM difficulties in many studies (Corcoran & Frith, 2003).

The Intelligence Quotient (IQ) of all participants was estimated using the Block Design and Vocabulary or Information WAIS-III subtests (Wechsler, 1997).

Family history was assessed with the Family Interview for Genetic Studies (FIGS) (Díaz de Villalvilla et al., 2008; Nurnberger et al., 1994). Following the broad SZ spectrum criteria (Kendler et al., 1995), families were classified by history with binary coding, as having a positive family history when patients had at least one first- or second-degree relative with SZ, affective or non-affective psychosis, or schizotypal or paranoid personality disorder. Thus, family history values are shared by all family members.

NSS were assessed using structured clinical examination, the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989, Spanish translation of Gurpegui M y L. Pérez Costillas L, 1994). It consists of 26 items and is divided into four subscales: sensory integration, motor coordination, sequencing of complex motor acts, and "others". Sensory integration includes audiovisual integration, bilateral extinction, graphesthesia, right-left

confusion, and stereognosis. The subscale motor coordination encompasses dysdiadochokinesis (rapid alternating movements), finger-to-thumb opposition, finger-to-nose test, and tandem walk. The subscale sequencing of complex motor acts comprises the fist-edge-palm, fist-ring, Ozeretski, and rhythm tapping tests. The subscale "others" includes the assessment of hemispheric dominance, eye movement deficits, frontal release signs, and short-term memory. Each item was scored on a three-point scale, i.e., 0: No abnormality, 1 for mild but definitive impairment, and 2 for marked impairment (except for snout and suck reflex, which were scored 0 or 2). The NES shows high interrater reliability, high intraclass correlations for the total score and subscales and good internal consistency for patients with SZ and healthy controls (Mohr et al., 1996)

PA was evaluated using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), a retrospective interview that focuses on an individual's social and academic accomplishments before the onset of illness. The PAS evaluates PA during childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood (19 years and above). It assesses five domains, including sociability and withdrawal, peer relationships, academic performance, adaptation to school, and social-sexual functioning, and rates them from 0 (normal adjustment) to 6 (severe impairment). The study did not include adult PAS data due to concerns about validity (Horton et al., 2015) and the potential bias introduced by measuring after the disease onset. As a result, maladjustment ratings were only calculated for childhood, early adolescence, and late adolescence. Also, according to previous research (Bechi et al., 2020; Bucci et al., 2016), we computed distinct scores for Social and Academic PA at each stage of development. This was achieved by averaging the sociability and withdrawal, peer relationships, and social-sexual functioning items to represent the social domain and educational performance and adaptation to school items to represent the Academic domain. PA data were available for patients and relatives but not for controls.

2.3 Statistical analyses

All data were processed using IBM SPSS Statistics Version 29.0 (SPSS IBM, Armonk, NY: IBM Corp).

Sociodemographic and clinical data were compared between groups using ANOVA or chi-squared tests when appropriate.

The effect of age, years spent in education, and IQ on HT and NES performance for each group was tested using the Pearson correlation test. Within groups, differences in HT performance according to sex or family history were tested using Student's t-test. From all these analyses, sex and family history showed a significant effect in relatives on HT ($p = 0.046$ and $p = 0.002$, respectively), and age and IQ on NES ($p=0.029$ and $p=0.003$) in relatives. According to these analyses age, sex and IQ were added as covariates in all the subsequent analyses, and family history in the patients' and siblings' intragroup analyses (not in controls as in this group it is a constant=0).

HT performance, NSS and PAS differences between patients and their siblings were assessed through linear mixed models (LMMs) with family member (patients/sibling) as the fixed-effect factor, sex, age and IQ as fixed-effect covariates, and family as the random effect (subjects nested within families). When the analyses included non-related groups (patients vs. controls and siblings vs. controls), the same models were used for the comparison without including the family random effect.

The impact of the markers of altered neurodevelopment (NSS and PA) on HT performance, when taking into account the group and the family, was assessed using a linear mixed model, with HT as the dependent variable, family status (patients/sibling) as the fixed-effect factor, sex, age, IQ and neurodevelopment variables as fixed-effect covariates and family as the random effect (when the analyses included related groups (patients vs. siblings).

Within patients, siblings, and controls, the relationship between HT performance and neurodevelopmental markers was tested using linear regressions (adjusted for age, sex, IQ, and family history).

3. RESULTS

3.1 Sample characteristics

The sample's sociodemographic and clinical features are presented in Table 1. Patients had a larger percentage of men and were younger than siblings and controls. Also, patients showed a lower IQ and fewer years in education compared to controls but did not show differences with siblings.

Their DSM-IV-TR diagnoses were SZ (n=32) and psychotic disorder not otherwise specified (n=6). Patients' mean age at onset was 22.12 (SD=3.83), and the mean duration of illness was 26.40 months (SD=24.44). All were treated with antipsychotic monotherapy: 94.7%, with second-generation antipsychotic (24 risperidone, five olanzapine, three amisulpride, two ziprasidone, two clozapine) and 5.3% with haloperidol.

Table 1. Sample description and statistical comparisons between patients (P), siblings (S) and controls (C). Proportion (%) or mean scores (standard deviation) are given. Differences between groups were tested with ANOVA.

	Patients (n=38)	Siblings (n=26)	Controls (n=47)	ANOVA F/χ2 (p)	Post-hoc significant differences
N male/female	28/10	11/15	25/22	6.89 (0.032)	P>S
Age at interview	24.92 (3.90)	28.79 (5.22)	27.46 (4.51)	6.38 (0.002)	S>P, C>P
Years of education	13.43 (3.12)	14.81(4.14)	16.30 (3.24)	7.19 (0.001)	C>P
Estimated Intelligence Quotient (IQ)	90.03 (15.23)	94.15 (15.04)	107.15 (11.00)	18.35 (<0.001)	C >S, C>P

3.2 Neurological Soft Signs in SSD patients relative to their siblings and healthy individuals

Differences in NSS Motor Coordination were found between patients and siblings and between patients and controls (F=5.17 p=0.027 and F=9.38 p= 0.003, respectively) (Table 2, Figure 1). Patients presented higher scores than relatives (estimated mean difference = 0.96) and controls (estimated mean difference = 1.11). Although the mean score of siblings was higher than that of controls, the difference was not statistically significant (see supplementary material for linear mixed model complete results of patients/siblings, patients/controls, siblings/controls; Tables S1, S2, S3 respectively).

The comparison of NSS complex motor sequencing between patients and siblings and between patients and controls showed significant group effects (F=15.04, p < 0.001 and F=23.60, p < 0.001, respectively). Patients presented higher scores than relatives (estimated mean difference=2.23) and controls (estimated mean difference=2.72). Also, siblings presented higher scores than controls (F=4.99, p=0.029, estimated mean difference = 0.90) (Table 2) (see supplementary material for the complete results of the linear mixed model of patients/siblings, patients/controls, and siblings/controls Tables S4, S5, and S6, respectively).

The NSS sensory integration scores of patients, siblings and controls did not differ significantly (see supplementary Tables S7-S9).

Table 2. ToM and NSS: clinical description and statistical comparisons between patients (P), siblings (S) and controls (C). Mean scores (standard deviation) are given. Linear Mixed Models (LMM) for pairwise group comparisons with sex, age and IQ as fixed-effect covariates and subjects nested within families when related groups were analysed. Only significant differences are given.

	Patients (n=38)	Siblings (n=26)	Controls (n=47)	Group Comparison (LMM)
HT	15.74(4.07)	18.46 (1.42)	18.38 (1.68)	P<S*, P<C
NSS Sensory Integration	1.71 (1.66)	1.62 (1.33)	1.40 (1.42)	
NSS Motor Coordination	1.34 (1.81)	0.42 (0.81)	0.18 (0.44)	P>S*, P>C**
NSS Sequencing complex motor acts	3.68 (2.70)	1.69 (1.83)	0.62 (1.15)	P>S***, S>C*, P>C***

* p< 0.05, ** p< 0.01, *** p<0.001

3.3 Premorbid adjustment in SSD patients relative to their siblings.

Patients and siblings showed significant differences in social PA during childhood and late adolescence (F=4.83, p=0.032 and F=13.03, p<0.001, respectively), with patients scoring higher than siblings (adjusted mean difference 0.68 and 0.86, respectively). Also, patients showed worse total PA in late adolescence (estimated mean difference = 3.81, F = 10.81, p=0.002) (Table 3) (see supplementary Tables S10-S17).

Table 3. Premorbid adjustment Scale (PAS) in patients (P) and siblings (S): clinical description and statistical comparisons between groups. Mean scores (standard deviation) are given. Linear Mixed Model (LMM) for group comparisons with sex, age and IQ as fixed-effect covariates and subjects nested within families. Only significant differences (p<0.05) comparisons are given.

		Patients (n=38)	Siblings (n=23)	Group comparison (LMM)
Childhood PAS [a]	**Total**	5.05 (3.71)	3.13 (2.49)	
	Social	1.05 (1.16)	0.39 (0.62)	P>S *
	Academic	1.47 (1.09)	1.17 (0.81)	
Early adolescence PAS [a]	**Total**	7.86 (4.16)	4.74 (3.19)	
	Social	1.22 (1.01)	0.68 (0.67)	
	Academic	2.01 (1.21)	1.35 (1.00)	
Late adolescence PAS [a]	**Total**	10.24 (4.72)	5.00 (2.80)	P>S **
	Social	1.66 (0.96)	0.65 (0.56)	P>S ***
	Academic	2.64 (1.73)	1.52 (1.14)	

* p< 0.05, ** p< 0.01, *** p<0.001

3.4 Analysis of ToM performance in patients with SSD relative to their first-degree relatives and healthy individuals and its association with neurodevelopmental markers.

HT scores are given in Table 2. A comparison of HT performance between patients and siblings and between patients and controls showed significant group effects (F=5.67, p=0.02) and (F=3.95, p=0.05), respectively. Patients presented lower scores than relatives (estimated mean difference = 2.26) and controls (estimated mean difference = 1.68). The scores of the siblings and controls did not differ significantly (see supplementary Tables S20-S22).

Next, we included the neurodevelopmental markers to analyse their effect on the HT performance differences between SSD patients and siblings. No significant effects of NSS or PA were detected and HT performance differences between the groups remained significant; however, in most models, the difference in HT means between the groups decreased as compared to the initial model (see supplementary Tables S23-S24).

4 DISCUSSION

This study aimed to enhance the understanding of ToM variability by examining whether it is affected by early indicators of neurodevelopmental deviances, such as NSS and PA.

Our previous research (Giralt-López et al., 2020, 2024) has shown that, in addition to the more severe ToM deficits observed in patients compared to their relatives and controls, ToM performance may also be influenced among healthy individuals by clinical vulnerability factors, such as schizotypy, basic symptoms, and psychotic-like experiences. This suggests that ToM deficits are not only associated with SZ but also extend to its clinical vulnerability, indicating that ToM could serve as an endophenotypic marker and, therefore, could help identify particularly susceptible individuals, such as those with a genetic predisposition (e.g., relatives). In this sense, family-based studies have been considered a suitable design to deepen the potential role of ToM performance as a vulnerability marker. However, the inconclusive results obtained until now could be attributed to the fact that most of them have focused on first-degree relatives, with limited research specifically targeting siblings of individuals with SZ. Then, the current study adopts a sib-pair approach to control for cohort-related effects relevant to ToM competence and focuses on extending the analysis of ToM variability by assessing the effect of neurodevelopmental markers, given the widespread acceptance of the neurodevelopmental model in SZ (Birnbaum & Weinberger, 2017; Jones & Murray, 1991; Rapoport et al., 2012). Accordingly, NSS and PA were selected to represent the neurobiological basis of the disease and functional development before SZ onset.

First, our approach shows stronger evidence of neurodevelopmental deviations in patients compared to siblings and controls, particularly in specific domains of NSS, such as motor coordination and sequencing of complex motor acts. More concretely, concerning the latter, siblings exhibited an intermediate position between patients and controls, which would support its potential role as the best endophenotypic marker among the three analysed dimensions. In this sense, the specificity of motor domain deviations in NSS could be understood by recognising that motor deficits were linked to abnormalities in brain regions commonly implicated in schizophrenia, such as the cerebellum, basal ganglia, temporal lobe or prefrontal cortex (Luvsannyam et al., 2022). However, research on this field could not report a brain structural specificity for any NSS subscale (Rathod et al., 2020b; Zhao et al., 2014).

These results are aligned with meta-analytic data revealing significant differences in NSS prevalence among SZ patients, their non-psychotic relatives, and healthy controls, supporting the idea that NSS are familial and associated with the illness (Chan, Xu, Heinrichs, Yu, & Gong, 2010). More recent evidence consistently shows that NSS are more prevalent in patients with SZ than in their first-degree relatives, and they are more prevalent in first-degree relatives than in healthy controls, including findings in neuroleptic-naive first-episode patients, further validating NSS as valuable endophenotypes (reviewed by Petrescu et al., 2023; Tsapakis et al., 2023).

More concretely, focusing on specific dimensions, previous studies have shown that the motor coordination subscale is significantly more affected in patients compared to controls, regardless of the illness duration (Chan, Xu, Heinrichs, Yu, & Wang, 2010; Nathani et al., 2023). In studies that included first-degree relatives, findings indicate that patients score higher in motor coordination and complex motor tasks than relatives and controls. However, most of these studies have focused on older patients with a more chronic form of the illness (Chan, Xu, Heinrichs, Yu, & Gong, 2010; Petrescu et al., 2023). Two studies used samples similar to ours, with young patients in early disease stages. One study found increased NSS in motor coordination and sequencing in patients compared to relatives and controls, but no significant intermediate position for siblings (Cuesta et al., 2018). The second study did show an intermediate position for siblings but used a different NSS scale, hampering direct comparisons (Kong et al., 2022).

The fact that NSS are more present in relatives and, to a lesser extent, in controls dissuades the idea that they could be caused by antipsychotic treatments. Furthermore, most studies have not found associations between antipsychotic dosage and the severity of NSS (Compton et al., 2015; Hirjak et al., 2015; Peralta et al., 2010) although NSS tend to decrease in patients who respond adequately to treatment (Bachmann et al., 2014).

Focusing on the second indicator of altered neurodevelopment, PA, our findings, consistent with previous research, show poorer PA in patients than healthy siblings (Shapiro et al., 2009). This could have significant implications for monitoring individuals at high genetic risk, such as the children of those with SSD. Early identification of these high-risk subgroups could facilitate better management of environmental risk factors and enable closer monitoring for early signs of psychosis, potentially reducing the duration of untreated psychosis, which is associated with poorer outcomes.

After group differences analyses, our goal was to demonstrate whether the variability in these markers – indicative of early neurodevelopmental deviations - accounts for differences in ToM skills, a cognitive variable also linked to neurodevelopment (Baron-Cohen et al., 1999; Damasceno, 2020). When comparing HT performance between SSD patients and siblings, adjusted for NSS or PA, our study could not demonstrate any significant role of these neurodevelopmental markers contributing to ToM variability across groups. Additionally, beyond the between-groups effect, we also tested the association of these two neurodevelopmental markers with ToM within each group. However, unlike previous studies that identified a correlation between NSS and poorer ToM performance in patients (Herold et al., 2019; Romeo et al., 2014), our research does not find such relationship in the within-group analyses of patient, sibling, and controls. Then, our data does not support that specific NSS and ToM deficits might share common neural mechanisms as proposed by these

previous studies. Although in all studies age of onset and years of education are similar, our sample is characterised by including patients in the early stages of the disease (less than 3 years of evolution), while previous studies (Herold et al., 2019; Romeo et al., 2014) included older patients with chronic SZ of more than 10 years of evolution. It is also interesting to note that both studies adjusted the analyses by age and years of education but not by IQ, unlike our study, which included IQ in the analyses considering the reported association of neurocognitive symptoms (including attention, information processing, processing speed, reasoning and problem-solving, social cognition, working memory, and verbal and visual learning and memory) with NSS, reviewed in (Tsapakis et al., 2023). Accordingly, our findings are consistent with those reported in other developmental disorders, such as ADHD, that although they could confirm NSS as markers of atypical neurodevelopment and predictors of the severity of functional impairment, did not find a correlation with ToM abilities (Pitzianti et al., 2017).

Similarly to what was observed in the case of the NSS, our study could not add evidence supporting the recently reviewed and described relationship between ToM and PA in patients with schizophrenia (Punsoda-Puche et al., 2024). To the best of our knowledge, only one family-based study reports altered academic PA in relatives, including both parents and siblings. Although this study evaluated social cognition in the patient group (using a composite score that was not specific to ToM skills or their relationship with PA) it did not explore this dimension within the relatives' group (Bucci et al., 2018).

In summary, this study did not find evidence of a correlation between ToM and markers of altered neurodevelopment across the patient, sibling, and control groups, contrary to expectations. This is despite the well-documented ontogenic development of ToM abilities in the early stages of development (Baron-Cohen et al., 1985; Damasceno, 2020). Then, these results suggest they may potentially rely on different neurodevelopmental-related pathways. In this sense, it is remarkable that ToM, NSS, and PA all represent indirect approaches to understanding neurodevelopment, but from complementary perspectives. Specifically, NSS likely serve as a marker closely related to the central nervous system substrate, while PA acts as an indirect functional marker of altered neurodevelopment, and ToM reflects the cognitive level.

Attempts to describe the neurobiological roots of ToM should consider additional markers of altered neurodevelopment that correlate with ToM deficits. This could help identify a potential shared neurobiological substrate. With special focus on the relatives' group, who have a greater genetical risk (Gottesman, 1991), a comprehensive approach to define subgroups of family members at higher risk could involve integrating neurodevelopmental markers with indicators of clinical vulnerability, such as levels of schizotypy. Prior evidence has shown a relationship between these two types of risk markers, more concretely NSS (especially motor signs), were associated with some schizotypal dimensions in siblings of patients with schizophrenia (Mechri et al., 2010). Furthermore, it would be valuable to explore the role of environmental factors that may interact with early neurodevelopmental alterations and mediate reduced ToM abilities. Considering these interactions may provide a more comprehensive understanding of the mechanisms influencing ToM deficits.

Finally, it would be interesting if future studies could longitudinally examine the relationship between ToM and NSS. It would be of particular interest to evaluate this relationship also in patients in the acute phase, considering the potential attenuating effect that the remission of acute symptoms can have (at the same time related to the initiation of antipsychotic treatment) (Bachmann et al., 2014).

To properly understand our findings, it is essential to acknowledge the study's strengths and limitations. Strengths include using a family-based design with an affected-unaffected sibling approach, a control group for most variables, the use of the most suitable tool for evaluating Theory of Mind (ToM) within the psychosis continuum (Ludwig et al., 2017), and the inclusion of early neurodevelopmental markers. These aspects of our study help address the ongoing discussion about whether ToM characteristics are state or trait-related and provide insights into the complex traits linked to SZ risk. However, despite having a sample size comparable to previous studies, a significant limitation is that our sample size is still relatively small, which is a common challenge in family-based research that requires large, well-characterised families. Additionally, while ToM is a crucial element of social cognition, our study did not examine other areas, such as emotion processing and social knowledge and treatment.

In conclusion, in our sample, while patients showed more evidence of neurodevelopmental deviances (assessed through NSS and PA) than siblings and controls, such differences do not explain ToM variability. These findings encourage further exploration of endophenotypic markers or combinations of markers that can enhance the stratification of risk for conversion to psychosis, particularly within the general population and among siblings or children of patients who face an elevated risk due to their genetic predisposition. A more precise definition of these high-risk groups would enable the development of targeted interventions to mitigate this risk or concentrate efforts on early detection, ultimately improving the already proven cost-effectiveness of early psychosis care programs (Ologundudu et al., 2023).

5 CONFLICT OF INTEREST

The authors declare that there are no competing interests.

6 AUTHORS' CONTRIBUTIONS

MG-L: Conceptualization, Data curation, Formal analysis, Methodology, Visualisation, Writing – original draft. SM: Conceptualization, Investigation, Methodology, Resources, Writing – review & editing.

SC: Investigation, Writing – review & editing. MM: Investigation, Writing – review & editing. AS-M: Investigation, Writing – review & editing. NH: Investigation, Writing – review & editing, MOK: Conceptualization, Funding acquisition, Writing – review & editing. LF: Conceptualisation, Funding acquisition, Resources, Writing – review & editing. MF-V: Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft

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9 DATA AVAILABILITY STATEMENT

The dataset generated for this study is available on request to the corresponding authors.

10 ETHICS STATEMENT

The study involving humans was approved by the Ethics Committee of the University of Barcelona (IRB0003099). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in the study.

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5 DISCUSSION

The significant disability, high prevalence, chronic nature, and associated costs create a substantial burden for individuals with SZ, their families, and society. This situation highlights the need to identify predictors that can be directly applied to prevention, diagnosis, and treatment. However, the complexity of SZ, in terms of its aetiology, phenotypic variability and underlying pathophysiological mechanisms, makes achieving this particularly challenging goal.

Accordingly, the final goal of this thesis was to try to delimit some of the biological pathways that underlie the etiology of psychotic disorders and to increase knowledge that allows us to identify those healthy subjects at higher risk of transitioning to psychosis, with particular emphasis first-degree relatives. Certainly, the need to enhance detection, monitoring, and intervention in at-risk groups for conversion to psychosis is evident in the development of various early intervention programs for incipient psychosis that have emerged worldwide. Currently, risk groups for psychosis, which have received different names in different countries (e.g. Ultra-High-Risk (UHR) in Australia, At Risk Mental State (ARMS) in the UK, or “Estados Mentales de Alto Riesgo” (EMAR) in Spain) are defined by the presence of brief or subthreshold psychotic symptoms or by factors related to genetic load with loss of functionality. However, to date, strategies to prevent conversion to psychosis continue to report inconclusive results (209), apply mostly to psychosocial interventions and indicate the need for more tailored and sequential interventions that stratify patients to specific treatments matching their clinical profile (210). Therefore, there is no doubt about the usefulness of these criteria for developing care programs for incipient psychosis that, among other things, facilitate early detection and treatment, reducing the time of untreated psychosis, one of the most important prognostic factors.

In this attempt to find new vulnerability markers, this thesis focuses on deficits in ToM. On the one hand, this trait has the advantage of being linked to neurodevelopment from both an evolutionary and ontogenetic perspective. Also, the neurobiological bases of ToM are linked to brain regions, such as the prefrontal cortex, which have been reported

as altered both neuroanatomically and functionally in individuals with SZ (211,212) as well as in healthy siblings (213,214). Furthermore, from a more clinical approach, improving the knowledge of ToM's neurobiological bases and its involvement in the risk profiles, could drive forward progress towards targeted interventions or therapeutic strategies aimed at improving SC, a determining factor for the long-term prognosis of psychosis (215). On the other hand, this thesis, places the analysis of ToM in a broader context by incorporating other clinical, neurodevelopmental and genetic markers (that may signal an increased latent risk for SZ) to explain or define the variability in ToM with an integrative approach. The results derived from this approach are discussed in the following sections and also their main strengths and limitations.

TOM PERFORMANCE IN SCHIZOPHRENIA-SPECTRUM DISORDER PATIENTS, HEALTHY FIRST-DEGREE RELATIVES AND HEALTHY CONTROLS.

In our study, SZ patients showed impairments in inferring the mental states of others (i.e. intentions) via indirect speech, such as hints, measured with the HT, in comparison to controls. This result is consistent with previous studies that have used the same task (216–218) or other tools for assessing ToM (165,167,219,220). Most of these studies use a case-control methodology, but our work incorporates first-degree relatives (parents and siblings or only siblings). Although recruiting large samples of well-characterized families can be challenging, family-based studies offer advantages over case-control studies by controlling for genetic background and environmental influences, resulting in more robust and unbiased outputs. Among family-based designs, using siblings as control groups is especially beneficial in studying developmental disorders, as siblings are more equally exposed to environmental conditions (such as educational level) and age-related factors.

Then, thanks to this kind of design, we could investigate the properties of ToM as an endophenotypic marker by looking at how healthy relatives behave in relation to

patients and controls. In our study, the mean score of healthy relatives in the HT fell between the scores of the other two groups, but the differences between relatives and controls were not significant. Furthermore, these results are not different whether the family members include only siblings or siblings and parents. In this context, our study contributes to the state-trait debate, showing that ToM deficits are present in a stable phase of the early course of the disease and are also milder yet observable in unaffected relatives. In line with our findings, other studies have also observed no differences in relatives compared to controls in ToM performance (171,174). In contrast, other studies have suggested a genetic liability effect, with relatives demonstrating impairments in advanced ToM ability (170,172,221,222). In this regard, a review and meta-analysis revealed that ToM performance among relatives of patients with first-episode psychosis falls between that of patients and healthy controls) (170).

This heterogeneity of results could be explained by several different factors beyond the sample size of the studies.

First, different tasks have been used to evaluate ToM, but results have been inconsistent, particularly when assessing first-order ToM. The HT (which assesses social-cognitive component of ToM) and the Reading the Mind in the Eyes Test (which assesses social-perceptual component of ToM) are the most employed methods. Interestingly, two studies with a similar design to our research found results consistent with our observation. In HT, relatives showed intermediate performance between patients and controls, although differences between relatives and controls only approached significance (222,223). In relation to tasks using visual stimuli (social-perceptual tasks), typically used to explore affective ToM, two studies reported differences between relatives and controls performance (224,225) but one of them also explored cognitive ToM in the sample, with verbal ToM stories and could not find differences (225). However, this specificity to visual stimuli has not been consistently replicated (171,226). Interestingly, greater consistency has been observed in tasks assessing more complex, second-order ToM. These tasks require participants to infer one character's (false)

beliefs about another character's (false) beliefs (227,228). In such cases, healthy relatives and controls differences appear to be more pronounced (168,172,229).

Second, another factor potentially contributing to heterogeneity is that ToM abilities might decline over the course of SZ. This is consistent with Brüne's developmental model, which posits that ToM abilities decline in the reverse order of acquisition (220). Therefore, deterioration is first detected in complex ToM tasks, while the decline in first-order ToM tasks is observed later. This theory is consistent with studies that have observed a deficit in second-order mentalizing questions, but not in first-order inference items, in patients experiencing a first episode of psychosis (230). Thus, it can be deduced that tasks assessing higher-order forms of ToM could be more sensitive and especially appropriate for detecting ToM impairment in non-clinical samples such as healthy relatives. It is important to keep in mind that the loss of SC skills in its multiple facets is related to normal aging (231,232), which is why it is important to consider the age factor in the models, not only as a reflection of the patients' evolution time but also of aging itself in samples of healthy subjects.

Third, IQ has been considered in the models. Previous evidence shows that group differences are partially reduced after adjusting for IQ (222,223). Conversely, we did not include the educational level because of its association with IQ in our sample and the non-different mean years of education between our groups.

Fourth, the fact that all patients in our sample were in remission state and showed more prevalent negative than positive symptoms, and that ToM performance was not modulated by clinical severity (PANSS and CASH), seems to support that ToM behaves as a trait variable associated with the disease or its vulnerability more than a state variable associated with acute episodes. In contrast, a few studies have previously described significant associations between positive symptoms and ToM performance (219,233–235).

Fifth, although nearly all patients in our sample were treated with atypical antipsychotics, primarily risperidone, we were unable to include a quantitative variable for antipsychotic treatment. In this sense, it is necessary to highlight that the evidence seems to indicate that antipsychotic medication would improve ToM (236), possibly by stabilizing symptoms. Therefore, while the non-inclusion of the treatment data in our analyses could limit the interpretation, we could hypothesize that if considered, patients' performance on ToM could be potentially poorer, potentially revealing greater disparities with the siblings.

Finally, despite using an appropriate family-based design and adjusting for relevant confounders, our initial approach failed to identify differences in vulnerability, measured through ToM, between healthy relatives and controls. Therefore, it was crucial to extend or models by incorporating other markers of the risk for psychosis.

CLINICAL LIABILITY TO SCHIZOPHRENIA TO DISENTANGLE ToM PERFORMANCE HETEROGENEITY IN HEALTHY INDIVIDUALS (RELATIVES AND CONTROLS)

One factor to consider when explaining the heterogeneity of ToM capacities in healthy individuals is the variability in clinically defined liability, measured through schizotypy, BS and PLEs, that reflect psychosis as a continuum rather than a discrete category. These three clinical markers, in some way, define complementarily a subtype of the population considered at risk of conversion to psychosis while they do not necessarily have to converge on the same individual. On the one hand, schizotypy is considered the clinical risk marker most classically associated with a trait or genetic vulnerability (237) and it has proven to be useful in identifying families with a higher genetic predisposition to SZ (121). At the same time, this is the most studied marker in relation to ToM. Alternatively, BS and PLEs form a "state clinical vulnerability group", corresponding to attenuated and

brief subthreshold presentations, respectively, as described in high-risk criteria for psychosis.

In this context, in this thesis, we report that high levels of positive and negative schizotypy (related to cognitive-perceptual and interpersonal dimensions, respectively) are associated with poorer ToM performance in relatives, whereas this association only remains significative for negative schizotypy after adjusting for IQ. Also, we show that such association is detected in healthy relatives but not in control participants. These results are similar to those reported by Johnson et al. 2003, who indicated that the relationship between schizotypy and other measures of cognition is mediated by SZ genetic risk (238). In this sense, schizotypy symptoms seem to put individuals with familial risk at an increased risk of these ToM deficits, thus suggesting that some SC functions might be sensitive to SZ liability. To our knowledge, only three studies have explored this association in healthy relatives of individuals with SZ. Two of these studies found no significant correlations between ToM performance and schizotypy scores in the relative samples (239,240). Nevertheless, these studies did not employ the same strategy as ours to dichotomize the sample into low- and high-schizotypy scorers. This distinction is particularly relevant given that previous research suggests ToM deficits are predominantly observed in high-schizotypal samples (241). Furthermore, these studies primarily evaluated affective ToM rather than cognitive ToM and utilized tasks that lack empirical support as robust tools, such as the Hinting Task (HT), for studying the psychosis continuum (178). In a third study, Irani et al. (2006) used the Revised Mind in the Eyes Test (that employs visual stimuli to assess affective ToM) in a sample substantially smaller than ours (193). However, they could report accuracy differences between patients and controls and a trend whereby relatives were less accurate than controls in the ToM task performance, although this later difference only became significant when the SPQ social–interpersonal subscale was considered (using a group split method like our research) scores. This is consistent with the hypothesis that these social-interpersonal features (or negative dimension) are the best differentiators

between relatives and controls and might be the most important schizotypal traits associated with genetic vulnerability for SZ (190).

In the general population, the relationship between ToM and schizotypy has been widely researched, as reviewed by Bora (187). Some studies have identified ToM impairments linked to high levels of total schizotypy (242,243), while other studies, consistent with our data, have not found any association in non-related controls (244,245). The inconsistent findings regarding the association of total schizotypy and ToM performance in healthy individuals may stem from differing underlying reasons for ToM impairments in positive and negative schizotypy. Drawing a parallel with Frith's observations in SZ patients, where ToM deficits varied depending on the presence of positive or negative symptoms (246), individuals with positive schizotypy may struggle with ToM tasks due to distorted interpretations of others' intentions. In contrast, those with negative schizotypy may experience ToM difficulties because of limited experience or reduced interest in social interactions. Accordingly, some studies report that deficits in SC may be attributed to specific schizotypy traits, such as positive schizotypy (247–249) or negative schizotypy (250–252). Interestingly, one study found an association between positive schizotypy and worse cognitive ToM performance as well as a significant positive relationship between negative schizotypy and affective ToM deficits (253), suggesting that different aspects of SC are differentially affected by positive and negative schizotypy. Another fact that could explain the heterogeneity is the different ways of quantifying schizotypy levels. Some studies have used a continuous variable, while others, like us, have used median splits or the top and bottom 5% or 10% to emphasize the qualitative differences between groups. The latest review assessing the relationship between ToM and schizotypy in healthy individuals shows how this is more significant in the studies using extreme-group design than non-extreme-group design (187). We were not able to focus on an extreme group due to the limited size of our sample.

Targeting the group of family members, with the aim of detecting those at greater risk for psychosis, we expanded the study by incorporating clinical markers of vulnerability

related to the presence of subthreshold or brief symptoms, which indicate a greater proneness to psychosis and to verify its relationship with the execution in ToM and thus continue demonstrating its usefulness as a vulnerability marker. When we examined the influence of BS and PLEs as vulnerability markers on ToM variability, we found that the previously observed differences in HT performance between patients and siblings were no longer significant after accounting for clinical liability by incorporating these vulnerability markers (BS and PLEs) into the model. Hence, we interpret that the priorly observed differences are blurred when accounting for clinical markers, probably reflecting a similar performance between patients and a subgroup of siblings especially vulnerable to the disease. Furthermore, when we analysed the association between clinical liability markers and HT performance within healthy siblings we found that the addition to the models of the FCQ Depressiveness Factor and the CAPE negative scores (negative PLEs) improved the explained variance of ToM, with the higher scores in both factors being significantly related to lower HT performance. Thus, our data seems to point towards the role of SZ clinical proneness in modulating the ToM in healthy individuals.

While the limited sample size of the study warrants cautiousness in the interpretation of our findings, it is remarkable that they are consistent with not only our previous study ((254), but also with other studies describing the association of a trait liability marker for SZ (schizotypy) with SC deficits in relatives (193) and the general population (187). To our knowledge, the unique previous study that combines the evaluation of genetic risk (being a relative) and clinical risk (subthreshold or brief psychotic symptoms) could not report an association between clinical risk and ToM performance in relatives (240). Although the sample size in our study was comparable, the scale they used to quantify lifetime occurrence of subthreshold delusional symptoms, the Peters Delusions Inventory (PDI), does not permit to consider different symptom dimensions. Furthermore, all relatives in the study were assessed using the Scale of Prodromal Symptoms (SOPS/SIPS) to rule out the presence of attenuated positive or brief limited intermittent psychotic symptoms, potentially leading to the exclusion of higher-risk

relatives from the sample. To our knowledge, only one previous study analyses the association between ToM and PLEs, describing an association between positive PLEs and a deficit in ToM (255). All these results indicate the interest of further analyses to elucidate the role of this heterogeneity as a potential explanation of the divergent results across studies evaluating SC within healthy or at-risk relatives. In this direction, longitudinal studies of siblings might disentangle the pattern of ToM in those who would develop or not psychosis.

Regarding the specific association of the dimensions reflecting subclinical expressions of negative symptoms (SPQ Interpersonal, FCQ Depressiveness and CAPE negative dimension), it is partially consistent with accumulated evidence suggesting that ToM deficits are linked to negative symptoms in SZ (235,256–259). The same specificity has been described in SC dimensions other than ToM, such as emotion perception or management (258,260). It is important to note that SZ with a predominance of negative symptoms is a particularly severe form of the disease, characterized by earlier onset, poorer functionality (261), longer hospitalizations (262), and associated with indicators of early neurodevelopmental deviances, such a poorer PA (263) and lower intelligence (264,265). In the context of our results and shifting the focus from established illness to its vulnerability, the more negative dimensions of schizotypy, BS and PLEs could also represent a less severe but earlier manifestation of this neurodevelopmental vulnerability, in which early alterations in brain maturation led to deficits in the development of SC.

For all the above mentioned, our study contributes to the debate on whether ToM is a trait or state marker. We found that ToM deficits are present during patient stability and among relatives and that ToM deficits are associated with a higher vulnerability to psychosis within the groups of relatives. The observation of this effect, combined with the lack of differences in ToM-based vulnerability between healthy relatives and controls, stimulated our interest in integrating additional markers to better capture variability in ToM performance and improve the detection of psychosis risk. Then, in the

third chapter of our thesis, we focus on examining whether neurodevelopmental alterations, assessed using NSS and PA, are associated with more significant deficits in SC within at-risk populations, which could ultimately contribute to early detection of such vulnerabilities.

ASSOCIATION OF MARKERS OF ALTERED NEURODEVELOPMENT (NEUROLOGICAL SOFT SIGNS and POORER PREMORBID ADJUSTMENT) AND TOM

While the neurodevelopmental model is the most accepted etiological one in SZ, the role of early development markers has been little explored in relation to ToM variability, both patients and their family members. For this purpose, in this thesis, we have explored two indicators of altered neurodevelopment: NSS and PA.

Focusing on NSS, our study shows more evidence of neurodevelopmental deviances in patients than in siblings and controls, specifically in those domains involving motor aspects, such as motor coordination and sequencing of complex motor acts. More concretely, in relation to the latter, siblings exhibited an intermediate position between patients and controls, highlighting its potential role as an endophenotypic marker. Previous studies have shown that motor subscales are more affected in patients compared to relatives or controls. However, most of these studies have focused on older patients with a more chronic form of the illness duration in comparison to our sample (266–268). To our knowledge, only two previous studies explored a sample comparable to ours (young patients in the early stages of the disease). One reported increased NSS in motor coordination and sequencing for patients compared to both first-degree relatives and controls, though without significant evidence for an intermediate position of siblings (269). The other study demonstrated this intermediate position in a similar sample, but it was not specific to motor symptoms and used a different scale that did not differentiate sequencing of complex motor acts (270).

In this context, it is crucial to consider the potential influence of antipsychotic treatment on NSS. However, the observation that relatives and controls (who are untreated individuals) also exhibit NSS, though to a lesser extent, challenges the hypothesis that antipsychotic treatment is the cause of these subtle motor deficits. Even so, we must consider the possibility that the treatment has a modifying effect. However, the existing evidence to date would not support this idea (271–273). In this sense, most studies have not found associations between antipsychotic dosage and the severity of NSS, although NSS tend to decrease in patients who show adequate response to treatment (274).

Beyond considering the differences between the different groups in terms of the presence and type of NSS, we analysed the potential relationship these markers of altered neurodevelopment could have with ToM in each group. Unlike the few previous studies showing the correlation between NSS and poorer ToM performance in patients and indicating that they might share common neural mechanisms (275,276), our research did not find an association between NSS and ToM performance in the within-group analyses of patient, sibling, and controls. These inconsistent results can be explained by sample differences and different tools used to assess ToM. Although in all samples age of onset and years of education are similar, our sample is characterised by including patients in the early stages of the disease (less than 3 years of evolution), while previous studies included older patients with chronic SZ of more than 10 years of evolution. It is also interesting to note that both studies had adjusted the analyses by age and years of education, but not by IQ, unlike our study, which, due to its association with NSS, was included in the analyses. On the other hand, our findings are consistent with those reported in other developmental disorders, such as attention deficit and hyperactivity disorder, that, although they could confirm NSS as markers of atypical neurodevelopment and predictors of the severity of functional impairment, did not find a correlation with ToM abilities (277)

Focusing on the second indicator of altered neurodevelopment, PA, our findings, consistent with previous research (278,279), show poorer PA in patients compared to healthy siblings. This could have significant implications for monitoring individuals at high genetic risk, such as children of those with SZ spectrum disorders. Early identification of these high-risk subgroups and a better understanding of their variability could facilitate the management of environmental risk factors and enable closer monitoring for early signs of psychosis, potentially reducing the duration of untreated psychosis, which is associated with poorer outcomes. On the other hand, similar to the observed in the case of the NSS, our study could not add evidence supporting the recently reviewed and described relationship between ToM and PA (280), concluding that in our study, the intragroup analysis did not show an association between ToM performance and neurodevelopmental markers.

Subsequently, we examined whether these markers of altered neurodevelopment, NSS and PAS, significantly impacted HT performance differences between groups; in other words, if neurodevelopmental disturbances could underly the HT variability across groups. When comparing HT performance between patients and siblings, adjusted for NSS or PAS, our study did not report any significant influence of these neurodevelopmental markers. However, the slight decrease observed in the effect size (also reflected in the decrease in the mean differences of HT performance) suggests the interest of expanding the study of this relationship through studies with larger samples.

In addition, the integration of these results into our previous data on the role of clinical markers (with special focus on their negative dimension) in the characterisation of ToM in relatives suggests the interest of analysing both types of makers together in larger samples. This approach would be supported by the existing evidence that links SZ with pronounced negative symptoms to more severe neurodevelopmental disruptions, frequently reflected in the presence of NSS, as discussed in recent reviews (267,281). At the same time, to our knowledge, no study has attempted to make a similar approach based on other markers of altered neurodevelopment, such as dermatoglyphics or

minor physical anomalies, which invites to consider them as alternative or complementary markers to the NSS.

In summary, while ToM skills typically develop in early stages of life (19,20), we did not find a clear association between ToM and markers of altered neurodevelopment in our sample. From this perspective, it is worth noting that although our findings link both ToM impairments and more pronounced NSS to SZ, as well as motor NSS scales to the risk associated with being a first-degree relative, the two markers do not appear to be closely interrelated. This suggests they may involve distinct mechanisms underlying the risk and/or development of the disease; however, new analysis assessing clinical and neurodevelopment markers in an integrated manner could shed light on the potential common developmental roots of ToM and SZ.

ASSOCIATION OF GENETIC VULNERABILITY AND TOM

In this thesis we have used two approaches from a genetic point of view. First, we have incorporated the Family History (FH) variable, which emphasizes the study of familial genetic burden, complementing our use of clinical variables linked to familial risk. As implemented in our studies, such FH variable was recorded based on the index case of each family (the patient) and refers to the presence/absence of any other first and second-degree relative/s with a diagnosis within the psychosis spectrum. Therefore, the FH variable has the same value for all the family-members. In other words, a positive FH means that the patient has at least another family member affected; thus healthy relatives have at least two family members affected by a psychosis spectrum disorder (multiplex families). Second, through a more focused molecular genetic approach, we analysed the relationship between ToM and the polymorphic variability in a candidate gene from a functional perspective (the *OXTR* gene).

When we analysed the role of family history in the ToM variability in siblings, we observed that a higher familial load was significantly related to lower ToM skills. This is

in line with the study conducted by Tikka (2020), in which they compared ToM performance among patients with psychosis, a group of individuals at clinical high risk for psychosis, a cohort of siblings, and a control group. Their findings indicated that patients and both at-risk groups (familial and clinical) exhibited poorer ToM performance compared to controls, with no significant differences observed between the patient group and either of the risk groups (221). To our knowledge, no studies have looked at the role of family burden in relation to ToM deficits.

Using molecular-based approaches, some studies have also contributed to defining the relationship between the genetic liability for SZ and SC. In particular, GWAS have provided robust methods for quantifying individual genetic risk for SZ through the PRS, showing that PRS-SZ loading differed between groups of individuals with SSD, their relatives, and unrelated healthy controls (282). Such approaches have described an inverse correlation between PRS-SZ and some aspects of SC, such as emotion identification speed (283) and emotional recognition (284)). Also, the PRS-SZ has been inversely associated with interregional correlations (assessed through both structural and functional neuroimaging approaches) between the core and other face-processing brain regions in healthy young adults (285). However, a recent review (286) examined the evidence on the association between SC and PRSs predominantly for SZ, for autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder. Samples included either in people with mental disorders or controls. Among SC domains, emotion recognition was the most frequently explored. Overall findings showed that current PRSs for mental disorders do not significantly explain variations in SC performance.

Secondly, from a functional candidate gene approach, we have focused on the variability at oxytocin receptor gene (*OXTR*) and its potential relation to ToM. As outlined in the introduction, OXT is the most extensively studied neuropeptide regarding the biological bases of ToM and its behavioural effects are influenced by the distribution and expression of its receptor (OXTR), which is encoded by the *OXTR* gene.

Against expectations derived from this theoretical framework, our study found no family-based association between the *OXTR* gene and ToM. However, in controls and not in relatives or patients, the GG genotype modified the relation between schizotypy and ToM, making it significant. This suggests that among controls (with less liability load than relatives), high schizotypy may relate to poorer ToM performance conditional to the presence of the GG genotype.

This result is consistent with other studies that have provided evidence that *OXTR* polymorphisms are associated with different dimensions of SC in healthy individuals (287,288), although none have analysed the role of *OXTR* gene jointly with schizotypy. Despite family-based design is considered more robust and unbiased than case-control, to our knowledge, there is only a previous study with a similar design as ours. In that study, Wade et al. (2014) found an association between an *OXTR* polymorphism (rs11131149) and SC in 18-month-old children (289), and reported in the same longitudinal birth cohort an interaction between this *OXTR* polymorphisms and parenting behavior affecting ToM in 4-year-olds. These results highlight the role of the familial environment in early ToM development (290). Then, our results add to the heterogeneity across studies in relation to ToM genetic background in SZ, which is likely due to several factors such as the diversity of genotypes across studies, the variation in participants' ancestry and limited sample sizes. Also, we are aware that the consideration of only one gene is a restrictive approach in view of the complied data in a recent systematic review (291), that examines several genes-polymorphisms linked to ToM, across different psychiatric conditions, social behaviours, and neurodevelopment processes. Most of the reviewed data highlights the influence of genes involved in neurotransmission and hormonal regulation, *DRD4, DAT1, OXTR, OXT, COMT, ZNF804A, AVP, AVPR, SCL6A4, EFHC2, MAO-A,* and the *GTF2I* family on ToM abilities. However, the evidence remains inconclusive, with conflicting results regarding the association between specific genetic polymorphisms and ToM skills. Finally, our data and other family-based studies, also remark the need to consider environmental and

developmental factors for a much broader understanding of the ToM variability along the health-disease continuum.

Overall, our findings contribute to the ongoing discussion surrounding the potential for SC, specifically ToM, to serve as an endophenotypic marker of psychotic disorders. Building upon this framework, our study contributes to examining ToM variability by comparing patients with those at familial risk (siblings) and considering other clinical liability markers.

In particular, in line with other reported evidence (292), our data highlight the utility of clinical liability markers, particularly those related to the negative dimension, in identifying differences in ToM abilities within healthy individuals. The results suggest that ToM deficits are not only associated with SSD disorders but also with clinical vulnerability to these conditions. Moreover, our study demonstrates a significant relationship between familial load and reduced ToM abilities. Taken together, these findings support the notion that ToM could function as an endophenotypic marker, helping to identify individuals with heightened vulnerability, particularly within populations at genetic risk, such as siblings. This approach could help predict conversion to psychosis in risk groups, and thus perhaps optimize interventions in high-risk mental states. Taking into account that our findings point to those subclinical dimensions of vulnerability with a predominance of the dimension and considering that negative symptoms are predictors of greater long-term functional impairment, identifying individuals allows for the implementation of early therapeutic strategies that can reduce disease progression and preserve cognitive abilities. An intervention focused on training skills in ToM and other dimensions of SC could improve long-term outcome to a certain extent.

In contrast, our research did not find evidence of a significant role for neurodevelopmental markers in explaining ToM differences between groups, nor reveal a correlation between ToM and markers of altered neurodevelopment within the

separate groups of patients, siblings, and controls, contrary to what was expected. In this sense, considering the relationship of ToM with aspects closely related to development, the results invite to continue searching for other markers of altered neurodevelopment that may share a neurobiological substrate with ToM skills.

STRENGTHS AND LIMITATIONS AND FUTURE DIRECTIONS

Even though the sample size of our study is comparable to previous studies, it probably represents the main limitation of the studies included in the thesis. Contrasted with the sample size, our sample has the strength that the sample is very well characterised by multiple clinical and developmental variables. It is worth noting that one of the main disadvantages of family-based designs is the challenge associated with recruiting large samples of well-characterized families. At the same time, the family-based design is intrinsically associated with differences in sample sizes of the subgroups (more relatives than patients), which could represent a bias when conducting subgroups comparison analyses. Conversely, family-based approaches are associated with particular strengths. First, they provide a robust method for exploring genetic underpinnings while minimizing biases and confounding factors as they allow controlling for population stratification (or population structure), defined as the presence of a systematic difference in allele frequencies between subpopulations in a population. Such differences in genetic association studies usually refer to different ancestry; however, stratification can also respond to different sociodemographic or environmental exposures. Then, family-based designs, are also related to reduced confounding by environmental factors (since family members often share similar environmental exposures), and they are adequate for studying complex traits or diseases influenced by multiple genetic and environmental factors. Second, they allow the comparison between genetically related groups (patients and relatives) and also their assessment in relation to healthy unrelated subjects, which generates a perfect scenario for testing the

adequacy of a trait as an endophenotypic marker, due to the genetic vulnerability gradients along the three groups.

In relation to the SC assessment, while the Hinting Task (HT) is widely regarded as the most suitable tool for evaluating ToM, particularly within the psychosis continuum (178), a limitation of this research is that its findings are only applicable to the cognitive component of ToM. It does not account for the affective component of ToM or other dimensions of SC. Future studies should include larger samples and use different tasks to assess and differentiate ToM components (cognitive/affective, conceptual/perceptual) as well as other dimensions of SC, related not only to recognition but also to everything related to emotional processing, which could be explained by biological mechanisms other than ToM, which could help to continue outlining cognitive profiles of vulnerability. Given the heterogeneity of tasks used to assess SC, a detailed analysis is needed to clarify what each task specifically measures, whether affective or cognitive ToM, and how these relate to socio-cognitive or socio-perceptual processes. Additionally, considering other dimensions of SC, such as emotional processing, which may rely on biological mechanisms distinct from ToM, could further refine the cognitive profiles of vulnerability.

Also, its relevant to highlight that one of the important limitation in all research around the biological bases of cognitive phenotypes is to disentangle the effects of diseases and their treatments. For example, SZ, directly affects brain structure, function, and neurochemistry what difficults to determine whether observed cognitive phenotypes are caused by the disease itself or are inherent traits of the subject. Furthermore, the different treatments that the patient has received or receives in the moment of the assessment can significantly alter brain function and cognitive outcomes. For instance, antipsychotic could improve some cognitive symptoms while impairing others, and this could difficult our understanding of the underlying biological bases of the cognitive phenotype. According to some recent data showing that antipsychotic treatment can improve SC performance (293,294), the non-inclusion of quantitative treatment data in

our analyses could limit the interpretation of our results. In this case, if we had excluded the treatment effect, the patients' performance on ToM should be potentially worse and could show larger differences with relatives and healthy controls.

Future research should also continue the search for other markers of altered neurodevelopment in relation to ToM. The earlier and more accessible these markers are, the greater the potential for timely detection of individuals at risk of transitioning to psychosis. Early interventions are particularly crucial, as therapeutic effectiveness is higher during the brain's initial plastic stages.

In the context of genetic approaches, while family history remains a robust marker of genetic vulnerability, advances in genetic methodologies should be leveraged. Future studies should incorporate better-defined genetic risk profiles using polygenic risk scores PRS specific to SZ or other neurodevelopmental pathways. Additionally, to integrate environmental impacts, research should include comprehensive descriptions of environmental insults and epigenomic data. Combining genetic risk, environmental influences, and validated clinical and neurodevelopmental markers will enable the identification of more specific subgroups that could benefit from preventive interventions or tailored treatments. In relation to the study of specific genetic factors, a limitation of this study is that it analyses only a single SNP within a single gene (*OXTR*). This approach may not capture the full variability of genetic contributions to ToM. Genetic influences are often polygenic, and focusing on a single SNP may overlook other relevant variations or interactions within the gene or across different genes. Future studies incorporating a broader range of SNPs, incorporating PRS specific to SZ or neurodevelopmental pathways or a genome-wide approach could provide a more comprehensive understanding of the genetic factors involved. Research should also include detailed environmental and epigenomic data to integrate genetic and environmental impacts. Combining these factors with clinical and neurodevelopmental markers will help identify subgroups for targeted preventive or therapeutic interventions.

Exploring the anatomical and neurochemical underpinnings of this marker will further elucidate the biological basis of SZ and should be incorporated into future research. Advancing knowledge of the mechanisms underlying cognitive phenotypes like ToM deficits is especially valuable for translational research, where insights into biological mechanisms drive the development of targeted treatments. In this regard, the use of more homogeneous samples could yield better responses to specific pharmacological treatments. For example, intranasal OXT, a treatment with promising potential, has thus far yielded inconclusive results (48,295). Greater understanding of ToM and its related mechanisms may help refine these therapeutic approaches, ultimately benefiting individuals at various stages of risk for SZ.

6 CONCLUSIONS

The specific conclusions derived from the present thesis are developed below

The specific conclusions derived from the present thesis are developed below:

I. In our sample, the comparison of Theory of Mind skills (assessed with the Hinting Task) between patients with schizophrenia spectrum disorders, their first-degree relatives and unrelated healthy controls, showed: a) worse performance in patients than in healthy individuals (relatives and controls), b) similar performance in relatives and controls.

II. Trying to explain the heterogeneity of Theory of Mind our research shows that first degree relatives with increased clinical vulnerability to schizophrenia, as indicated by schizotypy, basic symptoms, or psychotic-like experiences (particularly in their negative dimensions) exhibit poorer Theory of Mind performance.

III. While patients show more evidence of neurodevelopmental deviances than healthy individuals (measured by means of neurological soft signs and premorbid adjustment), such higher neurodevelopmental load is not related to Theory of Mind between or within-groups variability.

IV. Our data show that a family history of psychosis is associated with Theory of Mind skills. In particular, a higher familial load was significantly related to poorer Hinting Task performance in relatives.

V. V. The quantitative transmission disequilibrium test showed no association between the OXTR gene and HT performance within families. The polymorphism rs53575 at the Oxytocin Receptor gene was not related to Theory of Mind in patients nor relatives. However, among controls (who have a lower genetic load compared to relatives), high schizotypy is associated with poorer Theory of Mind performance in those carrying the GG genotype.

VI. This thesis supports the adequacy of combining Theory of Mind with other susceptibility markers as a strategy to constraint the variability underlying schizophrenia, enhancing the identification of individuals at higher risk, particularly among relatives of people with the disease.

VII. In healthy individuals, especially in family-related ones, certain markers of increased risk for psychosis are associated with variability in Theory of Mind, helping to explain the heterogeneity in their performance. Specifically, in this thesis, clinical and familial markers are shown to contribute to Theory of Mind variability, while neurodevelopmental markers do not, suggesting that they may stem from different neurodevelopment-related pathways.

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