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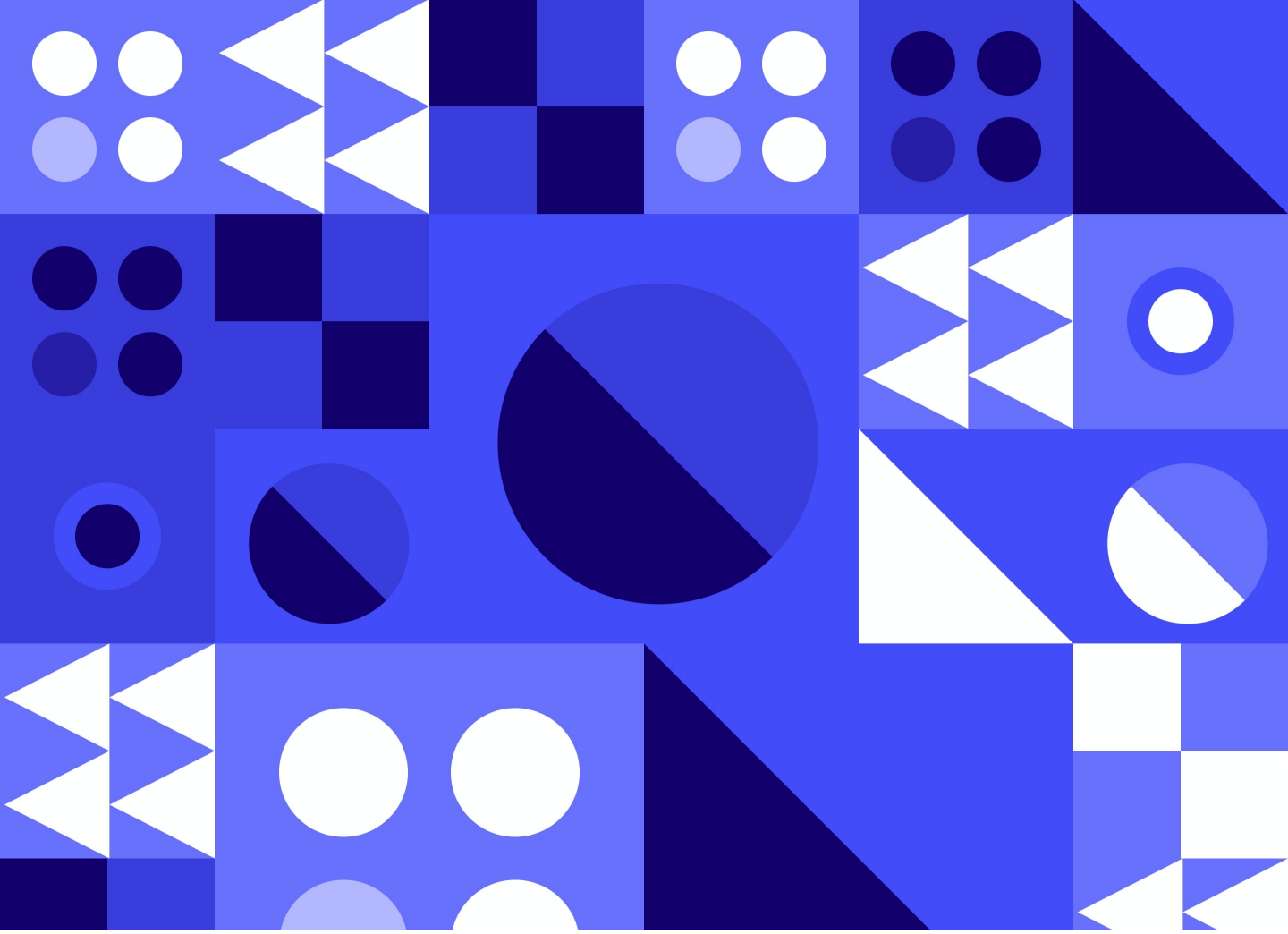
Towards personalized medicine in psychosis: the roles of social cognition and metacognition

Marta Ferrer Quintero



Doctoral thesis

TOWARDS PERSONALIZED MEDICINE IN PSYCHOSIS: THE ROLES OF SOCIAL COGNITION AND METACOGNITION

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Towards personalized medicine in psychosis: the roles of social cognition and metacognition.

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“It is not the actions of others which trouble us (for those actions are controlled by their governing part), but rather it is our own judgments”.

Marcus Aurelius, Meditations.

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GLOSSARY

FEP: First episode psychosis.

NIMH: National Institute of Mental Health.

SCIT: Social cognition and interaction training.

BCFT: Baron Cohen's Face Test.

ToM: Theory of Mind.

JTC: Jumping to conclusions.

BADE: Bias against disconfirmatory evidence.

MCT: Metacognitive training.

MERIT: Metacognitive Reflection and Insight Therapy.

LPA: Latent Profile Analysis.

SCIT: Social Cognition Interaction Training.

SCTP/PECS: Social Cognition Training Program / Programa de Entrenamiento en Cognición Social.

SCOPE: Social Cognition Psychometric Evaluation.

PREFACE

The present doctoral dissertation is a memory of the research work conducted between 2017 and 2022 as a predoctoral candidate at the Clinical and Health Psychology doctoral program at University of Barcelona and developed at Parc Sanitari Sant Joan de Déu with funding from Centro de Investigación Biomédica en Red – Salud Mental (CIBERSAM). Part of this dissertation was conducted in collaboration with the Green Lab (University of California Los Angeles), under the supervision of Dr. Michael Green and Dr. Junghee Lee, from August 2018 to November 2018.

The dissertation follows the article compilation format and is divided in four parts, supplementary material, and annexes. The first part summarizes the literature in the field. The second part presents the rationale for the present work and our approach to the research question. The third part is the empirical part. This dissertation follows the article compilation format. The fourth part discusses our results, and provides the limitations, future directions, and clinical implications in relation with the global objective of this work.

Study 1 was conducted with funding awarded to Dr. Elena Huerta-Ramos. Studies 2 and 3 are secondary data-analysis of two clinical trials testing the efficacy of Metacognitive Training and Individualized Metacognitive Training in people with first-episode psychosis, which were directed by Susana Ochoa as the principal investigator. The baseline data of the two databases were merged to conduct our analysis for this dissertation. This is the reason why in Annexes we present the ethical committee approval of both. Study 4 also stems from secondary data-analysis of a previous study at the Green Lab. To comply with data-protection policies, the approval of the ethics committee was not included, but we received explicit consent to include the published article as part of this dissertation.

ABSTRACT

People with psychosis experience a range of symptoms and impairments that significantly impact their lives and often concur with disability. The best predictors of functional outcome are social cognition and metacognition, which are often impaired in psychosis. Interventions to improve both domains are effective, but this efficacy does not always translate into better functioning. Delivering early, and targeted social cognitive or metacognitive interventions to patients with psychosis could be instrumental in preventing poor functional outcome and preventing relapse, but the grounds on how to personalize these interventions are unknown. Although it has been suggested that the approach should take sex differences, the refining of measurement instruments and the use of sophisticated statistical models, these have not been explored yet. Under this rationale, the present doctoral dissertation aims to:

1) validate a test of facial emotion recognition (Baron Cohen's Face Test) in healthy population, with the aim of detecting whether it is an appropriate tool to use in clinical research, 2) detect whether patients with first episode psychosis have different, clinically meaningful profiles of performance in social cognition and metacognition, 3) explore the sociodemographic, clinical, and neurocognitive characteristics of each profile, 4) examine if males and females with first episode psychosis are similar in their heterogeneity in social cognition and metacognition, 5) explore the role of social cognition and sex in functional outcome in people with established psychosis (schizophrenia).

This broad aim yielded four research articles. The main findings of this doctoral dissertation are a) Baron Cohen's Face Test is an adequate and reliable instrument to measure facial emotion recognition in Spanish population but it presents a ceiling effect, b) People with first-episode psychosis have distinct profiles of social cognition and metacognition that have specific clinical and neurocognitive correlates. Having worse social cognition is associated with worse clinical presentation, even if metacognition is preserved, c) Men and women with first-episode psychosis have

similar configurations of social cognition and metacognition. However, there are sex-specific profiles that should be considered when delivering treatment. Sex-specific profiles seem to be associated with more severity of the disorder than the common profiles.

These results suggest that people with psychosis can receive social cognitive or metacognitive targeted treatment as early as after the first episode, but these should be chosen considering the profile of each individual and their biological sex. Thus, patients with psychosis should always be carefully assessed for social cognitive and metacognitive performance.

RESUMEN

Las personas con psicosis experimentan una serie de síntomas y déficits que afectan significativamente a sus vidas y que a menudo concurren con la discapacidad. Los mejores predictores de funcionamiento son la cognición social y la metacognición, que a menudo presentan deterioro en personas con psicosis. Diversas intervenciones para mejorar ambos dominios son eficaces, pero esto no siempre se traduce en un mejor funcionamiento. Para ello, se ha propuesto que intervenciones en cognición social y metacognición tempranas y dirigidas podrían maximizar su efecto sobre el funcionamiento y la prevención de recaídas. No obstante, se desconocen los fundamentos que debería guiar su personalización. Aunque se ha sugerido que el enfoque debería tener en cuenta las diferencias de sexo, el perfeccionamiento de los instrumentos de medida y el uso de modelos estadísticos sofisticados, éstos aún no se han explorado en la literatura.

Bajo este razonamiento, la presente tesis doctoral pretende: 1) validar una prueba de reconocimiento facial de emociones (Test de Caras de Baron Cohen) en población sana, con el objetivo de detectar si es un instrumento adecuado para utilizar en la investigación clínica, 2) detectar si los pacientes con primer episodio de psicosis tienen perfiles diferentes y clínicamente significativos de rendimiento en cognición social y metacognición, 3) explorar las características sociodemográficas, clínicas y neurocognitivas de cada perfil, 4) examinar si los hombres y las mujeres

con primer episodio psicótico son similares en su heterogeneidad en la cognición social y la metacognición, 5) explorar el papel de la cognición social y el sexo en el resultado funcional en personas con psicosis establecida (esquizofrenia).

Este amplio objetivo dio lugar a cuatro artículos de investigación. Los principales hallazgos de esta tesis doctoral son: a) El Test de Caras de Baron Cohen es un instrumento adecuado y fiable para medir el reconocimiento de emociones faciales en población española, pero presenta un efecto techo, b) Las personas con primer episodio psicótico tienen perfiles distintos de cognición social y metacognición, con correlatos clínicos y neurocognitivos específicos asociados. Tener una peor cognición social se asocia con una peor presentación clínica, incluso si la metacognición está preservada, c) Los hombres y las mujeres con primer episodio psicótico tienen configuraciones similares de cognición social y metacognición. Sin embargo, existen perfiles específicos de cada sexo que deben tenerse en cuenta a la hora de aplicar el tratamiento, ya que éstos parecen estar asociados a una mayor gravedad del trastorno que los perfiles comunes.

Estos resultados sugieren que las personas con psicosis pueden recibir tratamiento en cognición social o metacognición específico desde el primer episodio psicótico, pero éste debe elegirse teniendo en cuenta el perfil de cada individuo y su sexo biológico. Para ello, se pone de manifiesto la necesidad de una correcta evaluación de sus habilidades cognitivo-sociales y metacognitivas.

RESUM

Les persones amb psicosi experimenten una sèrie de símptomes i deterioraments que afecten significativament les seves vides i que sovint concorren amb la discapacitat. Els millors predictors de funcionament són la cognició social i la metacognició, que sovint presenten deterioració en persones amb psicosi. Existeixen diverses intervencions eficaces per a millorar tots dos dominis, però això no sempre es manifesta en un millor funcionament. Per a això, s'ha proposat que les intervencions en cognició social i metacognició primerenques i dirigides podrien maximitzar el seu efecte sobre el funcionament i la prevenció de recaigudes. No

obstant, es desconeixen els fonaments que haurien de guiar la seva personalització. Encara que s'ha suggerit que l'enfocament hauria de tenir en compte les diferències de sexe, el perfeccionament dels instruments de mesura i l'ús de models estadístics sofisticats, aquests encara no s'han explorat en la literatura.

Sota aquest raonament, la present tesi doctoral pretén: 1) validar una prova de reconeixement facial d'emocions (Test de Cares de Baron Cohen) en població sana, amb l'objectiu de detectar si és un instrument adequat per a utilitzar en la recerca clínica, 2) detectar si els i les pacients amb primer episodi psicòtic tenen perfils diferents i clínicament significatius de rendiment en cognició social i metacognició, 3) explorar les característiques sociodemogràfiques, clíniques i neurocognitives de cada perfil, 4) examinar si els homes i les dones amb primer episodi psicòtic són similars en la seva heterogeneïtat en la cognició social i la metacognició, 5) explorar el paper de la cognició social i el sexe en el resultat funcional en persones amb psicosi establerta (esquizofrènia).

Aquest ampli objectiu va donar lloc a quatre articles de recerca. Les principals troballes d'aquesta tesi doctoral són: a) El Test de Cares de Baron Cohen és un instrument adequat i fiable per a mesurar el reconeixement d'emocions facials en població espanyola però presenta un efecte sostre, b) Les persones amb primer episodi psicòtic tenen perfils diferents de cognició social i metacognició, amb correlats clínics i neurocognitius específics associats. Tenir una pitjor cognició social s'associa amb una pitjor presentació clínica, fins i tot quan la metacognició està preservada, c) Els homes i les dones amb primer episodi psicòtic tenen configuracions similars de cognició social i metacognició. Ara bé, existeixen perfils específics per cada sexe que s'han de tenir en compte a l'hora d'aplicar el tractament, ja que aquests semblen estar associats a una major gravetat del trastorn, més que no pas els perfils comuns.

Aquests resultats suggereixen que les persones amb psicosi poden rebre tractament en cognició social o metacognició específic des del primer episodi psicòtic, però aquest ha de triar-se considerant el perfil de cada individu i el seu sexe biològic. Per tant, es posa de manifest la necessitat d'una correcta avaluació de les seves habilitats cognitivo-socials i metacognitives.

PART I: BACKGROUND AND THEORETICAL FRAMEWORK

1. PSYCHOSIS

The DSM 5 includes psychosis spectrum disorders as the set of clinical syndromes that concur with abnormalities in one or more of these domains: delusions, hallucinations, disorganized thoughts, disorganized behaviors, and negative symptoms [1] . According to the World Health Organization, approximately 24 million people live with schizophrenia, the most severe mental illness in the psychosis spectrum [2].

Although the prevalence of psychotic disorders is relatively low, it is a leading cause of disability, what carries significant societal, economical, and personal burden [3]. In Spain, the societal cost of psychotic disorders is approximately 8000 million € per year, 70% of which are indirect costs of absence from work and early retirement [4].

Symptoms of psychosis are diverse but are usually grouped by their similarities. Positive symptoms include hallucinations, delusions, disorganized thoughts, or bizarre behavior [5]. Although these are disruptive and usually require immediate medical attention, most patients with psychosis learn to cope with them and do not rate them as distressing as other constellations of symptoms [6], for instance, negative symptoms. Negative symptoms include the set of experiences that diminish the person's psychic activities. These are the most resistant to treatment and concur with high disability and withdrawal from society [7]. In the last years, negative symptoms are often conceptualized into two great domains: diminished expression, which includes an impoverishment of verbal and non-verbal communication- resulting in poor facial expressions and lack of spontaneity, and experiential symptoms, which refer to a lack of social motivation derived from an impaired ability to experience reward from social interactions and activities [8,9].

Although these are the two most classically reported clusters of symptoms, and central to the diagnosis of psychosis according to the DSM-5 criteria, psychosis concurs with substantial impairments in other domains that have a profound impact in their quality of life and prognosis [10]. A core component of psychosis is neurocognitive impairment [11,12] . Most people with psychosis have decreased abilities in executive functioning, speed of processing and attention [11,12], which are already apparent at the first episode of psychosis (FEP) [10] and are strong predictors of functional outcome [11]. Similarly, people with psychosis have important difficulties in understanding the social world and in elaborating complex representations of both the world and their own experiences [12,13]. All these

difficulties, together with considerable social and self-stigma [14] decrease the person's quality of life. Often, the lack of social integration and diminished quality of life lead people with psychosis to experience a high prevalence of depressive symptoms [15] and suicidal behaviour [16].

Despite advances in pharmacological and psychological treatment, improving social and functional outcomes remains a challenge [17]. This is because its efficacy is restricted to positive symptoms, but these are not the most debilitating for most patients.

In the last decades, shifts in the understanding of psychosis and its treatment have placed importance in understanding these patients from a broader and more integrative approach. Although psychosis was once thought to escape psychological treatment, meta-analytic findings now support its effectiveness [18], even in the absence of pharmacological treatment [19,20].

Another tipping point was the staging model of psychosis, which ranges from the at risk-mental state to treatment resistance [21]. This model was proposed to deliver better, safer, and timelier treatment to people with psychosis. Under this umbrella, there is now overwhelming evidence that delivering intensive psychological treatment to people at clinical high risk (CHR) or during the five years after the first episode can delay onset, improve trajectories of illness, prevent relapse and foster recovery [22–24]. These interventions often include antipsychotic treatment, cognitive behavioral treatment, family psychoeducation and vocational training or support [22]. Recently, efforts in detecting preventive strategies [25], risk factors [26] , and polygenic risk scores [27] are yielding a new understanding of psychosis and suggesting new treatment targets that promise new advances.

2. SOCIAL COGNITION

Problems of people with psychosis in understanding and engaging with the social world have been described since the first conceptualizations of schizophrenia [28], but it has not been until the last two decades that poor social engagement and function have gained attention as potential explanatory and therapeutic targets of psychosis.

A National Institute of Mental Health (NIMH) Workshop on Social Cognition in Schizophrenia defined social cognition as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others" [29]. Its goal was to conceptualize the domains that are significant in the symptoms and prognosis of psychosis:

- **Theory of Mind (ToM)** involves the ability to infer intentions, dispositions, and beliefs of the others.
- **Social perception** encompasses the correct identification of social roles, rules, social context, and relationships between persons.
- **Social knowledge** permits the correct interpretation and response to rules, goals, and social cues in social interactions.
- **Attributional biases** concern the causes that individuals attribute to events. Attributional biases are a cornerstone of all cognitive models of mental illness. Typically, the focus is whether people attribute evens to themselves or to external factors.
- **Emotional processing** scopes the perception of emotion in other people's faces, prosody, or body movement.

Table 1: Social cognitive deficits per domain and stage of illness.

	Clinical High-Risk [a]	First-episode psychosis [b]	Established illness [c]
Emotional processing	Significant impairments in facial emotion recognition (d = 0.48, 95% CI = 0.27, 0.69). The impairment seems restricted to recognizing, but not discriminating, emotions.	Impaired at an effect size comparable to established psychosis.	Large effect for emotion perception (Hedge's g = 0.89) and emotion processing (g = 0.89).
Theory of Mind	Moderate impairments in a global measure of ToM (d = 0.44, 95% CI= 0.19, 0.68). Most prominent impairments in verbal Theory of Mind. Could predict conversion to psychosis, but more research is needed.	Strong and consistent impairment of verbal ToM.	Large effect (Hedge's g = 0.96) compared with healthy controls.
Social perception	Not enough information to calculate mean effect size.	Limited evidence, suggest important impairment compared with healthy controls.	Large effect size (g = 1.04) despite a significantly lower number of published studies.
Social knowledge	Not enough information to calculate mean effect size.	Not reported	Not reported
Attributional bias	Not enough information to calculate mean effect size. Studies were analyzed separately, but results were inconclusive.	Not reported, but only subgroups of patients with FEP may exhibit a hostile attributional bias.	No significant differences between people with schizophrenia and healthy controls. Personalizing bias may be associated with paranoid traits, in clinical and healthy samples.

[a] Information extracted and summarized from van Donkersgoed et al. (2015)[39]. [b] Information extracted and summarized from Healey et al. (2016)[35]. [c] Information extracted and summarized from Savla et al. (2013)[30].

2.1. SOCIAL COGNITION AND SYMPTOMS

The association between social cognition and negative symptoms is consistent and well-reported [30,40,41], and most studies have found moderate to large associations between both domains.

In positive symptoms, the associations are less clear. For instance, Healey et al. (2016) found meta-analytic support for a relationship between all social cognitive domains and negative – but not positive symptoms [35] in patients with FEP. In contrast, previous [42] and recent [43] studies report strong links between social cognition and disorganized symptoms in established schizophrenia. Discrepant findings between the two stages of illness may be due to the adequate response to medication of patients with FEP, what can blur possible associations during remitted phases [35]. Savla et al. (2013) [30] argue that longer duration of illness and hospitalization status are important moderators in emotion processing and perception, and social perception. Hospitalization status can be considered a proxy for positive symptoms, as most patients are admitted when positive symptoms are exacerbated [30]. These explanations suggest that social cognitive deficits may have both state and trait-like qualities.

As per specific subdomains and symptoms, some studies have found that deficits in ToM are specific to paranoia [44,45], while other study found that that poor ToM correlates with auditory hallucinations [46]. Likewise, in the general population, poorer ToM seems to be associated with some forms of attenuated suspiciousness [47]. In the case of facial emotion recognition, the evidence is contradictory. Although most studies agree in that it is associated with negative symptoms [48–50], others have also reported associations with thought disorder [51] and overall positive symptoms [52]. An explanation of possible inconsistencies is that it seems that each emotion correlates with different symptoms: poor recognition of happiness and surprise seems associated with positive symptoms, negative symptoms are associated with more errors in recognizing surprise, happiness, sadness and contempt, and depression correlates with poorer recognition of happiness [53].

Regarding attributional biases, the literature is somewhat unclear because attributional biases often load in a single, separate factor [54,55]. It is likely because attributional bias refers to where the causes of events are places, while the rest of social cognitive domains involve perception and processing of social information. However, events do not necessarily need to be social to be interpreted. Likewise, some studies have considered attributional biases as part of metacognition [56,57]. In the present work, we will consider them as metacognitive phenomena, and will be discussed further in sections 3 and 4.

Finally, given the lack of studies on social perception and social knowledge, the information is limited and their specific effect on symptoms is unknown.

2.2. Social cognition and functioning

There is compelling evidence of the links between social cognition and functioning, often at a larger effect than neurocognition [58,59]. Studies using multifactorial models found that a path from neurocognition to functional outcome, mediated by social cognition, explains 25% of the variance [60].

However, measuring the predictive power of social cognition over functioning has proved easier than understanding how. One of the most accepted models derives from structural equation modelling that explores a pathway from perception to functional outcome [61]. In this model, there is a linear sequence from perception to functional outcome through social cognition, defeatist beliefs, and negative symptoms. Early perceptive deficits distort the development of social cognition, which precludes positive social experiences. Cumulative bad social experiences promote defeatist beliefs, which can lead to negative symptoms and, ultimately, poor functional outcome.

Pelletier-Baldelli and Holt (2020) found that negative symptoms are especially prominent in social situations, what lead them to pose that negative symptoms may be a functional consequence of poor social cognition. In a review of models, they found that the model with larger empirical support is a unitary one in which perceptual changes are the root of poor social functioning, with several mediating variables in between [62].

There are other important variables that may mediate the path from neurocognition to functional outcome, like internalized stigma, resilience, and treatment adherence [12], which are often overlooked. By including these factors in future research, we may gain a better understanding of psychosis and identify new targets of treatment.

2.3. Social cognitive interventions

Testing whether improvement in social cognition translates into better functional outcome seems the logical step after establishing the links between both. There are multiple intervention programs directed to improve social cognition available in different formats, implementation methods and modality. Most of them include a combination of psychoeducation, practice exercises and social stimuli. We summarize the most representative social cognitive intervention (SCIT) and an intervention developed and tested in Spain in table 2.

Most programs seem to improve at least one domain of social cognition, but these benefits do not seem to automatically translate into better functioning or decreased symptoms [63], what could be a consequence methodological limitations, heterogeneity in measures, and diverse operational definitions of outcome [64]. A recent, exhaustive, network meta-analysis[65] found that global programs to improve social cognition (interventions that focus in all social cognitive domains) have important effects on emotion perception, social perception, ToM and social functioning. However, these effects are somewhat limited in time.

Horan and Green (2018) highlight that not all patients seem to benefit from social cognitive intervention, and that patients may need bridging strategies to transfer skills from the research setting to daily life [64].

Most social cognitive interventions have been tested in people with established psychosis. In comparison, data on participants with ultra-high risk or FEP is fewer. Even if preliminary evidence seems promising [66,67], it is inconclusive. Given that the therapeutic window is broader during these stages, early social cognitive treatment may prove a valuable tool to promote recovery and prevent relapse.

Table 2. Two representative social cognitive interventions.

Intervention	Description	Evidence
Social cognition and interaction training (SCIT)[68]	18-24 weekly sessions. Group setting. Targets: emotion perception, theory of mind, attributional style.	Several clinical trials in different countries support its efficacy in improving social cognition and functioning [69–72] . Preliminary data on its evidence as an online training program [73]. Other study has failed to find significant differences in any domain [74]. Data on its long-term efficacy and translation to real-world outcomes is lacking.
Social Cognition Training Program [75] (SCTP/PECS)	24 weekly sessions. Group setting. Targets: emotion perception, theory of mind, attributional style, social perception, and social knowledge. Includes 4 sessions to adapt the content of the sessions to the specific thoughts and impairments of the participants. Freely available for research and clinical settings.	Effective in improving social cognition but not functioning [76]. A brief version of 12 sessions yielded similar results [77]. Replication of results in more trials is lacking.

3. METACOGNITION

Metacognition is a broad concept used across different disciplines of psychology that refers to "thinking about thinking". It includes being aware of one's own thoughts and desires and how these relate to one another. By its own definition, metacognition is an integrative and continuous cognitive process that allows humans to constantly incorporate new information into their selves [78]. It was first coined by Flavell, who defined the four most relevant aspects of metacognition[79]: metacognitive knowledge, metacognitive experiences, metacognitive goals and metacognitive actions or strategies.

Metacognitive knowledge refers to understanding that people are cognitive beings with diverse experiences, goals, and actions. For instance, in healthy population, a metacognitive knowledge event could be realizing that algebra is often difficult for most people, but easy and intuitive for one. Conversely, a pathological interpretation of the same example may be: *"I am the very best person at algebra in the entire world".* Metacognitive experiences are conscious reflections about cognitive processes. In the previous example, a person aware of being good at math should feel confident about their probabilities of passing an algebra exam. However, being convinced that one's exam will be a breakthrough in math reflects deviations in metacognition.

Metacognitive goals and strategies often stem from metacognitive experiences. Metacognitive experiences have to do with a "sense", for instance, that you have not learnt a chapter of a book well enough for the exam.

3.1. MODELS OF METACOGNITION IN PSYCHOSIS

Contrary to social cognition, subdomains of metacognition are not as clear and well identified. This is, partially, because metacognitive processes appear at a supraordinate level of all cognitive processes. Thus, it can refer both to the unawareness of having cognitive deficits because of brain damage (*anosognosia*) and to questioning whether a social interaction was appropriate. When applied to psychosis, metacognition has comprised several different models that have in common their interest in the subjective and psychological processes that frame how people interpret and respond to the world [13].

a) Well's metacognitive model

Well's metacognitive model was initially proposed for generalized anxiety disorder [80]. Their framework identifies that anxiety stems from positive metacognitive beliefs about dangerous future events *("Worrying about the future will help me prepare")* and negative metacognitive beliefs, that trigger negative appraisals and emotional reactions (*"I am worrying so much that I will go crazy").* This model could also explain the causes and maintenance of psychosis, but it does not hold strong scientific evidence [81], although recent research found that negative metacognitive beliefs are associated with psychotic symptoms, greater negative affect and are stronger predictors of negative affect over symptom frequency [82].

b) The integrated model of metacognition

Lysaker et al (2018) [83] postulated an integrative model of metacognition, which understands it as a spectrum of cognitive activities that include awareness of specific discrete experiences as well as an understanding of how those specific experiences are connected in one's broader life experience. This spectrum continuously interacts to generate a cohesive sense of oneself, what permits fitting events and experiences into a larger narrative. To permit integration, discrete components must be available at a sufficient level.

The components, usually measured with the Metacognition Assessment Scale (MAS) or its abbreviated version (MAS-A) [84,85] include: self-reflectivity (ability to form complex representations of oneself), understanding others' minds (capacity to form complex representations of other people), decentration (recognize that the others' mental states are influenced by a range of factors) and mastery (to respond and cope with psychological problems using metacognitive knowledge). Studies under this model have found that metacognitive capacity is associated with functioning [86,87] and self-compassion [88], among others.

c) The cognitive behavioral model of metacognition

Moritz et al [89] used the term "metacognition" as an explanation of how people gain awareness of their own cognitive distortions and how they can reduce overconfidence in wrong judgments, what ultimately foster the appearance of delusional beliefs. This model is rooted in previous knowledge of the cognitive biases that are implicated in psychosis. Cognitive biases are systematic errors in processing and generating meaning consistently across time and situations [90,91]. The nature of cognitive biases is not pathological per se- this is, all human beings

perform certain cognitive biases [92]. However, there are specific cognitive biases associated with psychosis, which are thought to be involved in the genesis and maintenance of delusions. These include biases in probabilistic reasoning [93], acceptance of disconfirmatory evidence or overconfidence in errors [94]. Interestingly, these biases are also present in healthy individuals that report psychotic like experiences [95], what gives further evidence of their important role in the emergence of psychosis. These biases represent general thinking styles that are extreme deviations of normal cognitive biases, and can also be found in neutral contexts [89].

Cognitive biases are not metacognitive phenomena by themselves. Rather, it is the poor awareness of their cognitive distortions that is a reflection of poor metacognitive monitoring [96]. According to the author, the metacognitive component central to his model is the reduction of overconfidence by sowing the seeds of doubt [97]. Following Koriat's tradition, this model sees the interplay between confidence and accuracy as a core metacognitive process [98].

The cognitive biases included in this model are:

Jumping to conclusions (JTC)

A tendency to make decisions using little evidence is referred to as "Jumping to conclusions" (JTC) [99]. People with psychosis, their healthy relatives [93], people at CHR of psychosis [100] and people in the general population with delusion proneness [101] present this bias, what suggests the important role of JTC in delusion formation. Although less replicated, other studies have found that JTC is associated with hallucinations and hallucination proneness [102].

JTC can be considered a general thinking style, but its presence together with poor belief flexibility facilitates the acceptance of salient information without considering further and precluding from reflecting from past learnings. This process impedes questioning whether a belief might be mistaken [103]. Indeed, meta-analytic findings confirm that the presence of the JTC presents liability to delusions [99], although it also warns that it is not a necessary nor sufficient cause for the onset of psychosis.

A broad corpus of research has examined the associations between JTC and other important variables of psychosis, and results suggest that the presence of JTC has a strong relationship with social cognitive impairment [104], worse neurocognition [102,105,106] and worse outcome [107].

Attributional bias

Attributional biases reflect the set of causes that people often attribute to events [29]. As such, they involve the style in which people tend to respond to certain (e.g., social) events [108]. One of the first cognitive models of psychosis, proposed by

Bentall, Kinderman and Kaney [109, 110], suggests that people with psychosis have defeatist/negative beliefs about themselves that can be activated by events. To preserve their self-esteem, patients displace the blame towards the others or to uncontrollable circumstances, thus resulting in delusions. This is generally referred to as personalizing and externalizing biases. A posterior development of this notion found strong evidence supporting that people with persecutory delusions exhibit a personalizing bias, this is a tendency to blame the others for negative events only [111].

However, literature on this topic has yielded conflicting results throughout the years. For instance, cumulative evidence seems to confirm that a hostile attributional bias (a tendency to interpret the other's behavior as hostile rather than other causes [112]) seems to be a state-dependent feature that is common to both diagnosed and undiagnosed samples, that activates in the face of stress and that is associated with paranoia [108]. Similarly, this seems to be the case with personalizing and externalizing biases. According to Bentall's new dynamic model of attribution self-representation cycles, attributional style fluctuates according to the events and in the face of changes in self-representation [113].

Bias against disconfirmatory evidence

Beliefs have a dynamic nature because they tend to evolve or change in the face of new information. This is a metacognitive ability coined as "belief flexibility" [103]. If this process fails, a person may adhere to false beliefs because they are unable to incorporate better alternatives (bias against disconfirmatory evidence, BADE). Holding to a false belief even if it has proven to be false is a hallmark of delusions [114].

Subclinical populations and patients at all stages of psychosis present the BADE [114], which is often more pronounced during active delusions [115]. The BADE seems to increase with severity of psychosis, but can be considered a part of the cognitive basis of psychosis, and its role seems more pronounced in the maintenance of delusions than in its generation [114]. Increasing the awareness of patients in their inability to correct their beliefs is then crucial in "fragmenting" current delusions and preventing relapse.

Overconfidence in errors

People with psychosis place unusually high confidence in the accuracy of their memory, what can raise the conviction threshold and help forming or maintaining delusional beliefs [116]. This effect seems to appear because people with psychosis are not aware of their poor performance in difficult tasks [116] and cannot reach a reasonable judgement of their accuracy. Notably, overconfidence in errors is not an artifact of psychosis. Rather, this bias is present in population at CHR and FEP

[117], and first-degree family members of patients [118] , therefore pointing to its role as a vulnerability factor for psychosis.

d) Common components

Although research under each model has framed their specific subdomains of metacognition and used tasks developed to measure them, there are some common components that most authors agree on their metacognitive nature:

Clinical insight:

Clinical insight is the ability to gain accurate and deep understanding of having a mental disorder, the need for treatment, the specific symptoms of the disorder and the personal and social consequences of the disorder [119]. Poor clinical insight is common in psychosis, which is not surprising because psychosis concurs with a distortion in reality [120], but it is sometimes restricted to a specific aspect of the disease, such as the need for treatment [121]. Unawareness of having a mental disorder predicts treatment non-compliance [122] and outcomes of psychosis [120]. However, good clinical insight is a double-edged sword for patients with psychosis because better illness awareness seems to predict depressive symptoms and suicidal behavior [123]. Therefore, given the strong links between clinical insight, treatment adherence, outcomes and suicidal behavior, clinical insight has become a major target of treatment [120] in which clinicians must achieve a balance between adequate insight and mood.

Clinical insight is usually treated as both a metacognitive and clinical concept. Clinical, given their associations to treatment compliance and outcomes, and metacognitive because being aware of a mental disorder necessarily requires evaluating whether one's own experiences are real or are symptoms, and whether a health professional should be trusted [124].

Cognitive insight:

Cognitive insight refers to the set of cognitive processes that permit questioning one's beliefs and appraisals, and to re-evaluate anomalous experiences or misinterpretations [125]. In this sense, cognitive insight differs from clinical insight in that it is concerned with thought processes and reasoning styles beyond psychiatric challenges [126]. Traditionally, it is measured with Beck's Cognitive Insight Scale [127], which yields two subscales: self-reflectivity and self-certainty.

Self-reflectivity refers to a person's ability for introspection and willingness to admit fallibility. Conversely, self-certainty refers to the confidence a person has in their beliefs and judgements [125]. It is suggested that the formula for good cognitive

insight is high self-reflectivity and low self-certainty [127]. This is because higher self-reflectivity has usually been associated with better outcomes and treatment response [128] , while higher self-certainty is associated with more delusions and worse cognitive function [129–132]. The differential associations between both suggest that improving cognitive insight requires specific interventions. For instance, a study found that self-certainty relies on acquired knowledge, while self-reflectivity is more associated with clinical illness [133], and thus, the therapeutical mechanisms to improve them may be directed to each.

There is, however, a caveat in improving cognitive insight, because similarly as with increased clinical insight, high self-reflectivity is usually associated with more depressive symptoms [134], but these association may decrease in time as high self-reflectivity enables distance from thoughts and mood [135].

3.2. Metacognitive interventions

The main difference between improving social cognition and improving metacognition resides in that social cognitive interventions aim to increase social cognitive abilities (e.g., scoring better in a ToM test), while metacognitive interventions aim to reduce the biases that foster the development of delusions and create meaning. Moritz et al (2019) have summarized the differences in approaching metacognitive deficits and highlight new developments [97]:

a) Metacognitive therapy (Wells et al):

Metacognitive therapy aims to detach individuals from their awareness to distressing thoughts, control ruminations and target unhelpful attentional strategies. Although this therapeutic approach is well established in other mental disorders [136], there is very preliminary but promising data in psychosis [137]: a pilot study with three treatment-resistant patients with psychosis found clinically significant improvement in delusions and PANSS total score [137].

b) Metacognitive Insight and Reflection Therapy (MERIT)

This approach has the goal of addressing fragmentation in cognition, emotion and volition relying in the integrated model of metacognition [138,139]. MERIT is an individual psychotherapy that should meet the needs of patients with psychosis. To this aim, MERIT works on eight elements that therapists should engage in [139]: a joint understanding of the patient's agenda, an ongoing therapeutic dialogue, patient's narratives, psychosocial challenges, reflection of the interpersonal

processes, consideration of the session's effect on patient's cognitive and emotional experiences, reflection about the self and others, and metacognitive mastery.

Clinical trials have endorsed the efficacy of MERIT [138,140]. However, it must be noted that this intervention is longer than others and that requires extensive training and experience from therapists.

c) Metacognitive training for psychosis (MCT)

This treatment was designed to target the cognitive biases that are implicated in psychosis. MCT uses a normalizing approach, thus considering cognitive biases as a deviation from normality, and encourages participants to gather more information and reduce overconfidence in their own judgements. Likewise, MCT raises metacognitive awareness for cognitive biases so that participants become aware of their own thinking processes. MCT consists of at least 8 weekly sessions in a group setting. The sessions cover topics such as jumping to conclusions, attributional style, flexibility in beliefs, facial emotion recognition, empathy, and memory. MCT is a manualized intervention, what means that most mental health professionals can deliver the intervention reliably. Meta-analytic evidence suggests that MCT exerts a small to medium effect size on symptoms compared to other interventions [141–143]. A recent, comprehensive meta-analysis [144] confirmed the beneficial effects of MCT in the short and long term in clinical symptoms, functioning, self-esteem and quality of life. Importantly, this approach also has evidence of efficacy in FEP [145], depression [146], negative symptoms [147] and obsessive compulsive disorder [148].

4. CURRENT CHALLENGES IN SOCIAL COGNITION AND METACOGNITION

4.1. MEASURING SOCIAL COGNITION AND METACOGNITION:

A prerequisite for accurate data, both in the clinical and research settings, is to administer psychometric tasks that are reliable, adequate and have good psychometric properties.

However, instruments for measuring social cognition and metacognition have generally had poor (or unknown) psychometric properties and have seldom been validated in more than one cultural context. In an admirable effort to obtain adequate social cognitive measures that are available to the research community, the SCOPE project selected and validated the best tasks for each domain of social cognition [112,149,150], albeit only in population in the United States. These are summarized in table 3. However, out of the aforementioned tasks, only the Hinting Task [151] and the Reading the Mind in the Eyes test [152] have been validated in Spanish. This is an important pitfall in research in social cognition in psychosis because different measures prevent comparability between studies and are a source of variance in meta-analytic studies. Furthermore, social cognition may be influenced by cultural contexts [153], what calls for validating measures in their specific cultural context. Another pitfall of current social cognitive measures is their lack of ecological validity [59]. Social interactions are complex by nature, but measures of social cognition simplify that complexity to develop tasks that are feasible to use in research and clinical practice. However, it is likely that this effect is overestimating the real social cognitive functioning of the individuals, as participants may compensate for their impairments by using more time to decide, verbal intelligence ability or learning effects.

Table 3: Final measures extracted and validated by the SCOPE project.

Domain	Test/s	Task
Facial emotion recognition	Penn Emotion Recognition Test[154]	Includes 40 color photographs of static faces expressing 4 basic emotions (happiness, sadness, anger, fear) and neutral expressions. Participants chose the correct emotion label for each phase.
	Bell-Lysaker Emotion Recognition Task [155]	Participants identified the emotion shown in 21 videos of a male actor providing dynamic facial, vocal-tonal, and upper-body movement cues
Theory of Mind	Reading the Mind in the Eyes Test [156]	Measures the capacity to understand mental states of others from expressions in the eye region of the face. Participants viewed 36 photos and chose the most accurate descriptor word from four choices for the thought/feeling that was portrayed.
	The Awareness of Social Inferences Test, Part III [157]	Participants watched short videos of everyday social interactions and answered four standard questions per video probing understanding of the intentions, beliefs, and meanings of the speakers and their exchanges.
	The Hinting Task [158]	Examines the ability to infer the true intent of indirect speech. Each passage ended with one of the characters dropping a hint, and participants explained what the character truly meant.
Attributional Style/Bias.	The Intentional Bias Task [159]	Assesses the tendency to attribute intentionality to the actions of others. Participants indicated whether 24 brief descriptions of actions occurred “on purpose” or “by accident.”
Social Perception	The Mini Profile of Nonverbal Sensitivity [160]	The MiniPONS is a multichannel test of accuracy in decoding interpersonal cues (face, body, and voice tone). Participants chose which of two behavioral labels best described the situation.
	The Social Attribution Task [161]	Participants viewed a short animation of geometric shapes enacting a social drama. The animation was shown twice, and participants then answered 19 multiple-choice questions about what happened

As for measures of metacognition, although an initiative like the SCOPE project is ongoing but not finished, the array of measures and their complexity is even larger given the heterogeneity in the concept of metacognition. Nevertheless, research studies on metacognition in psychosis have tended to use the same measures of cognitive and clinical insight, and the jumping to conclusions bias. These are summarized in table 4.

Table 4: Most common measures of metacognition validated in Spain

Domain	Measure	Task	Validated in Spain
Clinical Insight	Scale of Unawareness of Mental Disorders (SUMD) [119]	Clinicians rate the participant based in a semi structured interview. The SUMD yields the following scores: Awareness of having a mental disorder, awareness of the effects of medication and awareness of the personal and social consequences of having a mental disorder.	Yes, with an intraclass correlation coefficient between 0.94 and 0.97[162].
Cognitive insight	Beck's Cognitive Insight Scale (BCIS) [127]	The BCIS is a self-reported scale that yields three subscales: self-reflectivity, self-certainty, and cognitive insight.	Yes, with internal consistency between 0.59 and 0.62 [163]
Jumping to conclusions	The Beads Task [164]	Participants are shown two jars containing beads in two colors and in opposite ratios (85:15 and 60:40). The computer randomly selects one of the jars. Participants can either guess the jar the beads are coming from or request more beads. There is a third condition (60:40 ratio) in which participants extract positive and negative adjectives instead of colored beads (affective). Our outcome variable was the number of draws to decision (DTD). Fewer draws to decisions reflect higher proneness to jump to conclusions.	Translated, but not validated.
	The Fish Task [165]	This task uses the same rationale as the Beads Task, but uses fishes in two different ponds as stimuli, in ratio 80:20.	Neither translated nor validated.
Metacognition (global construct)	Metacognition Assessment Scale (MAS) [85]	Measures global metacognition. Yields four scales: self-reflectivity, understanding others' minds, decentration and mastery.	Neither translated nor validated.

4.2. THE FACTOR STRUCTURE OF SOCIAL COGNITION

Vaskinn and Horan (2020) recently identified some of the unresolved issues in the field of social cognition in psychosis [59]. A basic question that remains to be fully understood is its structure.

Etchepare et al (2018) conducted a systematic review of the studies that used factor analysis to determine the configuration of social cognition in psychosis [166] and identified two theoretical models with evidence for and against. The first one is low vs high order cognitive processes [167–169]. Low level processing is implicit, fast, automatic, and unconscious, while high order cognitive processes are explicit, conscious and require a certain degree of effort and flexibility. Under this umbrella, the authors found that the studies with findings consistent with this model considered emotion processing and basic processes of ToM, such as lie detection, as low-level processes. Conversely, high-level social cognitive

processes included the ability to solve interpersonal problems, managing emotions or inferring intentions in others. The second theoretical model is rooted in a distinction between affective (hot) and cognitive (cold) components of social cognition. The affective factor requires processing emotional information, while the cold component refers to cognitive tasks such as understanding mental states. To date, there is empirical – yet insufficient- evidence for both models [166], but inconsistency across studies in a possible factor structure.

4.3. How are social cognition and metacognition related?

From a theoretical standpoint social cognition and metacognition are two distinct constructs, but they are interrelated in that the perception of the social world necessarily influences how individuals incorporate and make use of this information. As previously discussed, social cognition refers to "the what" of a particular perception, while metacognition focuses on "the how". At the beginning of the present doctoral dissertation, social cognition was defined as *the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others* [29].

Adolphs (1999, 2001), however, defined social cognition as "constructing representations of the relations between oneself and others, and to use those representations flexibly to guide social behavior" and its aim as "constructing representations of the relations between oneself and others, and to use those representations flexibly to guide social behavior" [170,171]. A closer inspection at this definition indicates that, for some authors, the most important trait of social cognition is its metacognitive dimension. Similarly, Etchepare et al (2018) highlight that, to attribute mental states and emotions to the others, one must first acknowledge their own's [166]. These examples show theoretical discrepancies that are still present in the field. Lysaker et al (2021) emphasize that metacognitive events often happen in an intersubjective context, this is, contraposed to an actual or imagined audience [78], what implies that social cognitive abilities must shape that intersubjective context. Because social cognition operates at the perceptual level, and metacognition at the integrative/superior level, it could be expected that biased social information impedes adequate metacognition. For instance, perceiving faces as threatening (impairment in facial emotion recognition) may lead to the belief that the others are against you (personalizing bias), what could prompt the explanation that there is a plot to harm you (jumping to conclusions).

Surprisingly, few studies have examined the relationship between social cognition and metacognition directly: Some have suggested that the ability to infer other's peoples intentions and mental states (ToM) relate to the type of attributions that

individuals make about the causes of events [172,173]. Using principal component analysis, Lysaker et al. (2013) found that measures of social cognition and metacognition loaded in two different factors, which had distinct correlates: while the social cognition factor correlated with negative symptoms, poorer education and poorer premorbid adjustment, the metacognition factor correlated with disorganized thinking, frequency of social contacts and flexibility in abstract thought [174]. Hasson-Ohayon (2018) conducted a network analysis to determine the interaction between social cognition, metacognition and neurocognition, and their association with symptoms. They found neurocognition to be the most central domain, what indicates that social cognitive and metacognitive processes often interact through a circuit with paths subsumed in cognitive symptoms [175]. Recently, several studies have linked the jumping to conclusions bias to hasty social interpretation [176], and emotional processing and attributional bias [104].

Beyond their possible independence as separate constructs, it is currently unknown whether both domains follow a hierarchical structure, with social cognition as a bottom process and metacognition as a superior, integrative process.

5. TOWARDS PERSONALIZED TREATMENT IN PSYCHOSIS

Most clinicians agree that the treatment of psychosis should be personalized, but it seldom goes beyond the prescription of antipsychotic treatment and occupational therapy [177].

In a comprehensive effort to detect uncovered treatment needs and shortcomings, Maj (2021) et al. describe a set of deficiencies that likely affects the prognosis of patients [177]:

- Poor diagnostic efficiency and over diagnosis of schizophrenia in detriment of other primary psychotic disorders.
- Lack of appropriate psychological assessment: most clinicians focus mostly on positive and negative symptoms but neglect other equally important domains, such as neurocognition or social cognition. Likewise, the stage of illness is often overlooked when planning treatment.
- Overseeing the history of the patient.
- Choice of treatment modality: Most patients will receive antipsychotic treatment. Most psychological treatment is not evidence-based.
- Neglecting patient's needs: in most cases, the treatment is not recovery oriented.

The rationale for personalizing treatment in psychosis is not new, but advances to date have been modest. It is estimated that only 1% of predictive models in psychiatry can be considered for real-world implementation [178]. At the biological level, the challenge is our poor knowledge of the neurobiology of psychosis [179]. At the psychological level, personalized treatment has barely been considered, due to the lack of political involvement, poor training in psychological interventions, and the common misconception that psychological interventions are not as effective as pharmacological treatment [180]. To feasibly implement precision psychotherapy, the field first needs to achieve a consensus in instruments and outcomes, to support longitudinal clinical trials [181] and to develop more sophisticated models that provide better predictors of diagnosis and prognosis [180].

5.1. DISENTANGLING HETEROGENEITY

Research has demonstrated that people with psychosis are heterogeneous in their clinical presentation [182], outcomes [183] , neurocognitive abilities [184] and recovery [185]. Stringent diagnostic criteria often fails to reflect the reality of people with psychosis [186], and averaging results in clinical trials may obscure the

characteristics of the patients that indeed respond to a specific treatment strategy [187]. To illustrate this effect, cluster analysis has repeatedly failed to find the proposed DSM-IV subtype criteria [188–190].

Strategies to personalize treatment must necessarily take individual differences into account so interventions can be tailored to patients' needs, ideally by directing targeted treatment to homogeneous subgroups of patients [191,192]. With the surge of data-driven methods, the prospects of effectively predicting and prescribing personalized treatment have increased considerably. A recent review on machine learning applied to psychiatric settings [193] suggests that these can improve medication prescription, predict whether a patient will respond to cognitive behavioral psychotherapy or even analyze therapeutic alliance. In the case of psychosis, Tandon and Tandon warn that these methods must be used carefully as the field is still in its infancy [194].

To date, even if further refinement and replication are lacking, the field of psychosis research is quickly benefiting from these methods. Some examples of these are summarized in table 5. Data-driven algorithms can compute enormous amounts of predictors and detect non-linear relationships between them [193], what achieves more clinically relevant results. It is expected that future years will see unprecedented advances in our understanding of psychosis. However, whether these can be effectively implemented in clinical practice will depend on several barriers and facilitators that are just emerging [191].

a) Subgrouping social cognition and metacognition

Although at a lesser extent than in neurocognition or biological variables, several studies have attempted to understand individual differences in social cognition and metacognition.

Clustering methods in measures of social cognition in samples with schizophrenia have yielded two or three groups that vary in the extent of impairment, but not in specific subdomains [195–198]. Interestingly, all reported a cluster of patients (25 - 48% of the sample) who had preserved social cognitive abilities, which challenges the conception of universal and pronounced impairments in social cognition. Each cluster seems to be associated with specific correlates. For instance, Etchepare et al (2019) found that their Low-SC cluster had older participants, lower educational background, poor emotional vocabulary, and more neurocognitive deficits [197]. Hajduk et al (2018) found that their intact cluster was younger, had higher premorbid functioning and had fewer negative symptoms relative to the severe cluster [198]. Rocca et al (2016) also found that patients with more social cognitive impairment were older, had a lower academic background and were associated with less functioning, more disorganized symptoms, and worse

neurocognition [196]. Finally, Vaskinn et al (2021) reported that their mild social cognitive subgroup had better education and neurocognitive functioning than more severely impaired group [195]. Taken together, these results suggest that social cognitive impairment may not be as pervasive as previously thought, what calls for further research and, possibly, new treatment developments to fit different profiles of patients.

There are even less studies identifying patterns of deficits with metacognitive variables. A study by Lysaker et al seeking to find profiles across clinical insight and symptoms found that only around 22% of participants had preserved insight, while the other profiles had associations between insight and symptoms (impaired insight/high negative symptoms, impaired insight/high positive symptoms, impaired insight/diffuse symptoms) [199]. Interestingly, the profile impaired insight/high positive symptoms grouped more women than the other three groups. Another study [200] found three clusters of insight and depression, which yielded that higher insight was associated with increased depression. The three groups differed in their social cognitive levels – which were better in those with better insight.

Massé and Lecompte (2015) found three subgroups of people with FEP using three subscales of the MAS-A scale. One cluster had better overall metacognitive ability, but the other two groups differed in understanding mental events in the others or in metacognitive mastery [201]. Patients with better metacognition were more often women and people living independently, but those with worse scores tended to have worse social functioning.

Table 5. Summary of selected studies using data-driven methods in psychosis.

Author	Main aim	Method	Variables	Findings
Amoretti et al (2021) [185]	Clusters with distinct trajectories in FEP	Fuzzy analysis clustering	PANSS [a]	Three clusters at baseline: mild symptoms, negative symptoms, and positive and severe symptoms. Five clusters at follow up: minimal symptoms, mild symptoms, moderate symptoms, negative and depressive symptoms, and severe symptoms.
Mas et al (2020) [202]	Response to antipsychotic treatment	K-means clustering	PANSS and UKU [b]	Four clusters: drug not toxic and beneficial, drug beneficial but toxic, drug neither toxic nor beneficial, drug toxic and not beneficial. Clusters differed in awareness of illness, but not in treatment adherence.
Oomen et al (2021)	Cognitive subgroups	Hierarchical cluster analysis	Composite BACS [c] Z-score	Three clusters: a preserved group (n=76), a moderately impaired group (n=74) and a severely impaired group (n=54). Participants in the severely impaired group had more severity of illness and functioning at baseline and at one year follow-up.
Ochoa et al (2013) [203]	Cognitive subgroups	K means cluster analysis	Neurological soft signs, obstetric complications, and family risk	Three profiles: higher neurodevelopment contribution, higher genetic contribution, and lower neurodevelopment contribution (cluster 3). Patients in cluster 3 had cognitive performance comparable to healthy controls, while the other two clusters presented more impairment.
Liao et al (2021)[204]	Quality of life	K means cluster analysis	World Health Organization Quality of Life Scale-Brief	Three clusters according to the level of quality of life (good, moderate, poor). These were predicted by depressive symptoms.
Honer et al (2015) [205]	Response trajectories to clozapine	K means longitudinal cluster analysis	BPRS [d] total score at six points of assessment (six weeks).	Two trajectories: Over 70% were assigned to an early and marked improvement trajectory. Around 30% were assigned to a treatment-resistant trajectory.

[a] Positive and Negative Syndrome Scale [206], [b] UKU Side Effect Rating Scale [207], [c] Brief Assessment of Cognition in Schizophrenia [208] , [d] Brief Psychiatric Rating Scale [209].

5.2. SEX DIFFERENCES IN PSYCHOSIS

Biological sex is the variable most frequently associated with individual differences in psychosis. Sexually dimorphic development of the brain affects the biological underpinnings of psychosis that are thought to be apparent right from the beginning of psychosis [210,211], but differences also appear in severity, onset, duration of illness, lifetime course, response to treatment, functioning and quality of life [212–214]. Until recently, most research has been conducted in men [215]. With cumulative evidence warning that the study of psychosis must be understood in the light of sex differences [216], the past two decades have seen a burst in studies that take them into account. Table 6 summarizes the findings of two integrative reviews [213,214] in sex differences in FEP and established psychosis. In CHR, differences seem slightly more nuanced. Men seem to have more negative symptoms and lower social functioning, but women have an increased risk of affective psychosis [217].

a) Estrogens and psychosis

The direction of these differences, such as a later onset of psychosis in women and a second peak of incidence during the perimenopause, lead to explore whether female sexual hormones may exert an effect in the development and maintenance of psychosis.

It is now accepted that gonadal steroids, in particular estrogens, through their influence in brain development and functioning [218], exert protective effects in psychosis. Estrogens and testosterone have an important influence in the development of the brain from late gestation to puberty. Some of the roles of estrogens in the brain are [218,219]:

- Promote neuronal sprouting and myelination.
- Enhance synaptic plasticity.
- Facilitate neuronal connectivity.
- Acts as an anti-inflammatory.
- Modulate neurotransmitter pathways, especially the dopamine pathway.

Based in the above observations, Riecher-Rössler and Häfner [220] suggested that estrogens provide protection against psychosis. This hypothesis is consistent with a later age of onset in women, an increased incidence of psychosis in women over 40, better course of illness in women, improvement of symptoms during pregnancy but an increased risk for relapse or first episode of psychosis soon after delivery or miscarriage/abortion [221–223].

Subsequent research testing the possible beneficial effects of adjunctive oestrogen or oestrogen modulators in patients with psychosis has yielded positive effects in cognition [224,225] and symptoms of psychosis [226,227].

Table 6: Summary of sex differences between men and women with psychosis.

Domain	Results
Age of onset	Consistently reported that men have an earlier age of onset than women (18-25 vs 25-35 in men and women respectively). However, this difference seems to disappear in patients with a family history of psychosis. Women have two peaks of incidence: after menarche and during perimenopause.
Symptoms	Still inconclusive, as studies have yielded conflicting results. However, the studies that found gender differences describe higher presence of negative and disorganization symptoms in men and higher prevalence of affective symptoms in women. In patients with late onset psychosis (over 40 years), men seem to have less symptoms than women.
Premorbid functioning	Most literature has found that women have better premorbid functioning than men. Men seem to have longer duration of untreated psychosis. This difference is usually not statistically significant but could be clinically significant.
Social functioning	Most studies report better social functioning in women than in men in all stages of illness.
Neurocognition	Gender differences in cognitive function in people with schizophrenia remained controversial. The studies that found gender differences indicate higher levels of functioning in women especially in language, executive functioning, and memory.
Substance use and abuse	Men usually report more substance use and abuse, especially cannabis. Furthermore, a study suggested that the risk of developing psychosis is higher in men who use cannabis than in women.
Course of illness	While still inconclusive, women usually present higher rates of remission, less days of hospitalization and better response to typical antipsychotic medication.
Sex differences in the brain	The normal sexual dimorphism in brain structure seem to be disrupted in psychosis. Women with psychosis usually have an abnormally big pituitary. Differences between genders in: cortex, volume of the amygdala, hypothalamus, orbito-frontal and anterior cingulate, grey matter volume asymmetry, insular cortex and cortical folding.

b) Medical and psychosocial differences

Beyond biological and clinical factors, males and females with psychosis present differences in other psychosocial aspects that have an important impact on illness, such as parenting [228], prevalence of traumatic life events [229], identity[230] and needs and recovery [231–233].

Most women with FEP tend to take less time to ask for help once the symptoms begin [234]. Although this difference does not reach statistical significance, reducing the duration of untreated psychosis is crucial in maximizing treatment efficacy [22].

Longer time in men to seek help, even if it cannot be statistically supported, may have detrimental clinical consequences.

As reported in table 6, women often have a later age of onset and present better premorbid and prospective functioning than men. This effect permits women achieve most adult milestones (marriage, parenting, work) [235] before the illness begins. As such, their needs differ throughout the lifespan in different ways. For instance, they may need support to maintain their partners and career. A more important issue specific to women is pregnancy, childbirth, maternity, and menopause [235,236]. These are periods of increased risk of relapse that require close monitoring and strong psychosocial support [212]. Furthermore, reproductive issues are seldom contemplated in psychosis treatment programs, and issues as contraception, abortion, sexuality and family planification are often overlooked [235].

Because psychosis is more pervasive in men, and premorbid deficits more severe, these patients experience a chain of adverse life events (less academic performance, less social support, more antisocial behaviour, higher rates of drug abuse) [235] that require specific detection and treatment. Likewise, when illness is established, men need more assistance with daily life activities and personal care [237]. All together, these differences have led to the proposal that treatment of men and women with psychosis should be personalized and sex-sensitive [238,239].

c) Differences in social cognition and metacognition

Healthy women tend to exhibit a small but consistent advantage in social cognition compared to healthy men [240,241]. It could then be expected that better social cognition in women with psychosis may protect them from poorer functional outcome. However, most of the recent literature has failed to find differences in participants with psychosis [242,243], although the few studies that reported sex differences in social cognition have found superior performance in women, albeit limited to some subdomains [244,245].

Sex differences in metacognition have scarcely been studied, although the few available studies suggest conflicting results. While there are no apparent sex differences in metacognition at the high risk [246] and in established psychosis [247,248], women with FEP seem to present less self-certainty than men [248]. Conversely, another study showed that expressive deficits and poor social functioning have a bigger interference in self-reflectivity in women than in men with schizophrenia [248].

Interestingly, the role of sex in social cognition and metacognition may only be apparent when examining data beyond mean differences. For instance, a recent work reported different effects of metacognitive training in men and women with FEP [249], and a study found a profile characterized by high positive symptoms and

low clinical insight that included mostly women [199]. With regards to social cognitive and metacognitive treatment, recent studies have found that MCT exerts differential effects in both sexes [249], and male sex is a moderator of poor response to social cognitive training [65].

Thus, these results suggest that even if sex differences are not apparent in terms of magnitude, there may be underlying mechanisms that modulate treatment response and the associations between ability and functioning.

PART 2: RATIONALE AND OBJECTIVES

1. RATIONALE

The introduction section of the present doctoral dissertation discusses several issues in our current understanding and treatment of psychosis. These can be summarised as:

- Psychosis is a prevalent mental illness that often leads to disability.
- The first episode of psychosis is a stage of the illness that is particularly sensible to intensive treatment, what can delay or reduce the course of the illness.
- Two key therapeutic targets of treatment are social cognition and metacognition, as these are strongly related to functioning and outcome. However, both interventions only seem effective at the medium effect size, what suggests room for improvement.
- Evidence suggests that social cognition and metacognition either interact or overlap to some extent, but there is insufficient knowledge as to how.
- Measures of social cognition and metacognition often have poor psychometric properties or are not validated in different cultural contexts.
- The clinical presentation and course of the disorder are highly heterogeneous, what indicates that most patients with psychosis need a treatment that is tailored to their specific needs.
- Understanding heterogeneity in psychosis can provide a better knowledge of the disorder and enable personalized treatment by identifying subgroups of patients that share similar clinical profiles. To meet this aim, data-driven statistical methods show great promise, but this is an emerging line of research.
- Men and women with psychosis present important differences in most biological and clinical variables related to psychosis. Sex is the most consistently reported variable as a predictor or moderator of different features and outcomes of psychosis. However, its role in social cognition and metacognition is not sufficiently clear.

Delivering early and targeted treatment is a priority for researchers and clinicians, but this is an emerging field that will benefit from studies setting the foundations on how to personalize treatment for psychosis.

This strategy seems particularly important regarding social cognitive and metacognitive interventions given their strong links with symptoms and outcome. Most studies have found them effective, but only at a medium effect size. Conversely, the few studies exploring heterogeneity in social cognition and metacognition have reported that not all patients exhibit the same degree of impairment. Rather, important percentages of the samples appear to either have preserved abilities or moderate deficits. It is then likely that clinical trials using averaged statistics could be obscuring who benefits from the intervention and who does not. Equally important, subdomains of social cognition and metacognition have specific associations with symptoms, treatment compliance and outcome. Thus, it seems likely that the patterns of deficits in both domains may affect treatment response and course of illness. This is crucial for patients at the early stages of psychosis because their room for recovery is larger.

Another question is how social cognition and metacognition interact. Evidence in this regard is conflicting. Some studies have provided evidence of their independence, but some others have found associations between subdomains. Similarly, theoretical models overlap both constructs to an extent, what contributes to the lack of clarity. This question merits exploration, as understanding how both appear together may point to new treatment and personalized treatment strategies.

Based on this rationale, this work aims to understand whether unravelling heterogeneity in social cognition and metacognition can lead to personalized-treatment strategies.

2. OBJECTIVES

The overarching aim of this doctoral dissertation is to understand whether the heterogeneity in social cognition and metacognition in psychosis grants the development of personalized social cognitive and metacognitive interventions. This broad aim is divided into the following sub-objectives:

1. To validate a test of facial emotion recognition (Baron Cohen's Face Test) in healthy population, with the aim of detecting whether it is an appropriate tool to use in clinical research.
2. To detect whether patients with first episode psychosis have different, clinically meaningful profiles of performance in social cognition and metacognition.
3. To examine if males and females with first episode psychosis are similar in their heterogeneity in social cognition and metacognition.
4. To explore the sociodemographic, clinical, and neurocognitive characteristics of each profile.
5. To explore the role of social cognition and sex in functional outcome in people with established psychosis (schizophrenia).

A secondary global objective of this dissertation is to understand how social cognition and metacognition appear together in patients with psychosis.

3. HYPOTHESES

a) Baron Cohen's Face Test will present sound internal consistency and test-retest reliability, indicating that it is a valid measure of facial emotion recognition in general Spanish population.
b) People with first-episode psychosis can be qualitatively classified on the basis on their social cognitive and metacognitive abilities using data-driven methods.
c) Men and women with psychosis will differ in the configuration of their social cognitive and metacognitive abilities, what will yield distinct latent profiles in each sex.
d) Profiles will differ in symptoms, neurocognition and functioning, indicating that each profile has distinct, clinical meaningfulness.
e) Profiles with low social cognitive scores will also present low scores in metacognitive variables.
f) Biological sex will moderate the relationship between social cognition and functional outcome in established psychosis.

4. APPROACH

We have tackled the objectives of this work from the following approaches:

1. The foundations of personalized treatment are adequately profiling individuals to understand their needs of treatment. This requires careful measurement of social cognition and metacognition. However, there were no validated tasks of Facial Emotion Recognition in the Spanish context. Thus, we chose to validate Baron Cohen's Face Test (BCFT) [250] in healthy Spanish population to support subsequent studies. BCFT has the advantage of being short and easy to administer and correct, it is free for clinical and research purposes, has been translated to more than ten languages and has demonstrated its clinical utility in psychosis [251] . The test consists in twenty images depicting ten basic and ten complex emotions. Participants must see the photograph and decide the emotion the actress is feeling between two choices
2. To retrieve profiles of social cognitive and metacognitive abilities, we conducted Latent Profile Analysis (LPA) in two existing databases that had previously been built to test MCT in a large sample of patients with FEP. LPA is the perfect statistical method to meet this objective because it assumes between-subject heterogeneity in a range of variables that cannot be explained by known, observable variables [252], thus identifying meaningful subgroups of individuals.
3. Sex is the variable that has most consistently been found to affect the aetiology, clinical presentation, prognosis, and functioning and treatment response of psychosis. Thus, it seems necessary to consider biological sex as a potential variable to guide the personalization of treatment. This is especially true because there is data that suggest that men and women respond differently to social cognitive and metacognitive interventions, but most studies have failed to find sex differences in performance.
4. Including a sample of participants with established psychosis can help obtaining a bigger picture of individual differences. Thus, we decided to explore whether sex moderates the predictive power of social cognition over functional outcome in established psychosis.

PART 3: EMPIRICAL SECTION

1. OVERVIEW OF STUDIES

The broad scope of the main objective requires its operationalization into sub studies, each of which aimed to address one a specific objective of this work. Figure 1 conceptualizes the four studies, their rationale under the broad aim of this doctoral dissertation, and their specific objectives.

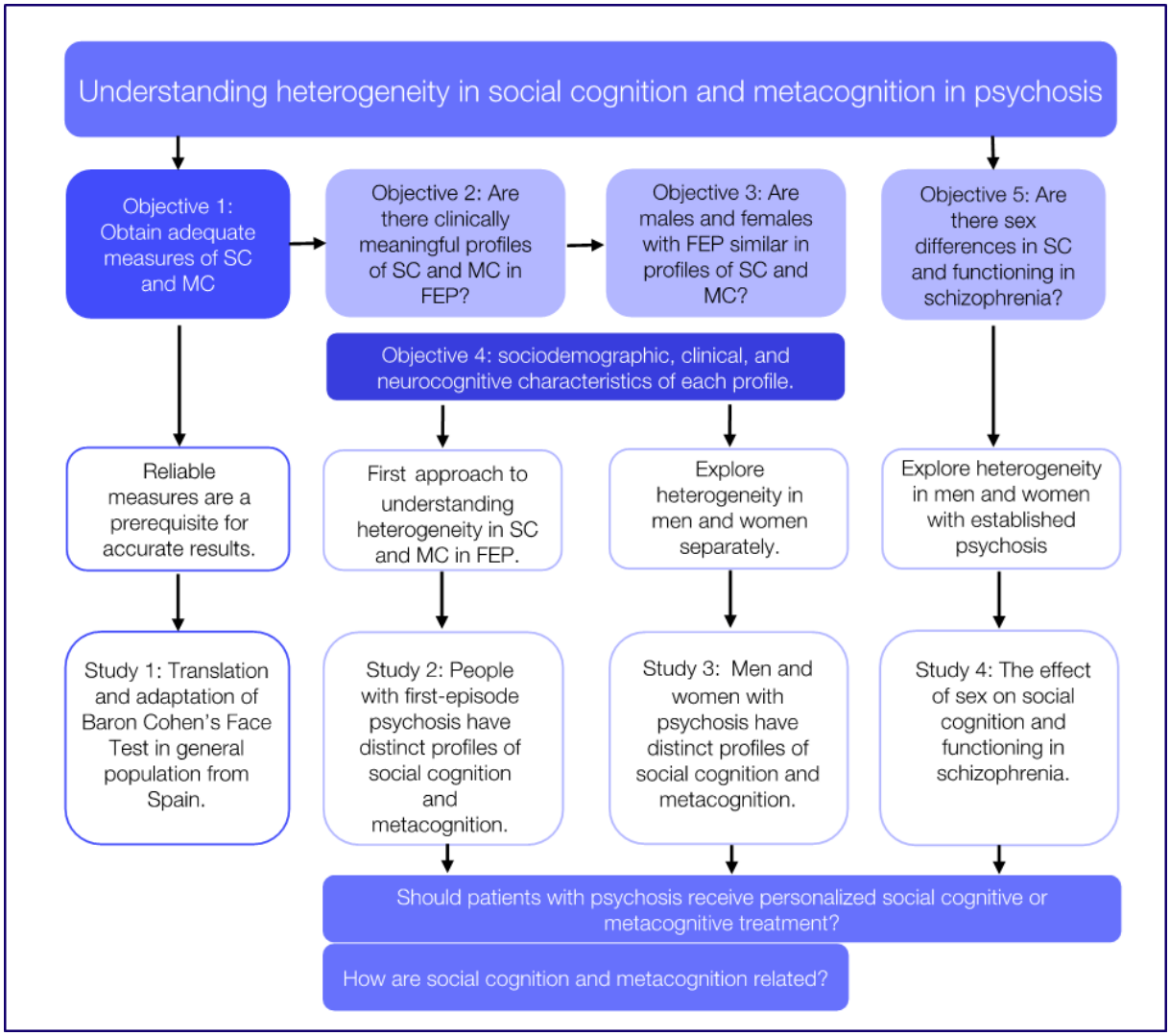

Figure 1. Summary of the compendium of studies, its objectives, and its rationale.

2. COMPENDIUM OF STUDIES: AIMS, METHODS AND RESULTS

2.1. STUDY 1: TRANSLATION AND VALIDATION OF BARON COHEN'S FACE TEST IN A HEALTHY POPULATION FROM SPAIN.

Authors	Elena Huerta-Ramos*, Marta Ferrer-Quintero* ; Juana Gómez-Benito; Fermín González-Higueras; Daniel Cuadras; Angel Luis Del Rey-Mejías; Judith Usall; Susana Ochoa. *The two authors share the first authorship.
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Impact factor (2020)	1.681
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Citation	Huerta-Ramos E, Ferrer-Quintero M. Translation, and validation of Baron Cohen's Face Test in a general population from Spain. Actas Esp Psiquiatr. 2021;49(3):106–19.
Objective(s)	Objective 1: To validate a test of facial emotion recognition (Baron Cohen's Face Test) in healthy population, with the aim of detecting whether it is an appropriate tool to use in clinical research.
Rationale within the thesis	This work is cross-sectional to the present doctoral dissertation. Given the lack of validated measures of facial emotion recognition in Spanish population, a pre-requisite to obtaining good quality data and reliable measurement of FER is to use a task that has adequate psychometric properties.
Considerations	Baron Cohen's Face Test can be downloaded freely for research and clinical use at https://www.autismresearchcentre.com/ . The test is included in annex 2.

Table 7. Summary and details of study 1.

TRANSLATION AND VALIDATION OF BARON COHEN'S FACE TEST IN A HEALTHY POPULATION FROM SPAIN

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ABSTRACT

Introduction: Facial emotion recognition is considered the foundation of effective social functioning, but it has been found impaired in several clinical populations. How- ever, there are few validated tests to measure the ability. To the best of our knowledge, there is no validated measure in a Spanish population. We translated and validated Baron Cohen's Face Test in a general Spanish population.

Methods: The test was administered to 211 (63.3% female) healthy volunteers between 19 and 70 years of age. We used tetrachoric matrices to obtain item per item test-retest reliability and internal consistency. We used confirmatory factor analysis to test for unidimensionality. We used Pearson correlations to examine associations between variables.

Results: The mean score was 18 (SD=1.38). Cronbach's alfa was 0.75. Guttman Lambda 3 indexes yielded 17 out of 20 items to have excellent test-retest reliability. Gender or age differences in performance were not found. The test

seems to comply with a one-dimensional structure: CFI=0.889; TLI=0.873 and RMSEA=0.047.

Conclusions: Baron Cohen's Face Test could be a valid measure of FER, although it is not sensitive to age or gender. Because it presents a certain ceiling effect, it could not be appropriate to detect excelling performance.

Keywords: Baron Cohen Face Test, facial emotion recognition, validation, psychometric properties, general population.

INTRODUCTION

Facial emotion recognition (FER) is instrumental in competent social functioning. It has been thoroughly explored both in healthy subjects [1–3] and in different clinical populations [4–7]. Despite an extensive corpus of literature on the topic, most instruments to measure FER have poor or unknown psychometric properties. There are numerous validated datasets of pictures (see [8–14] for different examples). Depending on their particularities, these datasets can offer precise control of variables such as age, gender, ethnicity, and ecological validity, but they are very large, and they have caused methodological differences across studies that have limited comparability. There is a myriad of tasks that measure FER, but their psychometric properties are generally poor [15] or proper validations are lacking. Some of them are the Ekman-60 Faces Test [16] , the Japanese and Caucasian Brief Affective Recognition Test (JACBARTT) [17], the Facial Emotion Recognition Test (FERT) [18], the Bell Lysaker Emotion Recognition Test (BLERT) [19] the Reading the Mind in the Eyes Test (RMET) [20] or The Videotest of Emotion Recognition [21]. Reviewing all the tasks and tests that measure FER is beyond the scope of this work, but we suggest consulting Passarelli et al, 2018 [18] for a complete review. Some of these tasks have been validated in some countries but not in others and some have been extensively used in research without having appropriate validations. Furthermore, most of them a relatively long or may appear as unnecessarily thorough in certain settings. A short version of The Assessment of Social Inference Test (TASIT) [22] has proven to be reliable as a screening measure [23], but there is little literature on short but sound tasks that are sensitive to use in clinical practice on other domains of social cognition.

In healthy population, there is sound evidence for females performing better than men since childhood and through adulthood [24, 25] and for age to be a moderating

variable. Despite inconsistency in some results, meta- analytic findings point to decay in the ability with age in all emotions but an unimpaired recognition of disgust, consistent with the natural aging brain [26, 27]. The influence of the academic background in performance has been less studied than other demographic variables. The only study specifically examining a possible association found a significant positive correlation between educational level and the FERT and a significant interaction between age and schooling, favouring younger more educated subjects [28]. To the best of our knowledge, there are very few validated FER tests in Spanish population. The RMET has recently been validated in Spanish population [29, 30], but its psychometric properties are not excellent. Another well-validated test in the Spanish population is the The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) [31], but it must be noted that the MSCEIT assesses all domains of social cognition instead of just FER.

Baron Cohen's Face Test (BCFT) [20] is a FER test originally developed in the construction of the RMET. This test is free for research and clinical use and it can be downloaded from the Autism Research Centre (https://www.autismresearchcentre. com/arc_tests). According to this website, this test has been translated to more than ten languages, but despite thorough searches, we have not been able to find literature on its validation or reference values in any healthy or clinical population. It is possible that clinicians and researchers could be using this test with no knowledge of its psychometric properties. Furthermore, cultural and language backgrounds have been reported to influence neuropsychological measures [2], which raises awareness on validating tests in different cultural and ethnic populations.

Our aim with this study is to validate Baron Cohen's Face Test in a Spanish population, to investigate the psychometric properties of the instrument and to explore its sensibility to demographic variables.

METHODS

The Face Test was translated and adapted following the ITC guideline [33]. Because the test does not include any complete sentences but isolated words, a team of three people (bilingual English-Spanish, native Spanish and native English speakers) translated them attending to the frequency of use, European-Spanish forms and adapting the options of response to the stimuli's gender. A pilot version of the test was reviewed by peers so flaws could be detected and corrected.

Inclusion criteria included participants between 18 and 70 years of age who had signed the electronic informed consent. Exclusion criteria contemplated mental illness at the moment of the study, severe chronic mental illness, intellectual disability, developmental disorders, brain injury or dementia.

We used a snowball sampling method carried out by three researchers in three hospitals in three different regions in Spain Parc Sanitari Sant Joan de Déu, Comunidad Terapéutica de Jaén and Hospital Clínico San Carlos. This approach was chosen to ensure we reached the maximum number of community participants from various regions in Spain. The first participants were chosen from the immediate social and working circles of the researchers and were sent an online survey to be completed from any electronic device, containing the tests listed below, a demographic form and questions on the participant's history of mental health. First participants were encouraged to disseminate the survey. Responses were inspected individually. Subjects using psychoactive medication at the time of the assessment were excluded, with the exception of the use of benzodiazepines as muscle relaxers.

The sample was recruited from July 2016 to January 2017 (including re-test). Three months after the first administration, 37 participants were sent a re-test online survey that included Baron-Cohen's Face Test and the Eyes Test. Participants were selected based on a randomized list. 24 participants replied to this survey. Data were allocated in a server of the hospital that complies with all the safety requirements for the storage of health and research data.

Baron Cohen's Face Test [20]: consists of 20-items showing pictures of an actress displaying an emotion. Participants must choose which emotion the actress is feeling between two different choices of response. Half of the items display basic emotions, whilst the other half displays complex mental states. Examples of stimuli are displayed in figure 1.

The Reading the Mind in the Eyes Test [20]: The Eyes Test consists of 36 pictures of facial affect circumscribed to the eye region. Subjects must choose the emotion the eyes depict amongst four different response options. A glossary is provided and encouraged to use if the subject does not know the meaning of them.

Data Analysis

Data analyzed with IBM SPSS Statistics 22 and R34. We used tetrachoric correlation matrices to calculate Cronbach's alpha, test-retest reliability, and factor analysis. This approach was used to ensure a better adjustment to binary items. We used Cronbach's Alfa to test internal consistency. The intraclass correlation coefficient is not the optimal approach for binary items; therefore, we used Guttman Lambda 3 to test item by item time stability and Pearson correlations to test the full test time stability. Convergent validity was examined with a Pearson correlation between the total score in the Face Test and the total score in the Eyes Test. We used t-tests for independent measures to calculate differences between two samples. We used ANOVA tests to find mean differences

among groups. We used Pearson correlations to test correlations between variables. All the tests were run with a 95% confidence interval.

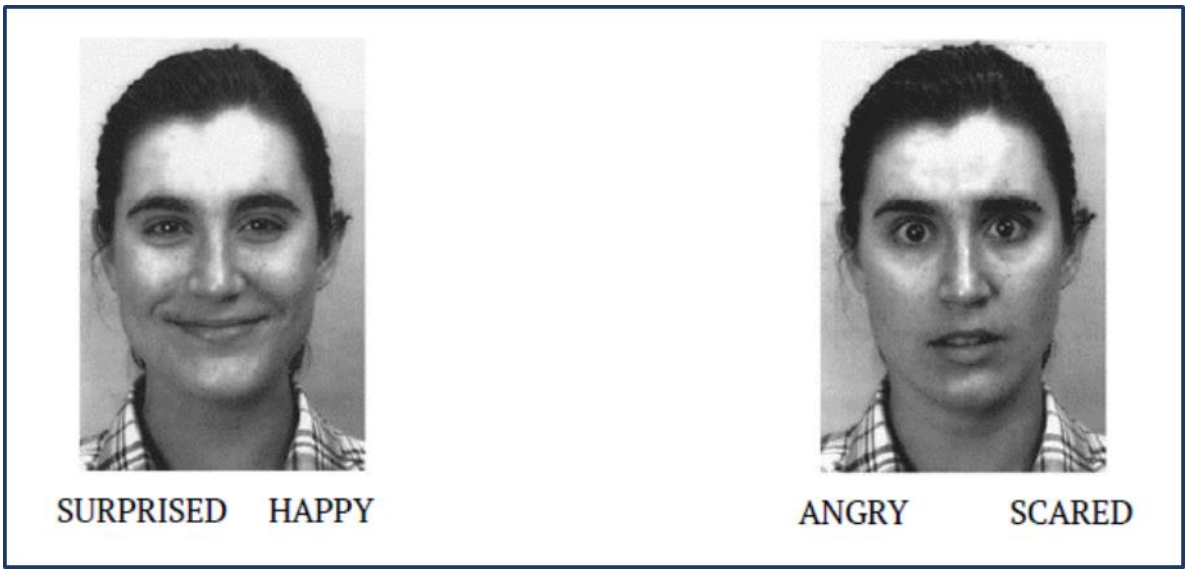
Ethics

The study was designed according to the World Medical Association Declaration of Helsinki35 and it was approved by the Ethics Committee of Parc Sanitari Sant Joan de Déu as the coordinator center.

RESULTS

Initially, 286 people started responding to the online survey. A total of 8 subjects were excluded due to having a mental disorder. Other 67 subjects started responding to the survey but did not finish so their data could not be analyzed. The final sample included 211 participants, 134 females and 77 males between 19 and 70 years of age. Participants covered a scope of 15 different regions in the Spanish territory.

Figure 1. Stimuli 3, “surprised” vs. “happy” and 4, “angry” vs. “scared”.



Normative data and psychometric properties

Our sample had a mean score of 18(SD=1.38), distributed between a minimum score of 14 and a maximum score of 20. To test internal consistency, we calculated Cronbach’s alfa based on the tetrachoric correlation matrix, which

yielded a value of 0.75 showing good internal consistency. This value would not be significantly increased by removing any item. We calculated the convergent validity by correlating the total score of the BCFT with the total score of the Eyes Test, which showed a low but significant correlation ($r=0.192$, $p<0.005$). Test-retest stability as measured by the Pearson correlation between the first and the second application of the tests was $r=0.372$, $p=0.088$. Subsequently, we used the tetrachoric correlation matrix to obtain the Guttman lambda 3 indexes for each item. This index is equivalent to Cronbach's alfa [36]. Table 2 below exposes the agreement indexes for test-retest reliability.

Dimensional structure

A one-factor solution was tested, as this is the model suggested by the author. We performed a one-factor confirmatory factor analysis (CFA) for all the items. We did not include item 1 because it had a negative variance and 3 and 4, that remained constant. We used the diagonally weighted least squares (DWLS) estimator, with which we obtained: Comparative Fit Index (CFI) = 0.889; Tucker-Lewis Index (TLI)=0.873 and Root Mean Square Error of Approximation (RMSEA)= 0.047.

Table 1. Demographic information (n=211)

Age in years (Mean, SD)	40,01 (13,07)
Gender (%)	
Female	63,3
Male	36,7
Formal education (%)	
Primary	5,8
Secondary	16,4
3-year university degree	13
5-year university degree	39,1
Masters	20,3
PhD	5,3

Table 2. Agreement indexes for test-retest reliability

Guttman Lamda 3 Values	Items
> 0,8	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13, 14, 15, 16
0,60 - 0,8	7, 17, 19
0,40 - 0,60	12, 20
0,20 - 0,40	18

Moderating variables: gender, age and academic level

No differences between genders were found (t(209)=0.865; p=0.388). Correlations between the total score in the test and age were not significant (r=-0.075, p=0.280). We performed a one way ANOVA between the academic level and the total score in the test. We did not find differences between groups (F(5,200)=1.886; p=0.098). We found a weak but significant correlation between performance in BCFT and academic level (r=0.153; p=0.028).

DISCUSSION

This work presents the validation of BCFT together with its reference values in a healthy Spanish population, obtains its psychometric properties and discusses moderating variables.

As for BCFT, this result is consistent with results found in general population, which find that the ability works generally well and reaches high performance with relatively small standard deviations [2, 26]. Our sample reached similar scores than the original test 20, who reported a mean of 9.13(SD=0.96) in basic emotions and a mean of 9.38(SD=0.62) in complex emotions. However, the test presented a ceiling effect in our sample. In this case, this effect could have happened because the test is short and the items only have two choices, facilitating the chances of guessing the right emotion even if the ability is impaired.

Regarding its psychometric properties, internal consistency reached a value of α=0.75, which would not be significantly increased by removing any item. Other tasks have yielded similar internal consistency: the JACBART has yielded Cronbach's alfa between 0.86 and 0.9217, the Videotest of Emotion Recognition reported two Cronbach's alfa , one for the accuracy index (0.74) and the other one for the sensitivity index (0.79) [21]. The validation of the MSCEIT in Spanish population obtained an alfa of 0.8031. In Spanish population, the RMET yielded an alfa of 0.5630. BCFT reached a slightly lower value that can be considered adequate. Literature reporting both internal consistency and test- retest reliability is very scarce. Test-retest reliability using the JACBART is between 0.44 for anger and 0.72 for sadness (computed with t-tests), which suggests a practice effect [17]. To the best of our knowledge, the only test-retest reliability data published for Spanish population is a test-retest study of the Reading the Mind in the Eyes Test, as studied with the Bland-Altman method, which yielded a score of 0.6329.

Test-retest reliability using the whole test yielded a moderate but significant correlation (r=0.372, p=0.088). To further evaluate test-retest reliability, we calculated the Guttman L3 index for each item to test time stability, as this is a

more appropriate approach for binary items. Guttman L3 index is equivalent to Cronbach's alfa and can be interpreted likewise [36]. In our sample, 17 out of 20 items had a value of over 0.6; which allows us to conclude that the test has excellent stability over time. The discrepancy between the test-retest correlation using the whole test and the item by item test-retest may be due to a smaller sample size at retest.

The test was designed following a one-factor model. We only explored a one-factor solution as exploring further factor solutions was beyond the scope of this project. Our results barely reached values to assume adjustment to a one-factor model. Future studies with this test should test for other factor solutions and confirm our findings.

To the best of our knowledge, this is the first published validation of this test. Future studies on this test should report psychometric properties to draw further conclusions. We did not find gender differences in performance. This is a surprising finding since a female superiority is found consistently across studies with a small but similar size effect [18, 25, 31]. Lyusin et al (2016) did not find gender differences either in their 7-item task. In their case, the authors attribute it to their more ecological paradigm, which they speculate could be balancing female's advantage [21]. However, it could be possible that a female superiority can only be detected with longer tests. Interestingly, a cross-cultural study comparing performance in FERT in Brazilian and French population did not find gender differences in the Brazilian sample, but found a female superiority in the French sample [28]. These findings highlight that some aspects of the interaction between FER and demographic variables may not be static across cultures. As a reason for these findings, the authors suggest that perceived gender stereotypes and gender equality measures could influence facial emotion recognition [28]. Similarly, we did not find an influence of age consistent with the literature [26, 27]. This is an expected finding in our study since our sample is clustered in the middle age and we lack sufficient subjects of young and old age.

We did not find any mean differences between different academic levels and performance. This is not consistent with some of the literature [16, 28]. According to Lindquist (2014), semantic memory plays a crucial role on labelling emotions, regardless of their valence [37]. We speculate although a broader education could provide more opportunities to interact with different emotional contexts and access to more emotional vocabulary, BCFT does not represent a semantic challenge.

Taken together, it seems that although BCFT presents adequate psychometric properties, it has a very low ceiling and it is not sensitive to the demographic factors that, according to the literature, play an important role in the recognition of facial expressions of emotion. These drawbacks may hamper this test's ability

to detect subtle decay in FER. However, from our data, it can be derived that because subjects in the general population reach ceiling performance, scores lower than a standard deviation truly reflect deficits in FER. However, this interpretation should be taken with caution until future research examines sensibility and specificity in different pathological populations.

This work should be interpreted in light of some strengths and weaknesses: As for strengths, this is the first validation published for BCFT, and one of the first validations of a FER test for Spanish population. This work could offer a framework for clinicians and researchers already using this test, and for other teams developing normative measures of FER for Spanish population. We were able to reach subjects from all the Spanish territory, which increases the validity of our results.

As for limitations, it must be noted that even if a translation is accurate, cultural differences and familiarity with the words can alter the difficulty of the item or induce different responses to the test. This is of particular importance regarding that the test was designed for British population and adapting it to Spanish may have influenced our subjects' responses. We believe this could be especially true for the ten items assessing complex mental states. Besides, this test is short, and it displays maximum intensity of the emotion. This is very likely to diminish the test's ability to detect excelling performance or subtle decay in FER. Although using an online survey allowed us to recruit a sample from different regions in Spain, losing face-to-face contact with the subjects could have hampered our results. Finally, we failed to recruit a balanced sample, in neither gender nor age or education. We believe our female sample is big enough to detect an advantage in performance, however, it has a small proportion of old and very young people and it over-represents subjects with higher education.

In spite of its limitations, we believe this work gives a valuable resource to researchers and clinicians in Spain. Further studies examining sensitivity-specificity in different populations or with subjects in old age and with less academic background are recommended.

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2.2. STUDY 2: "PEOPLE WITH FIRST EPISODE PSYCHOSIS HAVE DISTINCT PROFILES OF SOCIAL COGNITION AND METACOGNITION".

Authors	Ferrer-Quintero, M, Fernández D, López-Carrilero R, Birulés I, Barajas A; Lorente-Rovira E, Díaz-Cutraro L, Verdaguer M, García-Mieres H, Julia Sevilla-Llewellyn-Jones, Gutiérrez-Zotes A, Grasa E, Pousa E, Huerta-Ramos E, Pélaez T, Barrigón ML, González-Higueras F, Ruiz-Delgado I, Cid J, Moritz S, Spanish Metacognition Group, Ochoa S.
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Objective(s)	Objective 2: To detect whether patients with first episode psychosis have different profiles of performance in social cognition and metacognition. Objective 4: If we identify different profiles, to explore the sociodemographic, clinical, and neurocognitive characteristics of each profile.
Rationale within the thesis	This study is the first approach to studying heterogeneity in social cognition and metacognition by using a large sample of patients with FEP.
Considerations	None

Table 8. Summary and details of study 2.

PERSONS WITH FIRST EPISODE PSYCHOSIS HAVE DISTINCT PROFILES OF SOCIAL COGNITION AND METACOGNITION

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ABSTRACT

Subjects with first episode psychosis experience substantial deficits in social cognition and metacognition. While previous studies have investigated the role of profiles of individuals in social cognition and metacognition in chronic schizophrenia, profiling subjects with first episode psychosis in both domains remains to be investigated. We used latent profile analysis to derive profiles of the abilities in 174 persons with first episode psychosis using the Beck's Cognitive Insight Scale, the Faces Test, the Hinting Task, the Internal, Personal and Situational Attributions Questionnaire and the Beads Task. Participants received a clinical assessment and a neuropsychological assessment. The best-fitting model was selected according to the Bayesian information criterion (BIC). We assessed the importance of the variables via a classification tree (CART). We derived three clusters with distinct profiles. The first profile (33.3%) comprised individuals with low social cognition. The second profile (60.9%) comprised individuals that had more proneness to present jumping to conclusions. The third profile (5.7%) presented a heterogeneous profile of metacognitive deficits. Persons with lower social cognition presented worse clinical and neuropsychological features than cluster 2 and cluster 3. Cluster 3 presented significantly worst functioning. Our results suggest that individuals with FEP present distinct profiles that concur with specific clinical, neuropsychological and functional challenges. Each subgroup may benefit from different interventions.

Keywords: *social cognition, metacognition, latent profile analysis, recent-onset psychosis, phenotypes*

INTRODUCTION

People with first-episode psychosis (FEP) experience deficits in social cognition [1] and metacognition [2, 3] that compromise their abilities in thinking about their own and others' mental activities [4].

Social cognition refers to a broad area that includes perceiving, interpreting and processing information for adaptive social interactions [5]. There is consensus that social cognition is composed of four subdomains[6]: Emotional processing refers to the ability to perceive and use emotions. Theory of mind is the ability to attribute and represent mental states of others. Social perception encompasses decoding and interpreting

social cues in others, and Attributional Bias refers to the explanations an individual gives to social events and interactions.

Metacognition refers to "thinking about thinking" [3]. One of the many domains that fall under the umbrella of metacognition is cognitive insight, which refers to the set of cognitive processes that permit questioning one's beliefs and appraisals, and re-evaluating anomalous experiences and misinterpretations [7]. Other metacognitive constructs include cognitive biases, such as the Jumping to Conclusions (JTC) bias, which refers to the tendency of hasty decision-making. Given their role in the etiology and maintenance of psychosis, these have been thoroughly studied [3].

Deficits in social cognition and metacognition are not a consequence of neurocognitive impairment [8,9], but seem to be characteristics of the disorder [5,10,11]. Interestingly, social cognition and metacognition are being increasingly studied due to their contribution to functional outcome [12–16] and negative symptoms [17,18] in schizophrenia.

However, social cognition and metacognition do not only influence functional outcome. Instead, specific subdomains of each construct are uniquely associated to certain aspects of the illness, and of each other: Inability to take the perspective of others could impact clinical insight [19, 20], which, in turn, has been associated with depression [21], a higher number of relapses [22], worse social functioning [23], and poor adherence to treatment [24]. Furthermore, understanding sarcasm is a component of theory of mind (ToM) that has been found to be specifically impaired in those with more severe social cognitive impairment and worse functional outcome [25].

In addition, the Jumping to Conclusions (JTC) bias is related to severe and more pervasive delusions [26], worse neuropsychological functioning [27–29] and more compulsory admissions [30]; while self-reflectivity has been uniquely associated to negative symptoms and depression [31,32]. Similarly, personalizing bias seems to be associated to making more perseverative errors in cognitive flexibility tasks [33], while an externalizing attributional style for negative events is associated with persecutory and grandiose beliefs [34].

Given its established importance, recent research has focused on developing social cognitive and metacognitive remediation programs [35–37].These interventions have emerged as promising strategies to improve outcome [37,38], prevent chronic illness and relapse [22,39], and increase clinical insight [40,41]. Moreover, since deficits in social cognition and metacognition are already apparent at the ultra-high risk stage [42,43] they hold promise for early treatment in symptoms of psychosis. These interventions have yielded some clinical benefits [35, 44] , although at present their potential to improve functioning is less clear. However, a recent study found that an online social cognitive intervention based on neuroplasticity can lead to functional gains in schizophrenia [45]. Although the mechanisms of change to improve functional outcome may be similar to those in cognitive remediation, of which efficacy has been well established[46], it is yet to be determined which persons would benefit more from them.

There are two caveats in interpreting the results of the above studies: clinical trials often present averaged results, therefore blurring whether the intervention was successful for certain individuals. Likewise, it is possible that people with first episode psychosis present different profiles of social cognitive and metacognitive performance, and thus may benefit from a specific early therapeutic strategy. One way to overcome this issue is by finding subgroups of participants with specific profiles [47]. Recent studies have tackled this issue by using data-driven methods like profile analysis. These sophisticated statistical methods allow finding profiles of cases along the dimension of interest as they occur naturally, preventing a priori assumptions [48].

These methods have been used to profile persons with psychosis across multiple domains [5, 49, 50], including social cognition and metacognition. Grouping individuals with schizophrenia on the basis of variables of social cognition has consistently yielded three profiles according to the level of impairment [25, 51–53]. Conversely, studies using profile analysis in metacognitive variables have commonly found distinct profiles of persons according to symptoms [48] and insight and depression [4]. Lysaker et al., (2019) found that, independent of symptoms, poor metacognition impedes insight [48]. As for depression and insight, Lysaker et al., 2013 found that participants with fair insight and moderate depression reported more internalized stigma, while those with good insight and mild depression scored higher in social cognition and metacognitive mastery [4].

However, these studies were conducted with samples with chronic schizophrenia, and studies examining social cognition and metacognition profiles in FEP are lacking.

Identifying whether profiles of social cognition and metacognition are apparent in persons at the early stages of psychosis may provide insights into how to direct early treatment to promote recovery and prevent functional decline. Furthermore, understanding whether different profiles of social cognition and metacognition present differences in clinical and neurocognitive variables may help identifying what persons are at a bigger risk of chronic illness.

The current study aimed to obtain profiles of individuals with FEP on the basis of social cognition and metacognitive variables using a data-driven approach in a representative sample of participants. With this aim, we attempted to understand whether all persons with FEP present homogeneous impairments in all the domains of both constructs. Additionally, to explore the clinical presentation of each profile, we examined differences in demographics, clinical features, and neuropsychological variables among the groups. We hypothesize that patients with FEP present different profiles of social cognition and metacognition, and that profiles will differ in clinical, functional and cognitive variables.

METHODS

The design of the study is based on two research sources aimed to address the effectiveness of metacognitive treatment (MCT) in people with FEP, under the register numbers NCT04429412 and NCT02340559. The protocol for both studies can be accessed at https://clinicaltrials.gov/. For the purpose of this study, we only used the baseline measures of each clinical trial.

Participants

The participants were 174 individuals with FEP. Participants were referred by their psychologists and psychiatrists at one of the community mental-health services provided by the participant groups: Fundación Jiménez Díaz (Madrid), Servicio Andaluz de Jaén, Servicio Andaluz de Málaga, Centro de Salud Mental de Corporació Sanitària i Universitària Parc Taulí (Sabadell), Hospital del Mar, Consultas externas del Hospital de Sant Pau (Barcelona), Centro de Higiene Mental Les Corts (Barcelona), Hospital Universitari Institut Pere Mata (Reus), Institut d´Assistència Sanitària Girona, Hospital Clínico de Valencia and Parc Sanitari Sant Joan de Déu (PSSJD).

Inclusion criteria were: 1) a diagnosis of schizophrenia, psychotic disorder not otherwise specified, delusional disorder, schizoaffective disorder, brief psychotic disorder, or schizophreniform disorder (according to DSM-IV-TR); 2) <5 years from the onset of symptoms; 3) a score ≥3 in item delusions, grandiosity, or suspiciousness of PANSS in the last year; 4) clinical stability in the previous 3 months, and 5) age between 18 and 45. Exclusion criteria included 1) traumatic brain injury, dementia, or intellectual disability (premorbid IQ ≤ 70); 2) substance dependence.

Each participant was assessed at the site by an experienced member of the study. All examiners had been previously trained to reach satisfactory concordance indexes.

Instruments

Sociodemographic questionnaire: Data on socio-demographic variables, medical records and medication were collected at the site with a questionnaire created ad-hoc. We transformed the antipsychotic treatment to olanzapine defined daily dose (DDD) [54].

Clinical measures: The Positive and Negative Syndrome Scale (PANSS) [55, 56] was used to measure clinical and general symptoms. We used the 7-factor solution proposed by Emsley [57]. This solution was proven to be as sound as the 5-factor model, but separates anxiety and depression into two different factors, and includes a motor factor. The Spanish version of the Scale Unawareness of Mental Disorders (SUMD) [58, 59] was used to measure unawareness of the mental disorder.

Metacognition: The Beck Cognitive Insight Scale (BCIS) [60, 61] was used to measure cognitive insight. The BCIS includes two subscales that measure self-reflectivity and self-certainty, and a composite index (cognitive insight). The Beads Task [62] was used to measure the JTC. Participants are shown two jars containing beads in two colors and in opposite ratios (85:15 and 60:40). The computer randomly selects one of the jars. Participants can either guess the jar the beads are coming from or request more beads. There is a third condition (60:40 ratio) in which participants extract positive and negative adjectives instead of colored beads (affective). Our outcome variable was the number of draws to decision (DTD). Fewer draws to decisions reflect higher proneness to jump to conclusions.

Social Cognition: The Internal, Personal and Situational Attributions Questionnaire (IPSAQ) [63] was used to assess attributional style. The IPSAQ yields two subscales: externalizing bias and personalizing bias. The Faces Test [64, 65] was used to measure facial emotion recognition. A reduced version of The Hinting Task [66] was used to measure ToM. Our reduced scale is based on the items that reached better internal consistency in the Spanish validation[67], since the reliability of the whole scale did not reach satisfactory values. We used two research sources in this work: a subset of the sample was assessed with three stories at test and different stories at re-test to prevent learning effects. The other subset was assessed with 6 stories. To calculate a composite measure of the Hinting Task, we divided the total in each condition by the number of items of the test, yielding a measure between 0 and 2.

Functional outcome: The Global Assessment of Functioning (GAF) [68] was used to measure clinical and social functioning on a scale of 0-100.

Neuropsychology: The Wisconsin Sorting Card Test (WSCT) [69, 70] was used to assess cognitive flexibility, inhibition, strategic planning and perseverative behavior. For the purpose of this study, we included measures of errors, perseverative errors and non-perseverative errors. The Stroop Test [71] was used to measure selective attention, processing speed and resistance to interference. In this work, we have included the measure of interference converted into T scores. The Trail Making Test (TMT-A and TMT-B) [72, 73] was used as a measure of visuomotor attention, sustained attention, speed and cognitive flexibility. The TMT T-scores were obtained by subtracting the mean of the whole cohort to the direct punctuation, dividing it by the standard deviation of the whole cohort, multiplying the result by 10 and adding 50. We used two research sources in this work. Part of our sample was assessed with the Continuous Performance Test (CPT-II for Windows) [74]. The other subset was assessed with the MATRICS CPT [75–77] . To obtain a homogeneous measure of attention, we created the composite variable “Attention” by adding the D-prime scores of both measures standardized into T scores with a mean of 50 and a standard deviation of 10. The Weschler Adults Intelligence Scale (WAIS-III) [78] subtests Vocabulary and Digits were used to measure premorbid intelligence, and verbal fluency and working memory,

respectively. We obtained premorbid IQ by multiplying the scaled scores in the Vocabulary subtest by 5 and adding 50. We assessed verbal memory with the Complutense Verbal Learning Test (TAVEC) [79] This study included the subdomains of immediate recall, effect of primacy, long term recall, recognition and discrimination.

Ethics

Participants were given an informative sheet, and all of them signed an informed consent file for participation in this study. The protocol of this project was approved by The Ethics Committee of Sant Joan de Déu Research Institute (Comité de Ética de Investigación con medicamentos (CEIm). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Statistical analysis

We used SPSS Version 22 to conduct descriptive and comparative analyses. Latent Profile Analysis (LPA) was carried out using R Version 3.5.3 (R package *mclust)*. This method identifies profiles of individuals, called latent profiles, based on responses to a series of continuous variables. We determined the number of latent profiles analyzing 2–6 group models. The variables included were: Faces Test (total score), the Hinting Task (total score), the IPSAQ (personalizing bias and externalizing bias scores), the BCIS (self-reflectivity and self-certainty scores), and the three conditions of the Beads Task (DTD). The mean score of each variable was standardized prior to the analysis. We determined the optimal number of latent trajectories according to the Bayesian Information Criterion (BIC) [80]. We assessed the variable importance using a classification tree via the R package *rpart*. We used Kruskal-Wallis to assess mean differences in demographic, clinical and neuropsychological variables among the profiles. We used Dwass-Steel-Critchlow-Fligner pairwise comparisons (DSCF) to explore the direction of the differences among groups. We calculated U Mann-Whitney tests between the significant pairs to obtain the effect size, transforming the statistics to obtain Cohen's d.

RESULTS

Profile solution

Using LPA we identified three type-VEE distinct profiles of individuals with FEP (i.e ellipsoidal profiles with equal shape and orientation) according to BIC (BIC=-3600.651). Of all the metacognitive and social cognitive variables studied, the classification tree identified the 85-15 condition of the Beads Task and the Hinting Task as the most relevant variables in determining the profile structure.

Figure 1 describes each profile according to social cognition and metacognition variables. Table 1 summarizes the scores of the whole sample and of each profile in the social cognitive and metacognitive variables.

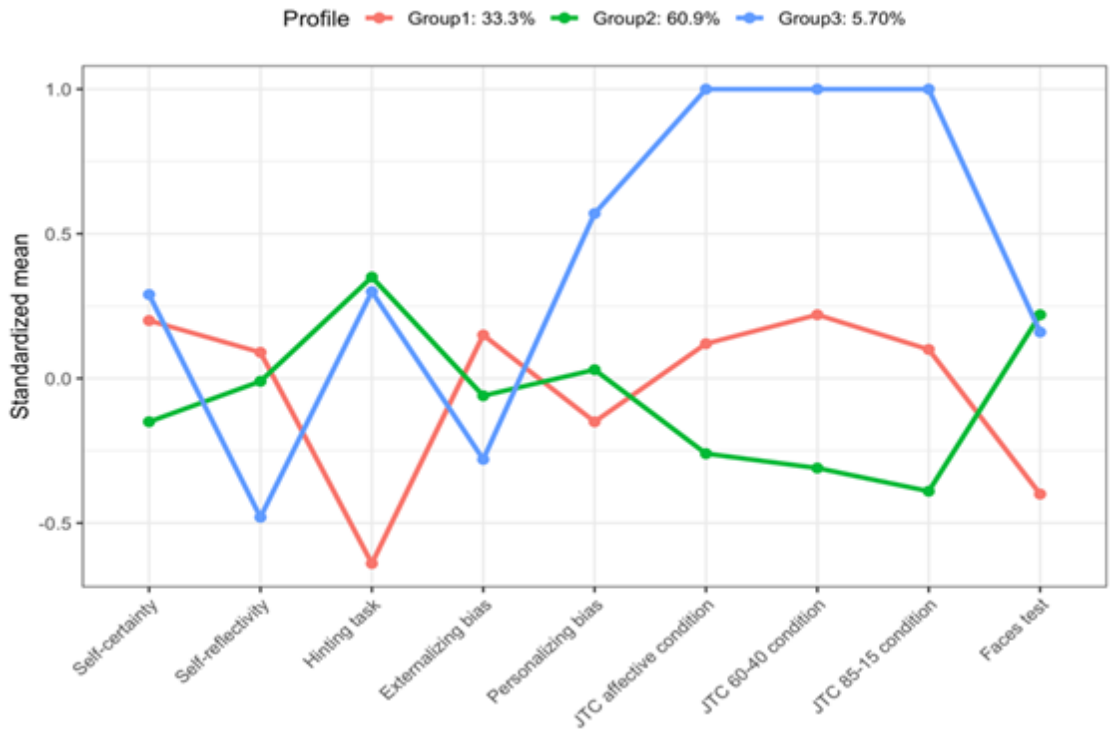
Profile 1 (33.3%) was characterized by prominent impairment in social cognition measures (facial emotion recognition and theory of mind). This profile was named "Low-SC". Profile 2 (60.9%) grouped participants with more proneness to JTC. We denominated this profile "JTC". Profile 3 (5.7%) presented an excessive number of DTD in the JTC tasks, higher scores in personalizing bias, more self-certainty, low self-reflectivity, and low cognitive insight. This profile was named "Rigidity".

Demographic, functional, and clinical characteristics

Table 2 details the demographic, functional and clinical characteristics of the sample and of each profile. When comparing profiles, we did not find differences in age (p=0.819), gender (p=0.501), or years of education (p=0.639). We found a trend to significance in the number of hospital admissions (p=0.055) that was confirmed as significant in subsequent pairwise comparisons (Profile1>Profile 2). We found significant differences in negative (p=0.05), positive (p=0.001), disorganized (p=0.02), depressive (p=0.02) and anxiety (p=0.02) symptoms. Pairwise comparisons indicated that the Low-SC profile achieved higher scores in all the variables, indicating worse symptoms. Similarly, there were significant differences among the groups in the SUMD. The "Low-SC" group had significantly less clinical insight.

Finally, we found significant differences among the profiles in the GAF (p=0.010). Participants in the "Rigidity" profile had significantly worse functioning than their counterparts.

Figure 1. Scores of each profile in all the social cognitive and metacognitive variables included in the latent profile analysis.



Values over 0 in self-certainty, self-reflectivity, externalizing bias, and personalizing bias reflect a bigger presence of the constructs. Values over 0 in the Hinting Task and the Faces Test indicate better performance in these measures. Values below 0 in the three conditions of the JTC denote more proneness to hasty decision making.

	Whole sample (N=174)		Cluster 1: Low S-C (N=58)		Cluster 2: JTC (N=106)		Cluster 3: Rigidity (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BCIS								
Self-reflectivity [b]	15.5	4.87	16.2	5.68	15.4	4.42	13.2	3.74
Self-certainty [a]	8.33	3.39	9.00	4.06	7.87	2.86	9.30	3.83
Cognitive Insight [b]	7.70	6.48	7.47	6.71	8.19	6.25	3.90	6.92
Hinting Task [b]	1.58	0.38	1.30	0.48	1.73	0.23	1.70	0.18
JTC [a]								
85-15	4.88	4.30	5.52	2.75	3.14	1.56	19.6	0.69
40-60	7.90	4.96	9.14	5.43	6.34	3.43	17.3	3.65
Affective	7.57	4.55	8.22	4.77	6.40	3.38	16.3	4.16
IPSAQ [a]								
Externalizing bias	0.983	3.87	1.67	4.84	0.70	3.13	0.10	4.43
Personalizing bias	1.21	0.669	1.13	0.82	1.23	0.56	1.59	0.57
Faces Test [b]	17.5	1.97	16.8	2.46	17.9	1.54	17.8	1.81

Table 1. Mean scores in the social cognitive and metacognitive variables of the whole sample and of each cluster.

a Higher scores represent more severity of the construct, b Higher scores represent better ability in the construct.

Neuropsychological characteristics of each profile

Supplementary Table 1 details the neuropsychological characteristics of the sample. The “Low-SC” group was significantly more impaired in working memory (p=0.039), and in immediate recall (p=0.037) than the other two profiles. We did not find any other differences among the profiles in any other neuropsychological variables.

Table 2. Sociodemographic and clinical characteristics of each cluster and the whole sample.

	Whole sample (N=174)		Cluster 1: Low S-C (N=58)		Cluster 2: JTC (N=106)		Cluster 3: Cognitive (N=10)		Kruskall Wallis			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	χ^2	p	DSCF*	Cohen's d
Socio-demographics and clinical characteristics												
Age (years)	28.1	7.50	27.7	7.8	28.2	7.29	28.8	8.31	0.40	0.82		
Gender (% female)	33.3%		31%		33%		50%		1.38	0.50		
Education (years)	13.16	4.35	12.68	4.37	13.39	4.29	13.40	5.05	0.89	0.64		
Number of admissions	1.24	1.45	1.58	1.73	1.07	1.10	1.10	0.87	5809	0.05	1-2	
Olanzapine DDD (mg)	16.94	47.26	11.46	6.23	20.73	60.31	8.88	5.27	3.61	0.16		
Comorbidities (% presence)	18.4		19%		16%		40%		3.36	0.19		
Diagnosis (%)									5.31	0.07		
Schizophrenia	39.7%		41.4%		39.6%		30%					
Psychosis (NOS)	27.6%		22.4%		32.1%		10%					
Schizoaffective disorder	10.3%		10.3%		8.5%		30%					
Delusional disorder	6.3%		8.6%		4.7%		10%					
Brief psychotic disorder	5.2%		13.8%		7.5%		10%					
Schizophreniform disorder	1.1%		3.4%		5.7%		10%					
Clinical and functional variables												
Emsley factors												
Negative	15.4	6.95	16.8	7.3	14.5	6.70	17.5	6.36	5.74	0.06	1-2	0.323
Positive	16.1	6.40	18.7	6.9	14.7	5.77	15.2	5.47	13.6	0.001	1-2	0.599
Disorganised	8.34	3.70	9.47	4.36	7.73	3.23	8.22	2.82	7.10	0.03	1-2	0.415
Excitement	5.49	2.73	5.93	3.15	5.33	2.57	4.60	0.843	0.81	0.66		
Motor	2.86	1.45	2.91	1.61	2.82	1.34	2.90	1.66	0.136	0.934		
Depression	4.64	2.31	4.98	2.29	4.30	2.18	6.30	2.87	7.56	0.023	1-2, 1-3	0.306, 0.374
Anxiety	5.82	2.34	6.57	2.67	5.43	2.08	5.50	1.96	7.37	0.025	1-2	0.424
GAF	59.5	12.4	57.5	12.1	61.5	12.1	50.6	12.0	9.18	0.010	1-2, 1-3, 2-3	0.319, 0.426, 0.472
SUMD (global)	6.13	3.59	7.22	3.87	2.88	3.00	5.00	3.68	7.90	0.019	1-2, 1-3	0.398, 0.43

DISCUSSION

In this work, we derived three distinct profiles of individuals with FEP based on social cognition and metacognition measures. Latent Profile Analysis is a statistical method that does not model potential noninvariance across latent profiles. The sensitivity of this method permitted detecting three cohesive and

clinically meaningful groups of persons with FEP. Each group presented specific clinical, neuropsychological and functional correlates.

We found a group with more prominent deficits in social cognition measures ("Low-SC"), namely Facial Emotion Recognition and Theory of Mind, another group that had a bigger tendency to present the Jumping to Conclusion Bias ("JTC"), and a group with worse cognitive insight scores and higher personalizing bias ("Rigidity"). The "JTC" profile had better clinical state and better neuropsychological functioning than the other two groups. The "Low-SC" profile had significantly more symptoms and worse neuropsychological functioning, while the "Rigidity" profile had the worst measures in functioning in absence of demographic or clinical differences. Members of this profile exhibited lower scores in cognitive flexibility.

To the best of our knowledge this is the first work exploring profiles of individuals on the basis of social cognition and metacognition in people with FEP. Previous studies on social cognition measures had consistently found that persons with schizophrenia can be profiled according to their level of impairment [25, 51–53]. Those with worse social cognition were older, had less academic background and were more neurocognitively impaired [51, 52]. Our results are consistent with these studies in that the "Low-SC" group had worse neuropsychological performance. We did not find differences in age and education, possibly because previous studies included participants with chronic schizophrenia.

Literature examining profiles on the basis of metacognition used measures of depression and insight [4, 48], therefore non-comparable to ours. However, in a similar approach to ours, Lysaker et al (2013) used principal component analysis to determine whether social cognition and metacognition are independent, finding clear evidence for two different factors that had specific correlations with different outcomes [21] . The results of our study support the notion that social cognition and metacognition are two independent constructs, since we obtained two profiles based either in metacognitive variables or in variables of social cognition. It is worth noting that the "Rigidity" profile encompasses metacognitive variables and attributional style, giving support to Buck et al (2016), who found that attributional style loaded in a distinct factor from the rest of social cognitive variables [81]. However, understanding how social cognition and metacognition interact and what type of patient may be more prone to developing more conspicuous deficits in one of the domains in the early phases of the disorder remains to be studied.

Lysaker et al., (2013) found that participants with worse social cognition had more negative symptoms, poorer education and poorer premorbid functioning [4]. Conversely, individuals with poor metacognitive awareness were associated with disorganized symptoms, frequency of social contacts, and flexibility in abstract

thought. Consistent with their results, we found that our profiles did not differ in age or education. We note that our sample which demonstrated more severe social cognition impairments had more positive, negative, and disorganized symptoms. It is likely that differences between the two studies are due to differences in measurement and in the sample, since we used different tasks and their study was conducted in a sample with established schizophrenia.

Because social cognition seems to be a stable trait of the disorder [5] , a history of social cognitive deficits and negative social experiences may have a more pervasive impact on the subjects after onset. Interestingly, we found that the "Low-SC" profile had significantly less clinical insight than the other two but did not display significant deficits in cognitive insight. Although this effect could be a consequence of more positive and disorganized symptoms, there is compelling evidence reporting significant correlations between ToM and clinical but not cognitive insight [19, 20], which agrees with our results. A reason for this could be that deficits in social cognition may render subjects less able of taking into account others' perspectives on illness, support and treatment [4]. The literature suggests that to develop insight, others' perspective when reflecting upon oneself must be taken into account [19], because assessing abnormalities of one's beliefs and perceptions require adopting not only first-person perspective but also third-person, including mental health professionals' views on treatment advice [9].

Poor metacognition has been linked to poor outcome [82]. Specifically, the JTC bias has been associated to an increased presence of delusions [26], worse neuropsychological functioning and lower IQ [27–29]. We did not find these results in our "JTC" profile, although it is likely that using the number of DTD instead of a categorical variable (presence/absence of JTC) can account for the differences in our results. An alternative explanation could be that more preserved social cognition may have allowed this subset of the sample to have better premorbid adjustment, ultimately buffering the impact of the disease and fostering recovery.

The "Rigidity" group presented a heterogeneous profile that comprised specific metacognitive impairments. One of the most conspicuous traits of this profile is the excessive number of DTD in all the conditions of the Beads Task. Moreover, this group exhibited more self-certainty, lower self-reflectivity, less externalizing bias and more personalizing bias than their counterparts, suggesting worse overall cognitive awareness. This profile could be compatible with a rigid cognitive style, in which individuals may tend to attribute negative events to other persons. Paired with more self-certainty, this group could have difficulties in realizing their interpretations are wrong, and their lack of self-reflectivity could perpetuate wrong attributions. Another interpretation could be an excessive metacognitive monitoring, in the sense that subjects may be constantly evaluating whether they have enough information to make a decision. Excessive metacognition could inhibit decision-making, such as in OCD [83]. This hypothesis could explain the

remarkably high DTD in this group. However, this group obtained significantly lower scores in WAIS-III Digits and clinically lower scores in attention. Previous results reported that self-reflectivity is not significantly associated to most neuropsychological domains [9], suggesting that poor self-reflectivity and neurocognitive domains may act through different pathways.

It would be plausible that participants with worse attention and less cognitive flexibility may need more information to effectively solve a problem, while poor self-reflectivity may compromise the subject's ability to synthesize and comprehend ideas. The interaction of both could diminish the patient's ability to incorporate new ideas into their self. This explanation is in agreement with findings by Berry et al (2015), who reported an association between personalizing bias and perseverative errors [33].

Recent evidence has highlighted that self-certainty influences dichotomous thinking in interpersonal thinking, while poor self-reflectivity could diminish the differentiation between the self and others [32]. In turn, poor synthetic metacognition could increase negative symptoms [84]. Because self-reflectivity allows persons to choose how to adapt to significant changes in life, such as a mental illness [3], high self-reflectivity may protect subjects from the impact of depressive symptoms [85], which suggests a possible link between low self-reflectivity and high depression in this profile.

There are clinical implications to our work. Persons with psychosis already present specific profiles of social cognition and metacognition at the first stages of the illness. Therefore, early treatment to the individuals' specific needs could be delivered soon after the first episode, when persons are more amenable to treatment. Although we found neurocognitive differences among the profiles, these differences are somewhat limited and do not suggest that cognitive remediation should be tailored to specific profiles of social cognition and metacognition. Instead, the "Low-SC" profile may benefit both from specific social cognition interventions together with cognitive remediation programs. However, participants in the "Rigidity" and "JTC" profiles could be more responsive to metacognitive training programs such as the MCT [36,37]. Profile 3 ("Rigidity") only grouped 5.7% of the sample. Although a small proportion of the sample, individuals in this group presented specific social cognitive and metacognitive characteristics that grant further research, as these individuals may be subject to more functional decline. Future studies should conduct clinical trials assessing the efficacy of each program in each patient profile.

Pre-morbid adjustment and course of the disorder may differ between the groups, and it remains to be determined what variables predict profile membership, as well as exploring differences in their course of illness. Likewise, strategies to place

an individual in their corresponding profile according to their performance in measures of social cognition and metacognition are encouraged.

There are limitations in light of which our work must be interpreted. The cross-sectional design of our study precludes us from testing causality. An important limitation to our study is that the only measure of functioning is the GAF. Although widely used in research, it fails to cover all nuances of functional outcome, as it is a general measure. We did not use a healthy control group. Therefore, the extent of the impairment in each variable is unknown. We did not retest our sample to test the stability of each profile, nor did we test our profile solution in an independent sample. The third profile comprised only 10 subjects. Although we used non-parametric tests, it is possible that the statistical power was not enough to detect all the relevant differences. Finally, this work selected some commonly accepted and validated measures of metacognition and social cognition. However, metacognition encompasses a broader number of subdomains (for instance, decentration and mastery[86]) that have proven to be important therapeutic targets[87]. Future research should explore profiles of patients including more measures of metacognition.

Overall, our results indicate that individuals with FEP do not present homogeneous deficits in social cognition and metacognition, but present different profiles of performance that have an impact in their clinical presentation. Understanding the clinical course of each profile and whether they respond differentially to targeted therapies could pose clinical advances in the early treatment of psychosis.

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2.3. STUDY 3: "MEN AND WOMEN WITH FIRST EPISODE PSYCHOSIS HAVE DISTINCT PROFILES OF SOCIAL COGNITION AND METACOGNITION"

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Objective	Objective 3: To examine if males and females with first episode psychosis are similar in their heterogeneity in social cognition and metacognition. Objective 4: If we identify different profiles, to explore the sociodemographic, clinical, and neurocognitive characteristics of each profile.
Rationale within the thesis	This study takes study 2 a step deeper by splitting the sample by sex. Sex is a key variable in understanding individual differences in psychosis because cumulative evidence has established important differences at the biological, cognitive, clinical, and functional levels of psychosis.
Considerations	None

Table 9. Summary and details of study 3.

MALES AND FEMALES WITH FIRST EPISODE PSYCHOSIS PRESENT DISTINCT PROFILES OF SOCIAL COGNITION AND METACOGNITION

Running title: Social cognition, metacognition, psychosis and sex

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ABSTRACT

Deficits in social cognition and metacognition impact the course of psychosis. Sex differences in social cognition and metacognition could explain heterogeneity in psychosis. 174 (58 females) patients with first-episode psychosis completed a clinical, neuropsychological, social cognitive and metacognitive assessment. Subsequent latent profile analysis split by sex yielded 2 clusters common to both sexes (a Homogeneous group, 53% and 79.3%, and an Indecisive group, 18.3% and 8.6% of males and females respectively), a specific male profile characterized by presenting jumping to conclusions (28.7%) and a specific female profile characterized by cognitive biases (12.1%). Males and females in the homogeneous profile seem to have a more benign course of illness. Males with jumping to conclusions had more clinical symptoms and more neuropsychological deficits. Females with cognitive biases were younger and had less self-esteem. These results suggest that males and females may benefit from specific targeted treatment and highlights the need to consider sex when planning interventions.

Keywords: *sex differences, profiles, psychosis, schizophrenia, social cognition, metacognition*

BACKGROUND

Sex differences in the onset and expression of psychosis are well documented and apparent since the first episode of psychosis (FEP) [1, 2]. Sex is one of the most predictive variables of clinical features at FEP [3], although this predictive power may be related to the large disparities that exist in other risk factors between the two sexes [4]. Men with psychosis have poorer premorbid adjustment, higher levels of substance abuse and dependence, and more negative symptoms [2, 5]. Furthermore, men usually exhibit worse social functioning [6] and male sex is a predictor of relapse after FEP [7]. Although the reasons behind better prognosis in women remain to be disentangled, there is cumulative evidence suggesting that disparities between both sexes start at a biological level, for instance at the genetic [8], neural [9] and hormonal [10] levels. Especially concerning the latter, a corpus of studies has shown the protective role of estrogens in psychosis [11] and its promise as a pharmacological treatment [12].

As well as biological variables, there are psychological constructs that deserve attention in their potential role for sex differences in psychosis, such as social cognition and metacognition. Patients with FEP experience significant deficits in social cognition [13] and metacognition [14]. Social cognition encompasses perception, interpretation, and information processing for adaptive social interactions [15], while metacognition refers to the spectrum of mental activities that involve the reflection upon one's and the other's thinking, and the synthesis of these phenomena into an integrated sense of the self and the others [16, 17]. Both social cognition and metacognition are important predictors of functional outcome when assessed globally [15, 18–20], but even specific subdomains of both constructs have distinct impacts in the disorder. The Jumping to Conclusions bias (JTC) has specific associations with neurocognition [21–24], inaccurate processing of social information [25], worse outcome [26], delusion forming and severity [22, 27, 28] and suicidal behavior [29] . Clinical insight has been related to treatment compliance, quality of life, depression, and symptoms among others [18, 30–32] but seems to be independent of neurocognition [33]. Attributional style has a clear influence in paranoia and persecutory delusions [34–36], and cognitive insight is related to depressive symptoms [37], and treatment compliance, symptoms and quality of life [18].

Research exploring sex differences in social cognition and metacognition is inconclusive, probably due to the tendency to present averaged results [38]. A majority of studies have failed to find significant differences between sexes in social cognition [39–41] or metacognition [42, 43]. However, exploring differences in social cognition and metacognition beyond mean differences has often lead to important results. For instance, Lysaker et al., 2019 sought to find levels of insight

across symptom profiles, finding a group characterized by positive symptoms and impaired insight that contained a majority of females. Cobo et al., (2016) found that clinical insight correlated with different variables in each sex [43]. Similarly, García-Mieres et al. (2020) found that women with psychosis present more extreme dichotomous thinking but a richer personal identity system [45]. Likewise, Salas-Sender et al., (2019) found that men and women with FEP responded differently to metacognitive training [46].

Differences in social cognition and metacognition in psychosis may not be apparent when comparing performance but may be rooted in discrepancies in information processing. Data driven methods permit capturing heterogeneity according to data, without testing preconceived hypothesis. In this sense, Latent Profile Analysis (LPA) seems an adequate technique to understand the possible configurations of social cognition and metacognition in males and females. LPA was designed to identify construct-based profiles [47], meaning that each profile captures latent attributes of a similar population. Furthermore, LPA is a person-based approach, what permits placing the focus in the characteristics of the individuals in predicting outcomes of interest [47].

In this work, we sought to explore whether men and women with FEP present different profiles of social cognition and metacognition using LPA. As a second objective, we tested differences in demographic, clinical and neuropsychological variables among the derived profiles. Given the exploratory nature of this study and the use of data-driven methods, we did not have a priori assumptions on the number of profiles and their characteristics or on the clinical differences among the profiles. We did, however, hypothesize that LPA is an adequate technique to detect configurations of social cognition and metacognition for each sex, and that profiles would have distinct clinical features.

METHODS

The design of the study and data collection stems from two research sources aimed to address the effectiveness of metacognitive training in people with FEP, under the register numbers NCT04429412 (conducted between 2015 and 2017) and NCT02340559 (conducted between 2012 and 2014). Data on the efficacy of metacognitive training of the clinical trial NCT02340559 has been published elsewhere [48]. Data of the clinical trial NCT04429412 has not been published yet. For the purposes of this work, only the baseline data of both clinical trials has been included in this study. Participants from the two sources did not differ in age ($t(170)=0.91$, $p=0.369$, CI [-1.336, 3.578]), sex ($\chi^2(1)=0.749$, $p=0.387$) or diagnosis ($\chi^2(5)=3.671$, $p=0.598$).

Participants

Participants were 174 (58 females) individuals with FEP. Patients were referred by clinicians at one of the community mental-health services of the participant groups: Fundación Jiménez Díaz (Madrid), Servicio Andaluz de Jaén, Servicio Andaluz de Málaga, Centro de Salud Mental de Corporació Sanitària i Universitària Parc Taulí (Sabadell), Consultas externas del Hospital de Sant Pau (Barcelona), Centro de Higiene Mental Les Corts (Barcelona), Institut Pere Mata (Reus), Institut d´Assistència Sanitària Girona, Hospital Clínic de València and Parc Sanitari Sant Joan de Déu (PSSJD). Inclusion criteria contemplated: 1) a diagnosis of schizophrenia, psychotic disorder not otherwise specified, delusional disorder, schizoaffective disorder, brief psychotic disorder, or schizophreniform disorder (according to DSM-IV-TR); 2) <5 years from the onset of symptoms; 3) a score ≥4 in item delusions, grandiosity, or suspiciousness of PANSS in the last year; 4) age between 18 and 45. Exclusion criteria included 1) traumatic brain injury, dementia, or intellectual disability (premorbid IQ ≤ 70); 2) substance dependence 3) Scores higher than 6 in the PANSS items "Hostility" or "Suspiciousness".

Measures

Sociodemographic questionnaire: Data on socio-demographic variables was collected on-site. Diagnosis and treatment were collected from the clinical history of the participants. We transformed the antipsychotic treatment to olanzapine defined daily dose (DDD) [49].

Clinical measures: The Positive and Negative Syndrome Scale (PANSS) [50, 51] was used to measure clinical and general symptoms. We used the 7-factor solution proposed by Emsley [52]. The Spanish version of the Scale Unawareness of Mental Disorders (SUMD) [53, 54] was used to measure unawareness of the mental disorder. Higher scores represent more unawareness of the mental disorder. We used the Rosenberg Self-Esteem Scale [55], where higher scores indicate better self-esteem.

Metacognition: The Beck Cognitive Insight Scale (BCIS) [56, 57] was used to measure cognitive insight. The BCIS is composed of two subscales: self-certainty and self-reflectivity, which are analyzed separately. Higher scores in self-reflectivity represent more ability to questioning one's beliefs. Higher scores in self-certainty represent more certainty in one's interpretations and misinterpretations. The Beads Task [58] was used to measure the JTC. Participants were shown a picture of two containers filled with 100 colored beads in reciprocal proportions. We used three trials with different conditions: a probabilistic trial with a 85/15 ratio, a second probabilistic trial with a 60/40 ratio, and a final trial with an affective condition in a 60/40 ratio. Participants were told that the computer had selected a container and that the goal of the task was to determine which container. To

this aim, participants were shown one bead at a time. The participant was instructed to see as many beads as they needed to guess what container the beads came from. Our outcome variable was the draws to decision in the three probabilistic conditions. Less than 3 draws to decision is considered indicative of presenting the JTC bias.

Social Cognition: The Internal, Personal and Situational Attributions Questionnaire (IPSAQ) [59] was used to assess attributional style. We used two indexes: personalizing bias and externalizing bias. Personalizing bias refers to a tendency to blame the others rather circumstances for negative events. Externalizing bias refers to a tendency to attribute the causes of negative events to others or circumstances rather than to oneself [60]. The Faces Test [61, 62] was used to measure emotion recognition. A reduced version of The Hinting Task [63, 64] was used to measure theory of mind.

Functional outcome: The Global Assessment of Functioning (GAF) [65] was used to measure clinical and social functioning on a scale of 0-100. Higher scores represent better functioning.

Neuropsychology: The Wisconsin Sorting Card Test (WSCT) [66, 67] was used to assess flexibility and inhibition. The Stroop Test (Stroop, 1935) was used to measure flexibility and inhibition. The Trail Making Test (TMT-A and TMT-B) [69, 70] were used as a measure of visuomotor attention, sustained attention, speed, and cognitive flexibility. The Continuous Performance Test (CPT-II for Windows) [69, 70] was used to assess sustained attention and impulsivity. MATRICS CPT [71, 72] was used as a measure of attention in a subsample of the participants. We created the composite variable "Attention" by adding the D-prime scores of both measures standardized into T scores. All the neuropsychological variables are presented in T scores. The Weschler Adults Intelligence Scale (WAIS) [73] subtests Vocabulary and Digits were used to measure premorbid intelligence and verbal fluency, and working memory respectively. The scores are presented in their conversion to IQ.

Statistical analysis

All descriptive analyses to explore the dataset were conducted using SPSS Version 22. We explored differences between sexes in all measures prior to conducting the Latent Profile Analysis using U-Mann Whitney tests. Effect size is reported using Cohen's d.

Latent Profile Analysis (LPA) broken down by sex was carried out using R Version 3.5.3 [74], and in particular the R package *mclust* [75]. This method identifies profiles of individuals, called latent profiles, based on responses to a series of continuous variables. The number of latent profiles was determined by analyzing 2–6 group models in which the variables included were: Faces Test (total score), the Hinting

Task (total score), the IPSAQ (personalizing bias and externalizing bias scores), the BCIS (self-reflectivity and self-certainty scores), and the three conditions of the Beads Task (trials to decision). Participants that lacked data in any of the aforementioned variables were excluded from the study. Of the initial 192 people that participated in the clinical trials, 174 were included in the LPA. Model selection to determine the optimal number of latent trajectories was performed according to the Bayesian Information Criterion (BIC) [76]. Additionally, we assessed variable importance by applying a classification tree via the R package *rpart* [77]. Model selection has been performed via Bayesian Information Criterion (BIC) for the specified LPA models numbers of clusters, which is fitted by EM algorithm [78] initialized by model-based hierarchical clustering [75, 79]. Additionally, the assessment of the variable importance was achieved building a CART model via recursive partitioning trees [80]. This ranking of variables is computed based on the corresponding reduction of predictive accuracy when the predictor of interest is removed using a measure of decrease of node impurity [81].

We used Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner pairwise comparisons to calculate mean differences among the clusters. Effect size is reported using epsilon squared.

RESULTS

Characteristics of the sample

A total of 174 patients with FEP were included in the analysis. Females were significantly older than males (p=0.013) and had received significantly more education (p=0.028). The samples differed in diagnosis (p=0.03), depression as measured by the PANSS (p=0.033), theory of mind (p=0.047), immediate recall (p=0.019), and long-term memory (p=0.034). We did not find any other significant differences between sexes. Full characteristics of the sample and comparisons by sex can be found in Supplementary Table 1.

Table 1. Mean scores of the social cognition and metacognition variables in each profile according to gender.

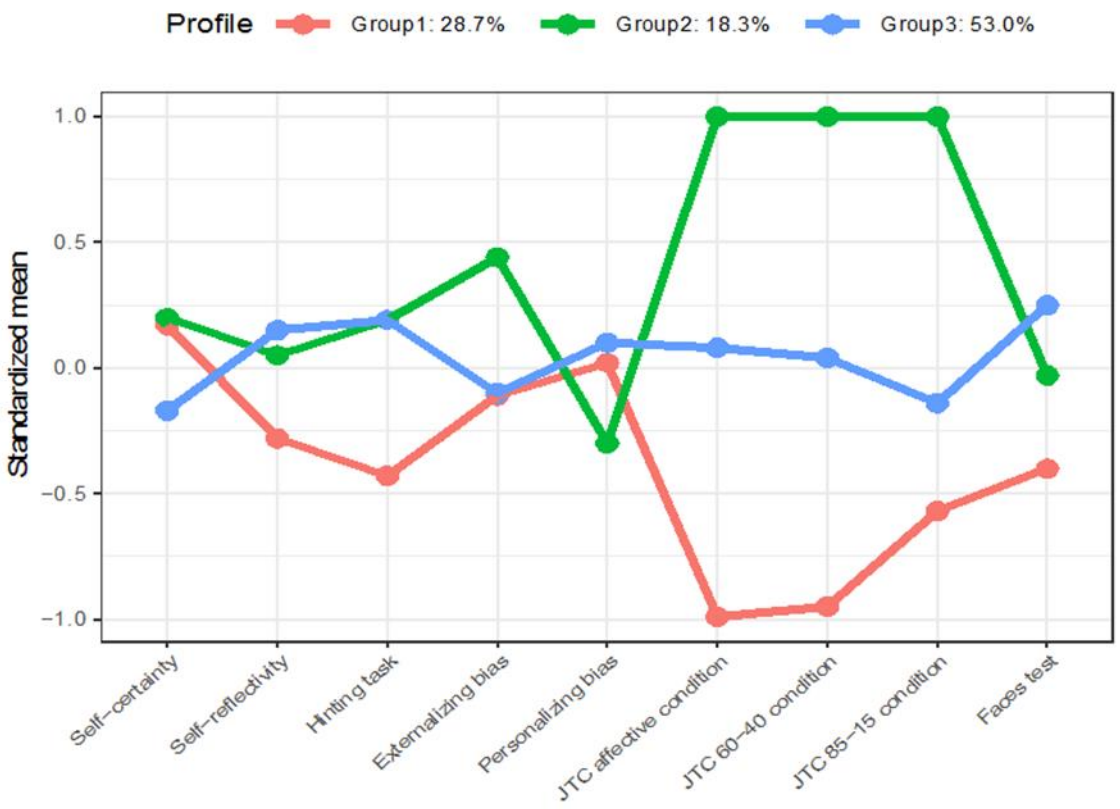
	Males						Females					
	Profile 1	Profile 2	Profile 3				Profile 1	Profile 2	Profile 3			
	JTC	Indecisive	Homogeneous	p	Pairwise comparisons	ε^2	Homogeneous	Indecisive	Cognitive Bias	p	Pairwise comparisons	ε^2
	N=33	N= 21	N=61				N= 46	N= 5	N=7			
	Mean (SD)	Mean (SD)	Mean (SD)				Mean (SD)	Mean (SD)	Mean (SD)			
Beads Task												
85-15	2.33(1.16)	9.90(6.14)	3.98(1.70)	0.001	1<3, 1<2, 2>3	0.406	4.15(2.53)	19.40(0.89)	4.1(3.18)	0.001	1>3, 2>3	0.241
60-40	3.12(2.17)	15.14(4.70)	8.18(2.48)	0.001	1<2, 1<3, 2>3	0.647	6.72(4.09)	18.00(2.00)	6.71(3.68)	0.002	1>3, 2>3	0.225
Salient task	2.88(1.74)	13.52(4.13)	7.72(2.18)	0.001	1<2, 1<3, 2>3	0.685	6.96(3.88)	18.20(1.64)	6.71(3.68)	0.002	1>3, 2>3	0.226
BCIS												
Self-certainty	9.12(3.090)	9.12(4.22)	7.78(2.74)	0.083			8.07(3.97)	8.40(3.64)	8.00(3.10)	0.964		
Self-reflectivity	14.33(5.06)	16.0(5.35)	16.48(4.07)	0.101			14.26(5.42)	15.20(2.84)	20.29(1.89)	0.009	1<3	0.165
Faces Test	16.52(2.81)	17.19(1.91)	17.90(1.50)	0.059			17.28(1.73)	18.40(0.54)	16.57(1.39)	0.072		
Hinting task	1.33(0.55)	1.61(0.28)	1.62(0.32)	0.053			1.70(0.33)	1.60(0.15)	1.52(0.24)	0.104		
IPSAQ												
Personalising bias	1.25(0.70)	1.04(0.71)	1.30(0.53)	0.205			0.092(0.46)	1.30(0.20)	2.75(0.62)	0.0001	1<3	0.366
Externalising bias	0.45(3.88)	2.52(4.86)	0.23(3.21)	0.099			2.54(3.35)	1.00(3.33)	-4.86(1.95)	0.0001	1>3, 2>3	0.3

Males

We identified three diagonal, variable volume, variable shape, coordinate axes orientation (VVI) profile profiles (i.e., diagonal profiles with variable shape, volume, and orientation aligned to the coordinate axes) according to BIC (BIC=-2854.815). Additionally, the CART classification tree assessed that the affective condition of the beads task (40%) and the 60-40 condition of the beads task (36%) were the most important variables in determining the profile structure. The Homogeneous profile (53%) comprised participants who scored around the mean in all the variables examined. The Indecisive profile (18.3%) presented an excessive number of trials (1 SD above the mean) in the three conditions of the Beads Task. The JTC profile (28.7%) included males that had significantly less (around 1 SD below the mean) draws to decision in the three tasks of the Beads Task, suggesting a bigger tendency to present the jumping to conclusions bias. Figure 1 shows the graphic representation of each profile in the male group. As for neuropsychological variables, we found that males in the JTC profile scored worse than their counterparts in profiles Indecisive and Homogeneous in TMT-A and TMT-B, and worse than males in the Homogeneous profile in total errors of WSCT. Males in the JTC profile scored better in our sustained attention measure than males in the Homogeneous profile. The mean scores of each variable included in the LPA and mean differences among profiles are presented in table 1.

Differences among the profiles in clinical and neuropsychological variables are displayed in table 2.Kruskal-Wallis tests yielded significant differences in positive ($p=0.03$) and disorganized ($p=0.03$) symptoms. Significant differences in positive symptoms did not survive subsequent pairwise comparisons. However, we found that males in the JTC profile had worse disorganized symptoms than males in the Homogeneous profile. Further, males in the JTC profile presented worse clinical insight than the other two profiles. We did not find other clinical differences.

Figure 1. Profiles of each group in the male sample with standardized means in each of the variables included in the LPA.



Group 1 refers to the JTC profile. Group 2 refers to the Indecisive profile. Group 3 refers to the Homogeneous profile.

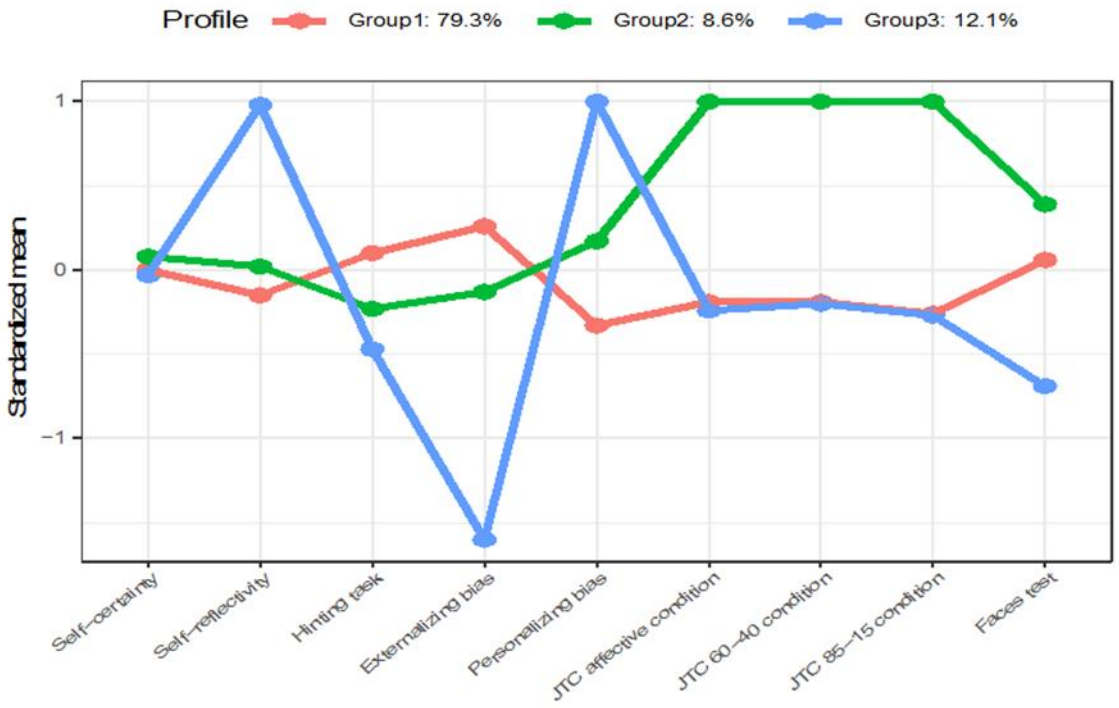
Females

We identified three diagonal, variable volume, equal shape, coordinate axes orientation (VEI) profiles for females (i.e., diagonal profiles with variable volume, equal shape, and orientation aligned to the coordinate axes) according to BIC (BIC=-1443.49). The CART classification tree indicated that the most important variables in defining the profile structure were the Personalizing Bias (32%) and Externalizing Bias (23%) subscales of the IPSAQ. The Homogeneous profile (79.3%) was the dominant group. Participants in this group scored around the mean in all the variables examined. The Cognitive Biases profile (12.1%) was defined by high self-reflectivity, very low externalizing bias, and very high personalizing bias. The Indecisive profile (8.6%) of the sample included participants with an excessive number of trials to decision in the Beads Task.

Figure 2 shows the graphic representation of each profile in the female group. Kruskal-Wallis tests yielded significant age differences (p=0.04) and self-esteem

(p=0.04). Subsequent pairwise comparisons indicated that females in the Homogeneous profile were significantly older than females in the Cognitive Bias profile. The mean scores of each variable included in the LPA and mean differences among profiles are presented in table 1. Differences among the profiles in clinical and neuropsychological variables are summarized in table 2.

Figure 2. Profiles of each group in the female sample with standardized means in each of the variables included in the LPA.



Group 1 refers to the Homogeneous profile. Group 2 refers to the Indecisive profile. Group 3 refers to the Cognitive Biases profile.

Table 2 . Mean scores and mean differences among the profiles in demographic, clinical and neuropsychological variables.

	Males						Females					
	Profile 1	**Profile 2**	**Profile 3**				**Profile 1**	**Profile 2**	**Profile 3**			
	JTC	*Indecisive*	*Homogeneous*	*p*	*PWC**	ε^2	*Homogeneous*	*Indecisive*	*Cognitive Bias*	p	PWC*	ε^2
	N=33	N= 21	N=61				N= 46	N= 5	N=7			
	Mean (SD)	Mean (SD)	Mean (SD)				Mean (SD)	Mean (SD)	Mean (SD)			
Age (years)	26.45(6.70)	26.05(8.06)	27.7(6.87)	0.474			31.24(7.86)	29.00 (5.97)	23.43(7.85)	0.046	1>3	0.108
Education (years) (%)				0.001						0.001		
Incomplete primary school	18.2	14.3	5				6.5					
Complete primary school	24.2	28.6	11.7				10.9	20	28.6			
Incomplete secondary school	27.3	9.5	28.3				13.0	20	28.6			
Complete secondary school	18.2	23.8	33.3				23.9	20	28.6			
Incomplete superior studies	6.1	14.3	8.3				17.4	40	14.3			
Complete superior studies	6.1	9.5	13.3				28.3					
Antipsychotic dose (DDD)	14.17(13.86)	9.03(4.19)	18.73(58.54)	0.372			22.38(62.61)	9.58(6.98)	12.51(8.75)	0.703		
Diagnosis (%)				0.001						0.001		
Schizophrenia	48.48%	33.33%	52.46%				26.09%	60	28.57%			
Psychotic disorder NOS	12.12%	28.57%	36.07%				30.43%	20	14.29%			
Schizoaffective disorder	15.15%	4.76%	1.64%				10.87%	20	42.86%			
Delusional disorder	3.03%	14.29%	4.92%				13.04%		14.29%			
Brief psychotic disorder	12.12%	19.05%	3.28%				13.04%					
Schizophreniform disorder	6.03%		1.64%				6.52%					
Emsley factors												
Positive symptoms	17.97(7.21)	17.71(5.60)	14.97(6.31)	0.021	1>3, 2>3	0.069	16.18(6.42)	13.60(3.91)	13.29(4.72)	0.465		
Negative symptoms	16.18(7.90)	16.76(6.46)	15.46(7.06)	0.680			14.36(6.77)	15.80(6.76)	15.29(5.22)	0.986		
Disorganised symptoms	9.82(4.28)	8.85(3.62)	7.80(3.32)	0.039	1>3	0.058	8.05(3.85)	7.20(3.27)	7.71(2.36)	0.875		
Excited symptoms	6.15(3.12)	5.52(2.50)	5.41(2.49)	0.408			5.43(3.14)	4.20(0.45)	4.43(0.79)	0.472		
Motor symptoms	2.91(1.87)	2.67(1.28)	2.98(1.44)	0.268			2.61(1.11)	3.40(2.19)	3.43(1.27)	0.121		
Depression	4.52(2.58)	4.76(1.95)	4.08(1.92)	0.333			5.09(2.51)	6.40(3.36)	5.29(2.21)	0.603		
Anxiety	5.94(2.38)	6.05(2.27)	5.74(2.28)	0.772			5.83(2.42)	5.00(1.22)	6.00(3.42)	0.837		
GAF	60 (12.71)	57.10(11.34)	60.11(12.97)	0.538			60.00(12.22)	54.2(9.12)	60.43(14.88)	0.467		
Rosenberg (total)	28.1(6.83)	27.0(5.20)	27.1(6.12)	0.668			27.3(5.42)	31.6(8.02)	22.7(6.52)	0.043	1>2, 2>3	0.110
BDI (total)	14.79(9.35)	15.86(7.61)	14.20(9.43)	0.501			14.46(9.12)	15.60(12.12)	22.86(7.49)	0.085		0.086
SUMD (global)	8.18(3.86)	5.81(3.63)	5.59(3.02)	0.040	1>3	0.096	5.80(3.97)	6.20(5.07)	4.57(2.15)	0.770		

*PWC: Pairwise comparisons

* Table 2 (continued). Mean scores and mean differences among the profiles in demographic, clinical and neuropsychological variables.

	Males						Females					
	Profile 1	**Profile 2**	**Profile 3**				**Profile 1**	**Profile 2**	**Profile 3**			
	JTC	*Indecisive*	*Homogeneous*	*p*	*PWC**	ε^2	*Homogeneous*	*Indecisive*	*Cognitive Bias*	*p*	*PWC**	ε^2
	N=33	N= 21	N=61				N= 46	N= 5	N=7			
	Mean (SD)	Mean (SD)	Mean (SD)				Mean (SD)	Mean (SD)	Mean (SD)			
WSCT (T)												
Total errors	39.71(9.34)	46.90(16.85)	47.46(12.62)	0.024		0.072	44.98(14.35)	43.60(5.81)	41.29(11.15)	0.968		
Perseverative errors	42.15(8.10)	47.33(17.21)	48.98(12.58)	0.063			44.95(15.13)	44.00(8.43)	44.43(7.44)	0.855		
Non-perseverative errors	40.25(7.93)	45.33(17.55)	46.61 (12.68)	0.063			45.45(14.14)	43.40(5.37)	39.71(13.00)	0.704		
Stroop test (T) - interference	85.58(19.11)	55.62(11.76)	55.22(12.21)	0.772			53.69(10.71)	50.75(5.06)	51.29(14.77)	0.551		
WAIS-III (T)												
Digits	40.96(7.96)	41.42(9.67)	45.49(9.93)	0.044	1<3	0.05	44.22(9.26)	48.66(6.41)	42.14(10.11)	0.534		
Vocabulary	85.58(19.11)	92.29(24.92)	95.57(18.32)	0,045	1<3	0.057	94.21(21.07)	97.00(7.58)	89.90(27.45)	0.593		
Attention (T)	51.40(12.11)	42.73(14.20)	46.00(6.12)	0.022	1>2	0.079	49.84(13.19)	36.65(15.60)	51.92(11.76)			
TMT (seconds)												
TMT-A	73.19(23.38)	64.24(17.26)	62.31(15.41)	0.049	1>3	0.055	65.94(24.34)	66.25(13.59)	64.58(11.72)	0.664		
TMT-B	107.38(81.88)	71.51(18.91)	70.06(23.28)	0.001	1>3	0.123	68.42(20.13)	59.82(14.00)	73.47(17.11)	0.434		
Tavec												
Immediate recall	39.6(9.20)	38.7(9.22)	39.5(9.92)	0.970			45.2(12.4)	43.9(15.1)	36.2(7.20)	0.109		
Short-term memory	32.6(12.3)	38.0(16.8)	35.3(17.7)	0.291			40.5(13.3)	39.1(9.58)	35.0(13.2)	0.633		
Long-term memory	30.7(14.2)	35.33(17.68)	33.94(16.26)	0.413			39.6(14.2)	40.3(10.5)	33.6(18.0)	0.735		

DISCUSSION

In this study, we conducted a latent profile analysis to obtain profiles of social cognition and metacognition in FEP according to sex. We identified three profiles in each sex. We found 2 profiles (Homogeneous and Indecisive) that were present in males and females, while we found 2 profiles (JTC and Cognitive Biases) that were specific to each sex. Consistent with our hypothesis, males and females with FEP present different profiles of social cognition and metacognition that are identifiable using LPA and that are associated with specific presentations of the disorder. Males in the homogeneous profile seemed to have a more benign course of illness than their counterparts, specifically than males in the JTC profile. Conversely, females in the homogeneous profile were older, had fewer depressive symptoms and more self-esteem than females in the Cognitive Bias profile.

These findings may have relevant clinical consequences, as our results suggest that having homogeneous levels of social cognition and metacognition could be indicative of a more benign course of illness, although this explanation should be clarified in future research.

We found a second profile common to both sexes (Indecisive), characterized by average scores in most variables except for draws to decision, which were a standard deviation higher than the mean. Females in this profile only presented significantly better self-esteem than the other profiles. Males in this profile had more positive symptoms than males in the homogeneous profile but scored significantly better in attention than males in the JTC profile. This profile grouped the least proportion of participants both in males (18.3%) and females (8.6%). Participants in these groups seemed to have a clinical state similar to participants in the homogeneous profile. However, the importance of its traits cannot be neglected. Although to our knowledge the role of an excessive number of DTDs in the beads task has not been studied, one interpretation could be excessive metacognitive monitoring. Participants could be constantly evaluating whether they have enough information to make a decision, which could inhibit decision making [30]. The particularities of this profile indicate that subjects with this profile could benefit from a different therapeutic approach.

Males in the JTC profile had worse neuropsychological performance, more positive and disorganized symptoms, and worse clinical insight. These results are consistent with previous studies reporting the association between a higher tendency to present JTC and more positive symptoms [22] and worse neuropsychological deficits [21–23]. Some studies have suggested that JTC could likely be a consequence of pre-existing neuropsychological deficits [22, 24]. On the

contrary, the association between clinical insight seems to be independent of neurocognitive abilities [33]. Notwithstanding, the three constructs have been associated with poorer outcomes [18, 20, 26], indicating that males in this profile could have a more troubled course of the disease and worse functioning.

Females in the Cognitive Bias profile had more personalizing bias and self-reflectivity, but less self-esteem than their counterparts. Further, we found a trend for significance in depression measured with BDI. Females in the Cognitive Bias profile scored higher in depression than the other two profiles. This presentation seems consistent with the insight paradox [31], a phenomenon in which more self-reflectivity is positively associated with more depression and less self-esteem [37].

Depression, self-esteem, and personalizing bias have been found not only to be closely associated with persecutory ideation and paranoia [34,35,59] but also with the severity of paranoia in subjects with FEP [36]. Females in this profile have more self-reflectivity, indicating that they have a better ability to reflect upon their processes. This ability may lead to a better awareness of their symptoms and difficulties, which could decrease self-esteem and increase depression. Ultimately, to preserve their self-esteem, females in this profile could blame other persons for negative events, which may, in turn, increase paranoid symptoms and perpetuate symptoms. This explanation, however, remains speculative as this study did not explore causality. Of note, females in the Homogeneous profile were older than their counterparts in the Cognitive Bias profile. Although examining hormonal differences between the profiles is beyond the aim of this work, it is possible that differences in estrogen levels are partially responsible for the clinical presentation of each profile. This hypothesis should be examined in future research.

Our work must be interpreted considering several limitations. First, our sample was not balanced in sex, which can have hampered our statistical power. Likewise, the sample size of each profile varied greatly. Therefore, although we used non-parametric tests to determine mean differences, some significant differences may not have been detected. Similarly, we did not conduct post-hoc analysis, as the comparisons presented in this work are qualitative comparisons based on the graphical representation of the clusters. We did not have a control group. Therefore, whether these profiles appear in the general population, the extent of the impairment and cut-off scores could not be calculated. We used a cross-sectional design that did not allow testing profile stability. There are other possible predictors of profile membership that were not collected in the present work, such as differences in personality [82] , that should be considered in future studies. These limitations notwithstanding, this is the first work yielding evidence of sex profiles in social cognition and metacognition. Future research confirming our profile solution, profile membership predictors, and illness course according to profile and sex are recommended, as well as understanding therapeutic

components of interventions that are more adequate to specific sexes and profile presentations.

There are relevant clinical implications to our work. A first implication is that males that present JTC and females that present higher self-reflectivity in conjunction with personalizing bias may have a worse presentation of the disorder. Importantly, the JTC and other cognitive biases are modifiable [83]. Therefore, the early identification of cognitive and metacognitive profiles may help clinicians deliver early targeted treatment, what could have a beneficial effect in prognosis. Patients with different profiles of social cognition and metacognition may respond differently to therapeutic approaches. A study assessing sex differences in response to metacognitive treatment in a sample with FEP [46] reported that females improved more in cognitive insight, personalizing bias and general symptoms than males. Conversely, males improved more in the salient condition of the Beads Task, but not females. Our results are consistent with them in that our profiles follow the same direction as their findings, and further support them in that future studies should study which contents of metacognitive interventions could be more beneficial according to sex and profile of impairment. While all the profiles could benefit from therapies that target metacognition, males could benefit from boosting sessions aimed at correcting the JTC, while females could benefit from boosting sessions directed to modify cognitive insight and attributional biases. Moreover, males that present JTC find optimal treatment in combining neurocognitive training with metacognitive therapy.

Finally, subjects with FEP do not receive an immediate chronic diagnosis, as the trajectories of the disease are heterogeneous. Predictors of profile membership and possible illness trajectories emerge in our work as promising topics for future research. Longitudinal studies assessing the prognosis of each profile and profile stability are encouraged.

Conflicts of interest: The authors declare that they have no conflict of interest. **Ethical standards:** All individuals were given an informative sheet, and all of them signed an informed consent file for participation in this study. The Ethics Committee of each participating center approved this project. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. **Financial support:** This study was funded by the Instituto de Salud Carlos III, Spanish Government, (PI11/01347, PI14/00044 and PI18/00212), by the Fondo Europeo de Desarrollo Regional (FEDER), Health Department of Catalonia, PERIS call (SLT006/17/00231), Progress and Health Foundation of the Andalusian Regional Ministry of Health, (PI-0634/2011 and PI-0193/2014), Obra Social La Caixa (RecerCaixa call 2013), Obra Social Sant Joan de Déu, BML (RTI2018-100927-J-I00) administrated by Ministerio de Ciencia e Innovación (MCI, Spain), by the Agencia Estatal de Investigación (AEI, Spain), and by the European Regional Development Fund (FEDER, UE), by Marsden (E2987-3648) administered by the Royal Society of New Zealand, and by grant 2017 SGR 622 (GRBIO) administrated by the Departament d'Economia i Coneixement de la Generalitat de Catalunya (Spain).

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2.4. STUDY 4: "THE EFFECT OF SEX ON SOCIAL COGNITION AND FUNCTIONING IN SCHIZOPHRENIA"

Authors	Marta Ferrer-Quintero, Michael F. Green, William P. Horan, David L. Penn, Robert S. Kern and Junghee Lee.
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Objective	Objective 5: To explore the role of social cognition and sex in functional outcome in people with established psychosis (schizophrenia).
Rationale within the thesis	This study has the added value of exploring sex differences in the moderating role of social cognition over functioning in patients with established psychosis. By including a sample with chronic illness, we will be able qualitatively compare these associations to the findings in first-episode psychosis.
Considerations	This publication stems from an international research stay at the Green Lab (University of California Los Angeles, UCLA) conducted between July and November 2018.

Table 10. Summary and details of study 4.

THE EFFECT OF SEX ON SOCIAL COGNITION AND FUNCTIONING IN SCHIZOPHRENIA

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ABSTRACT

Social cognitive impairment is a core feature of schizophrenia and plays a critical role in poor community functioning in the disorder. However, our understanding of the relationship between key biological variables and social cognitive impairment in schizophrenia is limited. This study examined the effect of sex on the levels of social cognitive impairment and the relationship between social cognitive impairment and social functioning in schizophrenia. Two hundred forty-eight patients with schizophrenia (61 female) and 87 healthy controls (31 female) completed five objective measures and one subjective measure of social cognition. The objective measures included the Facial Affect Identification, Emotion in Biological Motion, Self-Referential Memory, MSCEIT Branch 4, and Empathic Accuracy tasks. The subjective measure was the Interpersonal Reactivity Index (IRI), which includes four subscales. Patients completed measures of social and non-social functional capacity and community functioning. For objective social cognitive tasks, we found a significant sex difference only on one measure, the MSCEIT Branch 4, which in both patient and control groups, females performed better than males. Regarding the IRI, females endorsed higher empathy-related items on one subscale. The moderating role of sex was found

only for the association between objective social cognition and non-social functional capacity. The relationship was stronger in male patients than female patients. In this study, we found minimal evidence of a sex effect on social cognition in schizophrenia across subjective and objective measures. Sex does not appear to moderate the association between social cognition and functioning in schizophrenia.

INTRODUCTION

Social cognitive impairment is a core feature of schizophrenia. During the past two decades, a large body of work has shown the pervasive nature of social cognitive impairment and its critical role in poor functioning in schizophrenia [1–3]. However, surprisingly little is known about whether key biological variables, such as sex, moderate the level of social cognitive impairment and the strength of the association between social cognitive impairment and community functioning in schizophrenia.

While less is known about sex difference in social cognition in schizophrenia, several studies have shown the effect of sex on other core features of schizophrenia. For instance, female patients with schizophrenia tend to have older age of onset [4, 5], better premorbid functioning4, and better social functioning [6, 7]. Better social functioning of female patients raises an interesting question as to whether any key determinants of functioning, such as non- social cognition and social cognition, may also differ between male and female patients. For non-social cognition, studies on sex differences in schizophrenia have produced mixed findings, such that some found better performance in female than male patients [8–10], whereas others found the opposite [11, 12] or no difference between female and male patients [13–15]. As these studies focused on different domains of non-social cognition, it is possible that sex differences in cognition in schizophrenia may vary across non-social cognitive domains. The inconsistent findings of these studies raise a possibility that sex differences in social cognition in schizophrenia may differ depending on the type of measures (e.g., subjective versus objective measures), which in turn may affect the relationships between social cognition and functioning.

There is a pervasive impression that compared to males, females are generally better at processing social information, including emotional expressions. Several studies have empirically examined this possibility in healthy populations using both subjective and objective social cognitive measures across multiple domains of social cognition. For subjective social cognitive measures, on which participants self-reported their social cognitive abilities, females reported higher empathy [16] and higher emotional intelligence [17], compared to males. Studies with

objective social cognitive tasks present a more nuanced pattern of female advantage in processing social stimuli. A majority of studies on sex differences examined emotion identification or emotion discrimination using face stimuli. Several studies failed to find sex differences [17,18], while some found slightly better performance in females for emotion recognition, especially for negative emotions [19–21]. Similarly, when discriminating emotional body movement of point-light walkers, females performed slightly better at discriminating emotional body movement of point-light walkers [22] or comparably to males [23]. Females performed slightly better at understanding thoughts of another person [24] or the emotional state of another person [25] compared to males. Thus, it appears that sex differences in healthy samples are more consistently found using subjective versus objective social cognitive measures.

Several studies examined sex differences in social cognition in schizophrenia using objective social cognitive tasks. Female and male patients showed comparable performance when recognizing facial emotions [26–28] or understanding the thoughts of another person (i.e., mental state attribution) [26–28]. While these findings suggest a lack of sex difference in schizophrenia, most studies employed only objective social cognitive tasks and primarily focused on perception of emotional expressions or mental state attribution. Thus, it remains to be determined whether sex differences in schizophrenia exist for subjective social cognition or whether sex differences are present for other social cognitive domains beyond emotion perception and mental state attribution.

To examine sex differences in social cognition in schizophrenia, this study presents a secondary analysis of data from a two-site case-control study, Social Cognition and Functioning in Schizophrenia (SCAF) [29, 30]. Specifically, by adapting paradigms from social cognitive and affective neuroscience, the SCAF project assessed several social cognitive domains that have not been previously examined in schizophrenia, including self-referential memory and empathic accuracy. The SCAF project also included a subjective social cognitive measure of empathy. Thus, this data set is well suited to examine the following research questions: (1) whether there are sex differences in the levels of social cognitive performance of schizophrenia patients and (2) whether sex moderates the associations between social cognition and functioning in schizophrenia.

METHODS

Participants

This study included 248 patients with schizophrenia and 87 healthy controls from two sites: (1) University of California, Los Angeles (UCLA) outpatient treatment facilities in the Los Angeles area and mental health clinics at the VA Greater Los

Angeles Healthcare System (VAGLAHS) and (2) University of North Carolina (UNC)—Chapel Hill Schizophrenia Treatment and Evaluation Program and community mental health clinics in the Chapel Hill area. Healthy controls were recruited through internet advertisements. All participants provided written informed consents after procedures were fully explained, as approved by the Institutional Review Boards at University of California Los Angeles, VAGLAHS, and UNC.

Selection criteria have been described elsewhere [29]. Briefly, for patients they included: (1) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia based on a Structured Clinical Interview for DSM-IV (SCID)35, (2) age between 18 and 60 years, (3) sufficient competence in English language to understand testing procedures, (4) no clinically significant neurological disease as determined by medical history, (5) no history of serious head injury, (6) no evidence of substance or alcohol abuse in the month previous to testing, (7) no sedatives or benzodiazepines within 12 h of testing, (8) no history of intellectual disability or developmental disability, and (9) clinical stability. Selection criteria for community controls were: (1) age between 18 and 60 years, (2) sufficient competence in English language to understand testing procedures, (3) no clinically significant neurological disease as determined by medical history, (4) no psychotic disorder, bipolar disorder, or recurrent major depressive disorder according to SCID-I, (5) no schizotypal, avoidance, schizoid or paranoid personality disorder according to SCID-II, (6) no family history of psychotic disorders among first-degree relatives, (7) no history of substance or alcohol dependence and no substance or alcohol abuse in the month previous to testing, and (8) no sedatives or benzodiazepines within 12 h of testing.

Clinical symptoms of patients were assessed with the Scale for the Assessment of Negative Symptoms (SANS) [36] and the Brief Psychiatric Rating Scale (BPRS) [37]. Diagnostic interviews, BPRS, and SANS were administered by trained diagnosticians. To characterize neurocognitive ability of participants, we administered the MATRICS Consensus Cognitive Battery (MCCB) [38, 39]. The MCCB includes six different non-social cognitive domains (speed of processing, attention and vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving).

Measures

Five objective measures and one subjective measure of social cognition were administered. The objective measures include Facial Affect Identification [29], Emotion in Biological Motion [29], Self-Referential Memory [29, 40], Empathic accuracy [29,41] and the Mayer–Salovey–Caruso Emotional Intelligence Test 2.0 (MSCEIT) Branch 4 [42], and the subjective measure was the

Interpersonal Reactivity Index (IRI) [43]. As details of each measure are provided elsewhere [29, 43], we briefly describe each measure below. In the Facial Affect Identification task, participants were asked to decide which emotional expressions a face conveyed on each trial. The primary dependent measure was percent accuracy. For the Emotion in Biological Motion, participants were asked to decide which emotion (fear, anger, happiness, sadness or neutral) was described by the movement of a point-light walker stimulus. The primary dependent measure was percent accuracy. For Self-Referential Memory task, participants first completed an encoding phase in which they decided whether a trait word described themselves ("self-referential" condition), whether the word indicated a desirable trait ("other" condition), and whether it was upper case. After a delay period, participants were presented one word at a time and asked to decide if the word was presented during the encoding phase. The primary dependent measure was an index of sensitivity (d') for recognition of words.

We used two versions of an Empathic Accuracy task, and approximately half of the sample took the older version, and the other half took the newer version29. The key difference between the two versions was the diversity of individuals featured in the videos (i.e., targets), as the newer version was developed to include a broader range of age, racial and ethnic diversity. The dependent measure was the mean correlation across clips between the ratings of the targets on their own emotion and the participant's ratings of the targets' emotion. We did not find any performance difference between participants who received the older version and participants who received the newer version (see Supple- mental material for details).

The MSCEIT Branch 4, Managing Emotion, assessed emotion regulation in oneself and one's relationship with others using vignettes. Specifically, participants are presented with vignettes of various social situations along with the solution to cope with the emotions depicted in these vignettes. Participants are asked to indicate how effective each solution is using a scale ranging from 1 (very ineffective) to 5 (very effective).

Finally, the IRI was used as a measure of subjective social cognitive ability. The IRI, as a measure of empathy, consists of four subtests, each assessing a different aspect of empathy. The Fantasy subscale measures a tendency to transpose oneself into the feelings of a character in a movie or book. The Perspective Taking scale measures how a person will spontaneously adopt someone else's point of view. The Empathic Concern Scale assesses feelings of sympathy or concern towards the other. The Personal Distress Scale measures feelings of personal distress in unpleasant interpersonal situations. We analyzed both the total IRI index and the four subscales separately. In addition to measures of social cognition, we assessed functional capacity and community functioning of patients. Functional capacity was assessed using the University of California at

San Diego Performance-Based Skills Assessment UPSA [44]; and the Maryland Assessment of Social Competence MASC [45]. The UPSA consists of role-play simulation tasks that measure a participant's ability to negotiate real-world tasks. As a measure of social skills (i.e., functional capacity on social domain), the MASC employs a role-play approach in which participants are responsible for taking the conversation forward in a series of common interpersonal problems. Four role play scenarios were videotaped and coded by trained raters who achieved a median interclass coefficient of 0.85 on a set of 10 videos that were derived from a separate sample. Community functioning was assessed with the Role Functioning Scale RFS [46].

Statistical analysis

First, to examine whether female and male patients with schizophrenia differ on demographic and clinical characteristics, we conducted a series of two-way ANOVA with group and sex as between-subject factors for age, personal education, and parental education, and one-way ANOVA for clinical characteristics. Second, to examine whether female and male schizophrenia patients show different levels of performance on objective and subjective social cognitive tasks, we conducted a series of two-way ANOVAs with sex and group as between-subject factors for all tasks except the Self-Referential Memory task. For the Self-Referential Memory task, we conducted a repeated measures ANOVA with condition as within-subject factor and group and sex as between-subject factors. Significance thresholds for the objective social cognitive tasks were set at $p = 0.05$ because each cognitive task is considered a separate task that assesses a distinct social cognitive domain. The subjective social cognitive measure, the IRI, includes four subscales and a total score; thus, significance thresholds for the subjective social cognitive task were set at $p = 0.01(0.05/5)$. All p values represent two-tailed tests. For these analyses, we also report effect size (i.e., partial eta square) along with statistics. The general rule of thumb regarding the magnitude of effect size for partial eta square is: 0.01 = small effect, 0.06 = medium effect, and 0.14 for large effect [47]. Third, to examine whether sex moderates the associations between social cognition and functioning (i.e., functional capacity and community functioning) within the schizophrenia group, we conducted linear multiple regression analyses for objective social cognition and subjective social cognition separately. For objective social cognition, a social cognitive composite score was created by calculating the mean of the standardized objective social cognition variables using the mean and standard deviation of the control group. In the first block, the social cognitive composite score was entered, which allowed to compare the findings of this study to previous work on the relationship between social cognition in schizophrenia. Sex

(dummy coded) was entered in the second block. In the third block, the interaction between sex and the social cognitive composite was entered. A significant interaction would indicate that sex moderated the relationship between social cognition and functioning in schizophrenia. A similar regression analysis was conducted for subjective social cognition using IRI total score, such that IRI total score was entered in the first block, followed by sex in the second block, and a sex by IRI total interaction in the third block. Significance thresholds represent two-tailed tests and were set at a $p = 0.05$.

RESULTS

Demographic and clinical characteristics

Table 1 shows the demographical and clinical characteristics of the sample separated by sex. For age and parental education, we did not find any significant effect. For personal education and MCCB Neurocognitive Composite Score, we only found significant group effects. Within the schizophrenia group, we found a significant sex effect on SANS total ($F(1,244) = 63.49$, $p < 0.05$, $\eta 2_p = 0.025$), but not on age of onset and BPRS total. Female patients with schizophrenia showed lower levels of negative symptoms assessed with SANS compared to male patients with schizophrenia. For functional capacity and community functioning, we found a significant sex effect on MASC total ($F(1,236) = 9.42$, $p < 0.01$, $\eta 2_p = 0.038$) and on RFS total ($F(1,331) = 8.20$, $p < 0.01$, $\eta 2_p = 0.024$), but not on UPSA total. Female patients with schizophrenia showed higher levels of functional capacity on social domain and better community functioning compared to male patients with schizophrenia.

Table 1. Demographic and clinical characteristics

	Patients		Controls	
	Female (N=61)	Male (N=187)	Female (n=31)	Male (N=56)
Age	42.4 (12.4)	42.1 (12.4)	42.3 (9.6)	42.7 (10.4)
Personal Education (yrs)[a]	12.7 (1.8)	12.5 (1.7)	14.7 (1.9)	14.7 (1.9)
Parental Education (yrs)	13.8 (2.9)	13.5 (3.1)	13.4 (2.6)	13.3 (2.8)
Ethnicity				
Hispanic	5	16	3	6
Not Hispanic	56	171	28	50
Race				
Asian	1	6	1	2
Hawaiian/Other Pacific Islander	0	1	1	0
Black	29	73	10	15
White	30	99	18	38
More than one race	1	8	1	1
Age of onset (yrs)	22.4 (9.9)	21.1 (5.9)		
SANS [c]	7.0 (3.1)	8.1 (3.2)		
BPRS	45.9 (13.3)	45.1 (13.8)		
UPSA [c]	0.77 (0.12)	0.72 (0.13)		
MASC	3.68 (0.46)	3.46 (0.49)		
RFS [c]	18.1 (5.3)	17.2 (4.5)		
MCCB neurocognitive composite [b]	33.5 (13.0)	29.8 (12.7)	47.7 (12.6)	45.9 (12.1)

a. A significant effect of group ($F_{(1,331)}$=75.11, p<.001, η^2_p=.185) indicating that patients had lower levels of personal education than controls. b. A significant effect of group ($F_{(1,326)}$=84.44, p<.001, η^2_p=.206) indicating that patients showed poorer performance than controls. c. Significant sex difference within the patient group

Abbreviations: SANS, the Scale for the Assessment of Negative Symptoms; BPRS, the Brief Psychiatric Rating Scale-24 item; UPSA, the University of California at San Diego Performance-based Assessment; MASC, the Maryland Assessment of Social Competence; RFS, the Role Functioning Scale; MCCB, MATRICS Cognitive Consensus Battery

†† Values are given as mean (standard deviation).

Objective and subjective social cognitive tasks

Figures 1 and 2 show performance of patients and controls on objective and subjective cognitive tasks, respectively. Tables 2 and 3 show statistics from two-way ANOVAs and a repeated measures ANOVA. For Facial Affect Recognition task, Emotion in Biological Motion task and Empathic Accuracy task, we did not find any significant effect involving sex. Similarly, no significant main effect of sex or significant interaction involving sex was found for the Self-Referential Memory task. For the MSCEIT Branch 4, we found a significant effect of sex such that female participants performed better than male participants, and this sex effect did not differ between patients and controls as evidenced by a non-significant sex by group interaction. For the IRI, on Empathic Concern and Fantasy subscale, we found a significant sex effect, but no interaction between sex and group. Female participants reported significantly higher scores on Empathic Concern, and this pattern did not differ between patients and controls. On the Fantasy subscale, a sex effect was no longer significant after correcting for multiple comparisons. On the Perspective Taking and Personal Distress subscales, no effect involving sex was significant. Finally, for IRI total score, we found a significant effect of sex after correcting for multiple comparisons, but no group by sex interaction. Across both patient and control groups, females had higher IRI total scores.

Table 2. Performance on objective social cognitive tasks:

	Inferential statistics	P value	Effect size (η2p)	95% confidence interval of parameter estimates[a]
Facial affect recognition[b]				
Group	F(1,329) = 20.14	<0.001	0.06	[−0.11, −0.04]
Sex	F(1,329) = 1.88	NS	0.01	
Group by sex	F(1,329) = 0.001	NS	0.00	
Emotion in biological motion[b]				
Group	F(1,323) = 21.76	<0.001	0.06	[−0.121, −0.05]
Sex	F(1,323) = 1.19	NS	0.00	
Group by sex	F(1,323) = 0.57	NS	0.00	
Self-referential memory				
Group	F(1,325) = 1.98	NS	0.01	
Sex	F(1,325) = 2.82	NS	0.01	
Group by sex	F(1,325) = 0.10	NS	0.00	
Condition	F(2,650) = 227.04	<0.001	0.41	
Condition by group	F(2,650) = 21.08	<0.001	0.06	
Condition by sex	F(2,650) = 0.46	NS	0.00	
Condition by sex by group	F(2,650) = 1.41	NS	0.00	
Empathic accuracy[b]				
Group	F(1,316) = 24.13	<0.001	0.07	[−0.17, −0.08]
Sex	F(1,316) = 0.71	NS	0.00	
Group by sex	F(1,316) = 2.15	NS	0.01	
MSCEIT branch 4[b,c]				
Group	F(1,326) = 69.03	<0.001	0.18	[−15.72, −8.96]
Sex	F(1,326) = 5.83	<0.05	0.02	[−1.08, 8.82]
Group by sex	F(1,326) = 0.02	NS	0.00	

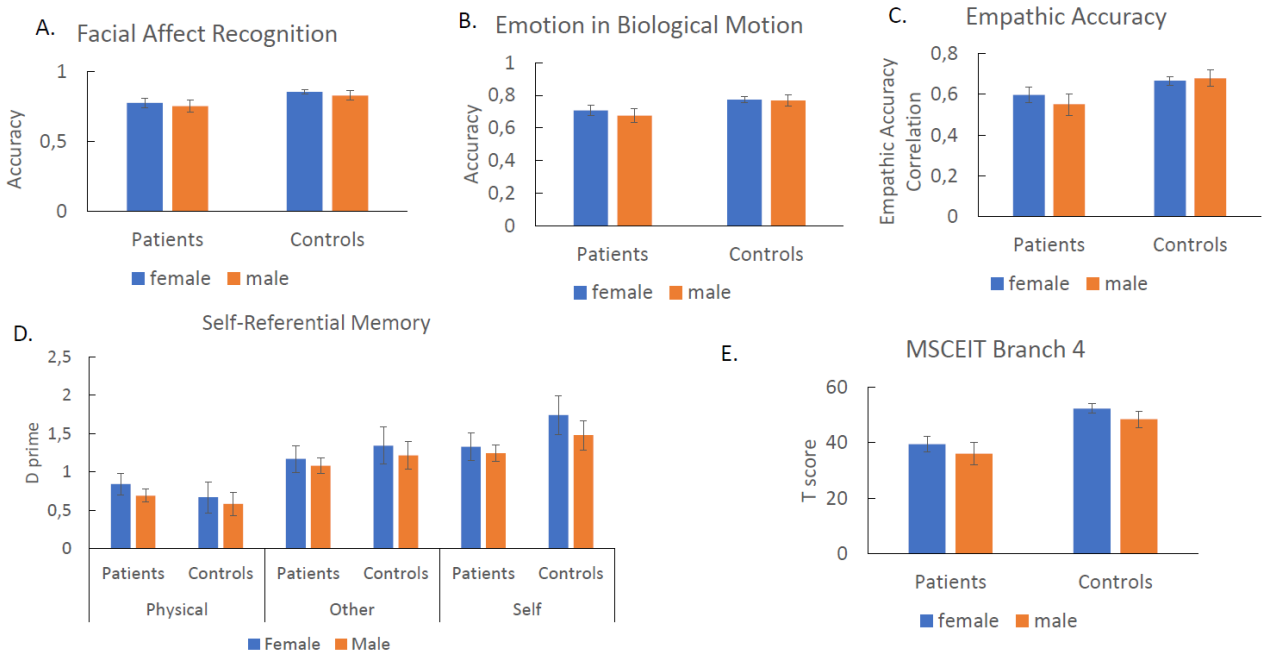
MSCEIT the Mayer–Salovey–Caruso Emotional Intelligence Test 2.0.

[a]*A 95% confidence interval for the parameter estimate is reported for significant group or sex effects.*

[b]*Females performed better than controls.*

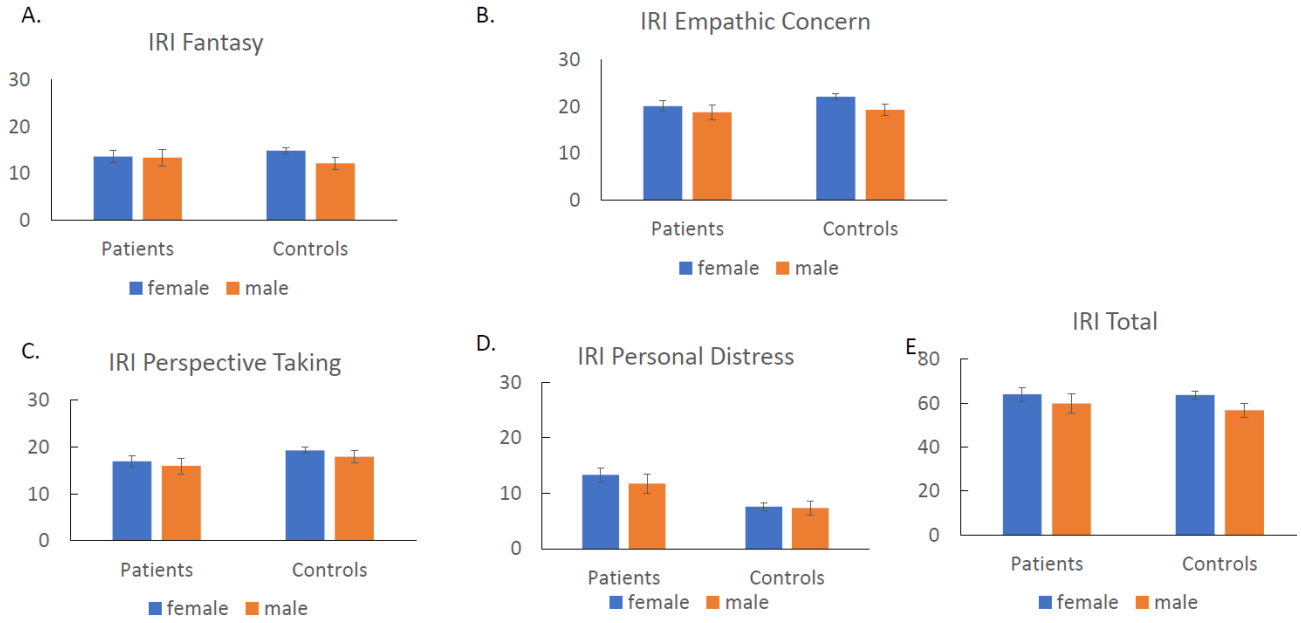
[c]*Patients performed worse than controls.*

Figure 1. Performance of patients and controls on objective social cognitive tasks



A Facial affect recognition, B Emotion in biological motion, C Empathic accuracy, D Self-referential memory, and E MSCEIT branch 4. Error bars indicate 95% confidence interval. MSCEIT the Mayer–Salovey–Caruso Emotional Intelligence Test 2.0.

Figure 2: Performance of patients and controls on the subjective social cognitive measure.



A IRI fantasy, B IRI empathic concern, C IRI perspective taking, D IRI personal distress, and E IRI Total. Error bars indicate 95% confidence interval. IRI the Interpersonal Responsivity Index.

Table 3. Performance on subjective social cognitive measures

	Inferential statistics	P value	Effect size ($\eta 2_p$)	95% confidence interval of parameter estimates[a]
IRI Fantasy				
Group	$F_{(1,329)}$=.00	NS	0.00	
Sex	$F_{(1,329)}$=4.46	NS	0.01	
Group by Sex	$F_{(1,329)}$=3.25	NS	0.01	
IRI Empathic Concern [c]				
Group	$F_{(1,329)}$=4.18	NS	0.01	
Sex	$F_{(1,329)}$=11.43	<.01	0.03	[.79, 4.79]
Group by Sex	$F_{(1,329)}$=1.42	NS	0.00	
IRI Perspective Taking [b]				
Group	$F_{(1,329)}$=11.32	<.01	0.03	[-3.45, -.56]
Sex	$F_{(1,329)}$=3.32	NS	0.01	
Group by Sex	$F_{(1,329)}$=.73	NS	0.00	
IRI Personal Distress [b]				
Group	$F_{(1,329)}$=61.78	<.001	0.16	[2.97, 5.86]
Sex	$F_{(1,329)}$=1.98	NS	0.01	
Group by Sex	$F_{(1,329)}$=1.20	NS	0.00	
IRI Total [c]				
Group	$F_{(1,329)}$=1.03	NS	0.00	
Sex	$F_{(1,329)}$=11.58	<.01	0.03	[1.65, 12.42]
Group by Sex	$F_{(1,329)}$=.77	NS	0.00	

a. 95% confidence interval for the parameter estimate is reported for significant group or sex effects.

b. Females performed better than controls.

c. Patients performed worse than controls.

Abbreviations: MSCEIT, the Mayer-Salovey-Caruso Emotional Intelligence Test 2.0; IRI, the Interpersonal Reactivity Index

Table 4. Linear multiple regression analyses to examine the moderating role of sex in associations between social cognition and functioning

		Step 1		Step 2[a]			Step 3[b]				
		R^2	AIC	R^2	Δ R^2	AIC	R^2	Δ R^2	AIC	Unstandardized coefficients[c]	
										female	male
Social Cognitive Composite	UPSA	.343**	-1075	.345**	.002	-1074	.363**	.018*	-1079	.05**	.093**
	MASC	.071**	-379	.097**	.026*	-384	.098**	.001	-382		
	RFS	.079**	1058	.080**	.001	1057	.081**	.001	1059		
IRI Total	UPSA	.000	-971	.013	.013	-972	.013	.000	-970		
	MASC	.023**	-362	.055**	.032**	-368	.055**	.000	-366		
	RFS	.002	1125	.026	.024**	1118	.026	.000	1120		

a. Step 2 included sex as a dummy variable.

b. Step 3 included interaction between sex and predictors.

c. For significant interactions, unstandardized coefficients are presented. The significance of unstandardized coefficients was examined using t-tests.

* denotes p<.05 and ** denotes p<.01.

Abbreviations: AIC, Araike Information Criterion; UPSA, the University of California at San Diego Performance-based Assessment; MASC, the Maryland Assessment of Social Competence; RFS, the Role Functioning Scale; IRI, the Interpersonal Reactivity Index.

DISCUSSION

This study examined the effect of sex on the levels of social cognitive impairment and the relationship between social cognition and functioning (functional capacity and functional outcome). Overall, the findings of this study do not strongly support a female advantage for social cognitive ability. For objective social cognitive tasks, we found a significant sex effect, but no sex by group interaction on the MSCEIT Branch 4, a measure of emotional regulation. Females performed better than males, and this effect was similar across patients and controls. A sex effect was not found on other objective social cognitive measures. Regarding subjective social cognition in both patient and control groups, females reported greater empathic concern than males. We did not find any sex differences on other subscales of the IRI. Finally, we found that sex moderated the association between objective social cognition and non-social functional capacity. This relationship between objective social cognition and functional capacity was stronger in male than female patients. However, sex did not moderate the relationships between objective social cognition and other measures of functioning. Nor did sex

moderate the relationship between subjective social cognition and functioning in schizophrenia. In this study, female patients showed less severe negative symptoms, better functional capacity in the social domain, and better community functioning than male patients. These findings add to the existing literature on sex differences in schizophrenia6,7 , suggesting that the course of illness differs between female and male schizophrenia patients. In this context, it is notable that we did not find strong evidence on sex difference in social cognition, a key determinant of poor functioning in schizophrenia. The lack of sex effect is consistent with recent studies showing comparable performance between female and male patients on social cognitive tasks[15,27]. Further, our regression analyses showed that sex moderated the relationship between objective social cognition and UPSA, but not other measures of functioning. Overall, the role of social cognition in community functioning in schizophrenia does not seem to differ much between female and male patients, suggesting that any intervention for improving social cognition is likely to have similar effects in both female and male patients. For objective social cognitive measures across both patients and controls, females performed better than males on a measure of emotion regulation, consistent with a previous study[25]. However, across both groups, females and males performed similarly on the measures of emotion identification, emotional biological motion and empathic accuracy. This is consistent with previous studies in healthy individuals that showed the lack of sex differences in emotion identification[17,18] and emotional biological motion perception[23]. Thus, it appears that females and males recognize or infer emotional social cues in a similar way but diverge when asked to regulate emotional responses in a social situation. As this study did not include any measures at a neural level, the question remains as to whether this pattern of sex differences across emotional domains exists at the neural level. Whereas other objective measures on emotional processing that this study employed primarily relied on visual stimuli or video clips, the MSCEIT Branch 4 used vignettes of social situations that required participants to rely on a language processing ability. It remains to be determined whether females and males perform differently on social cognitive tasks with greater demand on language processing. Beyond emotional processing, this study also found that females and males performed in a comparable way on the measure of self-referential memory. This is consistent with a recent neuroimaging study[31] in which females and males showed a similar pattern of neural activations related to self-referential processing. Similar to objective social cognitive measures, we found sex differences on the IRI Empathic Concern subscale, but not on other subscales. The Empathic Concern subscale involves one's emotional responses to others (e.g., feeling compassion). The Personal Distress subscale concerns one's own feelings of anxiety or distress in social situations, and the Perspective Taking subscale asks one's tendency to take another's perspective in social situations. Taken together, our findings from the subjective social cognitive

measure suggest that females may endorse greater emotional responses, such as sympathy or compassion toward others, but these greater emotional responses to others do not result in greater distress or anxiety. It is possible that the greater emotional regulation of females we observed with the objective social cognitive task may play a role in modulating one's own emotional feeling in the presence of greater emotional reactivity to others.

The findings of this study also raise a question as to what factors other than social cognition may be related to better community functioning in female patients. For example, higher cognitive reserve has been implicated in better social functioning in schizophrenia[32]. It is possible that female patients may have higher cognitive reserve. Schizophrenia patients tend to overestimate their ability to accurately perform on social cognitive tasks[33], which was related to poorer community functioning in schizophrenia[34]. It will be important to carefully examine whether these variables may differentially affect community functioning in female compared to male patients. Our study had several limitations. The study included chronic patients, so it remains to be determined whether a similar pattern of sex differences is observed in patients with recent-onset psychosis or in individuals at risk for developing psychosis. Similarly, as this study employed behavioral measures, it needs to be examined whether a similar pattern of sex differences in social cognition in schizophrenia is present at a neural level. This study only included one measure of subjective social cognition, so it will be important to examine whether sex differences can be observed on other domains of social cognition assessed with subjective measures. Finally, as the study sample was not balanced on sex, it will be important to replicate these findings using a more balanced sample that also better represents the general population of patients. In summary, this two-site case-control study used a large battery of measures across multiple social cognitive domains to examine the effect of sex on the levels of social cognitive impairment and the relationship between social cognitive impairment and functioning in schizophrenia. Our findings suggest that the sex difference in social cognition in schizophrenia is not strong and may vary from domain to domain. Sex moderated the relationship between objective social cognition and non-social functional capacity, but not other measures of functioning. Our finding of sex not moderating the relationship between social cognition and community functioning in schizophrenia also suggests that social cognition is less likely to explain better community functioning of female versus male patients with schizophrenia.

DATA AVAILABILITY: The dataset analyzed during the current study can be available upon request. **CODE AVAILABILITY:** The code used for data analysis can be available upon request. **ACKNOWLEDGEMENTS:** This work is supported by National Institute of Mental Health (MH087618 to M.F.G. and MH113856 to J.L.)

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PART 4: DISCUSSION, CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS.

1. GLOBAL DISCUSSION

Social cognition and metacognition are important targets of treatment in psychosis given their strong links with functioning [12,86,253,254]. With this doctoral dissertation, we aimed to provide grounds to base personalized social cognitive and metacognitive treatment for psychosis.

A crucial step towards personalized treatment is obtaining reliable measures that are accessible to clinical practitioners. As Maj et al. (2021)[177] discuss, the psychopathological evaluation of people with psychosis is often circumscribed to symptoms, what often results in administering the same treatment to patients with vastly different needs. There are validations in Spain for the most widely used measures of metacognition in psychosis, but not of social cognitive measures. Thus, as a foundation for this work, we validated BCFT, a test of facial emotion recognition that had been translated to ten languages, used in the study of autism spectrum disorders and had recently been validated in schizophrenia in France. This test is easy and quick to administer, what can promote its use in clinical contexts. According to our results, the psychometric properties of BCFT are adequate, which makes it a viable facial emotion recognition task. As indirect support for its usefulness in psychosis, in studies 2 and 3 we found that patients with FEP can be classified according to their scores in this task.

To date, the fields of social cognition and metacognition have mostly used variable-centred approaches[174,175], but studies examining how both constructs appear and are configured from a person-centred approach were lacking. In study 2, we showed that patients at the early stages of psychosis mostly present deficits either in social cognition or in metacognition. This was an unexpected finding. Although previous studies had reported that both are independent constructs[174,175], this had not been tested from a person-centred approach. According to our hypothesis, we expected that deficits in social cognition would reflect deficits in metacognition, but not necessarily the other way around. Rather, it seems that although social cognition and metacognition may interact during social interactions, the two domains are not configured in a hierarchical manner. It is then likely that people with FEP may benefit from treatment in the domains in which they have alterations.

Our results are indirectly consistent with the findings of preserved groups in previous studies using cluster analysis [196–198]. In contrast, the patients that did have

prominent social cognitive impairment seemed to report more severe psychopathology.

Our interpretation is that, because social cognitive deficits are present before onset [39], they may cause more cumulative negative social experiences, which may have a pervasive effect after onset and limit recovery.

As a second step, we considered biological sex as a crucial variable in personalizing treatment under the rationale that heterogeneity may not only be present at the diagnosis level, but also may vary according to important biological characteristics of the individuals. The relevance of sex in social cognition and metacognition could be rooted in that studies have consistently reported better premorbid functioning and outcome in women[213,214]. Coupled with better social cognition in healthy women, a natural hypothesis is that better social cognition and metacognition protect women from worse outcome.

In study 4, we tested this hypothesis directly in a large sample of patients with schizophrenia, using social objective and subjective measures of social cognition and social-information processing. The only significant finding was that sex moderates the relationship between objective social cognition and functional capacity. This means that women with better objective social cognition have more resources for non-social functioning, but it does not imply that these are effectively used in real-life situations. Although this provides partial evidence that better social cognition in women protects them from functional outcome, it does not suggest links between social cognition and better functioning in women.

It could be argued that study 4 only used measures of social cognition, our measure of subjective social cognition was the Interpersonal Reactivity Index (IRI)[255]. The IRI measures a tendency to transpose oneself into the feelings of a character in a movie or book, how a person will spontaneously adopt someone else's point of view, and feelings of personal distress in unpleasant interpersonal situations. Even if the IRI is not a direct measure of metacognition, it could be considered as a proxy measure for it because it requires evaluating one's own social behaviour and incorporating learnings of previous situations. Likewise, although MSCEIT branch 4 [256] was considered a measure of objective social cognition, this task requires that participants evaluate how effective different coping strategies could be in different social and emotional situations. This task demands that participants reflect on past similar experiences, their consequences, and their utility, what has a strong metacognitive component. We did not find neither a gender by group interaction in any of these tasks nor a moderating role of sex in the association between them and any measure of functioning. Thus, although we found sex differences in all measures of functioning, it remains to be determined what other factors buffer the impact of psychosis on social functioning in women. These may include hormonal [257] and

premorbid characteristics [258] that could not be explored in this sample but that should be studied further.

In study 3, we replicated study 2 but split by sex, under the rationale that the influence of both constructs may not a quantitative, but a qualitative one. In this case, we found three profiles in each sex: one sex-specific profile (JTC vs Cognitive Biases) and two common profiles (Homogeneous and Rigidity). However, we found qualitative differences beyond the profile configuration. While most women (79.3%) were included in the homogeneous profile, only 53% of men were. This finding suggests that most women have similar social cognitive and metacognitive ability. In both sexes, participants in the homogeneous profile had better clinical state than participants in the other profiles. This was especially true in the male sample.

Conversely, we found that the jumping to conclusions profile was only present in 21% of the male subsample. Although we found the same profile in study 2, it is likely because males dominated the sample. As discussed in the background section of this doctoral dissertation, the JTC bias is associated with more and worse delusions [93,101], worse neuropsychological functioning[105] and worse outcome[107]. But for global functioning, the same associations were present in our sample, what suggests that JTC could be a male-specific predictor of poor outcome. The female-specific profile was characterized by extreme personalizing bias and self-reflectivity, but significantly lower self-esteem than females in the other profiles. Although it did not reach statistical significance, we found a trend to significance in depression that is clinically significant. The presentation of this profile of females is consistent with the insight paradox[200], a phenomenon in which high self-reflectivity is positively associated with more depression and lower self-esteem[135]. Interestingly, these variables have been repeatedly reported in the literature to be associated with persecutory ideation and paranoia in psychosis [45,259,260], and with the severity of paranoia during the FEP stage[261].

Considering the findings of study 3, it seems that similar ability in all subdomains of social cognition and metacognition allows women to use all their cognitive resources, rather than basing their interpretations and cognitive processes on a single salient cognitive bias. From this perspective, a person that tends to experience the jumping to conclusions bias may quickly conclude that a person in the street is threatening, precluding them from re-evaluating the situation and reinforcing paranoid beliefs. On the contrary, a person with “homogeneous” social cognition and metacognition may still perceive the person as threatening but retain enough self-reflectivity to generate alternative explanations.

In the case of females in the Cognitive Biases profile, better self-reflectivity may make the person more aware of their symptoms and difficulties, what could decrease self-esteem and increase depression [262]. To preserve their self-esteem,

these females may resort to blame other people for negative events. This negative loop could increase paranoid symptoms and perpetuate symptoms [263,264]. This explanation would be consistent with the finding that women with psychosis tend to experience more depression than men [213].

Of note, in study 4 we found the well-described differences in functioning between males and females with psychosis, but not in the sample of study 3. This is probably because the whole sample had less than five years of progression of illness, a stage where recovery is common, and most patients still have adequate functional outcome.

Comparing participants at different stages of illness is a valuable tool in research as it provides insights into mechanisms of illness and prognosis of severity. Although including a sample of patients with established illness in the LPA goes beyond the aim of the present doctoral dissertation, we speculate that the clinical consequences of belonging to one of the found profiles can exert detrimental consequences as illness progresses. For instance, men and women in the JTC/Cognitive Biases profiles may experience more relapses and have worse therapeutic adherence. Furthermore, the fact that the JTC bias seems particularly present in men may account for variance in worse outcome.

The rigidity/indecisive profile was a puzzling finding. To the best of our knowledge, an excessive number of draws to decision in the beads task has not been studied in the literature. This appeared as a consistent profile in both study 2 and study 3. In the case of study 3, it grouped the least proportion of participants (18.3% in males, 8.6% females) and their clinical characteristics were like those in the homogeneous profiles. A recent network analysis [175] found that cognitive symptoms are central in the interaction between social cognition and metacognition. It is likely that these participants are constantly evaluating whether they have enough information to make a decision, which could inhibit decision making [124].

In summary, studies 3 and 4 highlighted that although men and females with psychosis are similar in terms of social cognition and metacognition, the differences have clinical value because they are associated with important factors throughout the stages of illness in prognosis and functioning.

SHOULD PATIENTS WITH PSYCHOSIS RECEIVE PERSONALIZED SOCIAL COGNITIVE AND METACOGNITIVE TREATMENT?

The results of the present doctoral dissertation suggest that a treatment targeted to the specific deficits of an individual could start as soon as in the first episode of psychosis, and that individualized interventions can be administered both at

the general and at the sex-specific levels. This can have important clinical implications because intensive, early treatment during the first stages of psychosis prevents or delays relapses and promotes recovery[24,265]. The field of personalized treatment, however, is still an emerging topic in research and in need for further knowledge. For instance, our results can be interpreted regarding treatment prescription or the personalization of interventions.

Prescriptive treatment

There are a plethora of social cognitive interventions that have proven their efficacy[64]. To date, the social cognitive intervention that accumulates more evidence is the SCIT [266], although using a culturally adapted social cognitive intervention like the SCORES[76] should be considered in our context. These are administered in group settings and can be administered by any mental health professional with appropriate training. This facilitates their cost-effectiveness and their implementation in public healthcare systems. Furthermore, most of them incorporate modules that permit contextualizing the contents of the intervention to patients' specific experiences.

In our sample, patients with poor social cognitive ability also tended to exhibit worse neurocognition. It is then possible that this profile of patients could benefit more from a combined social cognitive and neurocognitive remediation program.

As for treatment of metacognition, metacognitive training (MCT)[89] has demonstrated its short and long-term efficacy on most symptoms of psychosis [144] and FEP [145] at a moderate effect size. MCT consists of eight sessions that cover topics on social cognition and metacognition, and thus may be an appropriate treatment for patients with JTC and important cognitive biases. This is a low-threshold intervention that treats psychosis from a normalizing approach, an important factor to prevent stigma. Importantly, there is evidence that MCT is a gender-sensitive intervention. A recent study found that it reduces personalizing bias, general symptoms, self-certainty, and irrational beliefs in women, but is more effective in reducing JTC in men[249]. Because these results are consistent with our sex-based profile solution, it is indirect evidence of the ecological validity of our results and of the effectivity on MCT for both profiles.

Metacognitive training may be a contraindicated treatment in the Rigidity/Indecisive profile. MCT aims to sow the seeds of doubt in patients by encouraging them to seek more information before making their decisions and trusting them [89]. People grouped in these profiles already have difficulties in this aspect, and thus, may need an intervention aimed to increasing cognitive flexibility, such as cognitive remediation [267] or mindfulness [268].

Personalized treatment

Strategies to personalize treatment in psychosis are still under development, and it is more expensive and time-consuming than prescribing an existing treatment according to the characteristics of an individual. A compromise between prescription and personalization could be adapting existing interventions to the needs of the patients by reinforcing contents, implementing new modules, adding booster sessions, or finding co-adjuvant strategies to maximize efficacy.

For instance, Garety et al (2015) built on MCT training to focus intensively in JTC and belief flexibility, and found that this brief intervention improved reasoning processes and paranoia [269]. Recently, preliminary evidence suggests that each module in MCT improves specific cognitive biases, what implies that selecting modules according to patient's needs may be a strategy to personalize treatment [270].

2. CLINICAL IMPLICATIONS

As discussed throughout this doctoral dissertation, the importance of social cognition and metacognition in the clinical and functional consequences of psychosis merit its routine assessment. The first and immediate clinical implication is that clinicians and researchers now count on a validated and reliable measure of facial emotion recognition that can be used in the Spanish context. Because we validated BCFT in healthy population, its use is not only restricted to patients with psychosis and can be used in other mental illnesses or neurodevelopmental disorders.

A second clinical implication is that patients with first-episode psychosis are amenable to personalized treatment to improve social cognition and metacognition.

A third clinical implication is that men seem more prone to the metacognitive biases that are involved in the onset and maintenance of psychosis. In this sense, men with psychosis should be carefully screened for social cognitive and metacognitive deficits soon after the first onset of psychosis. Likewise, men may specially benefit from intensive metacognitive training (MCT). Importantly, MCT dedicates several sessions to improve facial emotion recognition and ToM. Given its well-established efficacy and that MCT is now recommended in therapeutical guidelines of psychosis, clinicians should consider delivering MCT to men with psychosis. Even if most women have similar abilities in all subdomains of social cognition and metacognition, this does not mean that they are preserved. Women in the homogeneous profile could benefit from MCT as it is a complete treatment

for social cognition and metacognition to restore possible deficits and prevent further decline.

3. LIMITATIONS

Throughout the present doctoral dissertation, we have placed emphasis in the importance of adequate and reliable measures. In study 1 we translated and validated a test of facial emotion recognition that was originally designed for English-speaking participants. It is possible that even if the translation is accurate, the familiarity of facial expressions and emotional states differs between cultural contexts. Likewise, we were unable to recruit a sample diverse in age and educational level. In studies 2 and 3, although we tried to rely on widely used and validated measures, it is possible that our results cannot be replicated when using different tasks. Additionally, a common pitfall of social cognitive and metacognitive tasks is their lack of ecological validity. This implies that even if our results yield accurate psychometric performance in each domain, these may not reflect the true social cognitive and metacognitive competence of the participants.

Despite counting on a big sample, data-driven methods often require larger samples. Given that some profiles were small compared to the others, we may have lost statistical power to detect other significant differences. We did not test profile stability. Although most participants in our sample originally had three points of assessment, they received different therapeutic interventions in metacognition between them. Our sample underwent an extensive assessment of clinical, cognitive, and neurocognitive variables, but other factors that we did not collect are important in understanding the clinical severity of psychosis. These include but are not limited to comorbidity, premorbid adjustment, a history of trauma, personality, or familiar history of mental illness. Likewise, we did not collect biological information on the subjects, such as genetic or hormone analysis.

These may prove important in predicting profile-membership or in further refining the clinical characterization of each profile, especially if considering biological sex.

Finally, we did not compare our results with other mental illnesses, healthy controls or with patients with psychosis at different stages of the disorder. Comparing our results with profiles in other mental illnesses may offer new findings into the specificity of social cognitive and metacognitive configurations of different disorders.

4. FUTURE DIRECTIONS

Some of our limitations can be addressed in future work. First, validating and studying the sensibility and specificity of BCFT in psychosis would offer an accessible task to measure facial emotion recognition in clinical settings.

Patients with psychosis have diverse clinical presentations and trajectories of illness. These are not only a consequence of illness, but also a reflection of a complex interaction between the biological underpinnings of illness and their personal and cultural contexts. To further understand diversity in social cognition and metacognition, an exciting line of research is to replicate our findings in larger samples across different countries. Similarly, longitudinal assessment of each cluster would provide unique insights in prognosis, relapse, and protective factors.

Replicating our analysis across stages of illness, such as clinical high-risk and established illness, would offer a clear picture of social cognitive and metacognitive deficits throughout illness that could highlight important preventive and therapeutic targets. This approach should also be considered in bigger samples that include people with other mental illnesses and healthy controls to obtain the specificity of our profiles, psychometric cut-off scores to place individuals in each profile and learn whether our findings represent deviations from normality or completely different cognitive configurations. These should also contemplate other important variables that are known to play an important role in mental illness, but that were beyond the scope of this work. These broad-scope studies will also pinpoint to new treatment-strategies, such as a combination between personalized and transdiagnostic interventions. Other data driven methods, such as trajectory modelling, could be an interesting approach to explore these issues longitudinally.

Profile-randomized clinical trials should be conducted to assess whether a personalized treatment based on each participant's profile is more beneficial than treatment as usual or that a general social cognitive and metacognitive intervention. These studies should also contemplate the cost-effectiveness of delivering personalized interventions versus classical treatment.

Differences in social information processing between males and females with psychosis should be investigated further. Although the scope of our work was small, it suggests strong differences between men and women that may have important clinical consequences. Therefore, both clinicians and researchers

should adopt a gender-sensitive perspective when considering the aetiology and treatment of psychosis.

Although there is no question in that data-driven methods can be key in improving our understanding of the aetiology and prognosis of mental illness, future research must explore both the ethical viability of delivering psychological treatment assisted by these models and the patients' acceptability of these strategies. Patients with psychosis often experience persecutory delusions that involve some sort of technological or electronic component, such as feeling that a microchip has been inserted in their brain to monitor their thoughts and actions. In this sense, using data-driven methods to support clinical decisions may be contraindicated for some patients. Furthermore, an overoptimistic reliance on computational methods may overlook the patients' preferences of treatment and personal needs.

5. CONCLUSIONS

The overall conclusions of the present doctoral dissertation are:

1. Baron Cohen's Face Test presents sound psychometric properties that confirm its adequacy to measure facial emotion recognition in Spanish population.
2. People with first-episode psychosis can be classified in clinically meaningful profiles according to their social cognitive and metacognitive competence. Each profile is associated with specific symptom severity, neurocognitive abilities, and global functioning.
3. Males and females with psychosis largely overlap in their configurations of social cognition and metacognition. However, there are sex-specific profiles that concur with worse clinical state.
4. Biological sex is not an important moderator of the relationship between social cognition and functional outcome in established psychosis.
5. Low social cognition does not affect metacognitive processes, and patients with poor social cognitive abilities may have preserved metacognition.
6. Social cognition and metacognition are important candidates for personalized treatment of psychosis given their strong associations with functional outcome and the high heterogeneity in their ability of patients with first-episode psychosis.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY RESULTS TO STUDY 2:

Supplementary Table 11. Neuropsychological characteristics of the sample and of each cluster.

	Whole sample (N=174)		Low S-C (N=58)		JTC (N=106)		Rigidity (N=10)		Kruskal-Wallis			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	χ^2	p	DSCF**	Cohen's d
TMT												
TMT-A	65,79	19,79	68,4	23,45	64,64	18,08	62,58	12,02	0.600	0.741		
TMT-B	76,58	42,36	85,86	63,54	73,07	26,76	60,99	11,22	4.056	0.132		
WAIS-III												
*Digits (T)**	43,82	9.38	41,31	9,47	44,84	9,09	47,74	9,61	6.513	0.039	1<2, 1<3	0.364
Vocabulary (IQ)	92.8	20.4	89.6	22.8	94.1	19	98	19.7	1.32	0.516		
WSCT												
Errors	45,08	13,15	43,89	12,51	45,12	12,1	51,3	23,22	2.445	0.294		
Perseverative errors	46,18	13,15	44,6	13	46,44	11,85	52,5	22,7	3.064	0.216		
Non-perseverative errors	44,65	13,04	43,58	12,43	44,73	12,03	49,9	23	2.042	0.360		
STROOP-Interference (T)*	54,14	11,15	52,77	9,57	55,35	12,03	49	7,79	3.767	0.152		
Attention (T)*	47,41	12,56	49,05	13	47,15	11,71	40,45	16,45	2.880	0.237		
TAVEC (T)*												
Immediate recall	41,01	10,77	38	9.21	42,7	11,28	40.3	11,01	6.61	0.037	1<2	0.409
Effect of Primacy	51,99	10,62	54.0	13.7	50.8	8,69	52,62	7,23	4.45	0.108		
Long term recall	35,29	15,59	32.5	15.30	36.84	15,5	35,51	17,31	3.71	0.156		
Recognition	39,75	19,74	41,77	17,69	41,77	17,69	41,48	15,34	3.21	0.201		
Discrimination	27,02	48,43	29,54	48,85	29,54	48,85	26,11	35,37	2.68	0.262		

*Presented in T scores ** Dwass-Steel-Critchlow-Fligner pairwise comparisons

SUPPLEMENTARY RESULTS TO STUDY 3

Supplementary table 12: Comparison of the sample of males and females in all the variables of the study prior to deriving profiles.

	Males	Females			
	N=114	N= 58	p	Confidence interval	Cohen's d
	Mean (SD)/ %	Mean (SD)/ %			
Age (years)	27.03(7.02)	30.1(8.01)	0.013	[-5.42, -0.73]	0.42
Education (years) (%)*			0.028		
Incomplete primary school	10,5	5,2			
Complete primary school	18,4	13,8			
Incomplete secondary school	24,6	13,8			
Complete secondary school	27,2	24,1			
Incomplete superior studies	8,8	17,2			
Complete superior studies	10,5	25,9			
Antipsychotic dose (DDD)	15.56(43.18)	20.07(55.74)		[-20.44, 11.43]	
Diagnosis (%)*			0.004		
Schizophrenia	47,4	24,1			
Psychotic disorder NOS	28,1	25,9			
Schizoaffective disorder	6,1	19			
Delusional disorder	3,5	12,1			
Brief psychotic disorder	9,6	10,3			
Schizophreniform disorder	3,5	8,6			
Emsley factors					
Positive symptoms	16.25(7.18)	14.6(6.51)			
Negative symptoms	15.95(7.18)	14.6(6.51)			
Disorganised symptoms	8.59(3.75)	7.93(3.06)			
Excited symptoms	5.66(2.69)	5.21(2.83)			
Motor symptoms	2.91(1.54)	2.78(1.25)			
Depression	4.33(2.14)	5.22(2.53)	0.016	[-1.617,-0.165]	0.39
Anxiety	5.84(2.29)	5.84(2.29)			
GAF	59.73(12.48)	59.55(12.23)			

	Males	Females			
	N=114	N= 58	p	Confidence interval	Cohen's d
	Mean (SD)/ %	Mean (SD)/ %			
Rosenberg (total)	27.39(6.16)	27.14(6.03)			
BDI (total)	14.49(8.88)	15.57(9.46)			
SUMD (global)	6.37(3.57)	5.69(3.67)			
Beads Task					
85-15	4.6(3.93)	5.47(4.98)			
60-40	8(4.99)	7.69(5.01)			
Salient task	7.39(4.40)	7.9(4.92)			
BCIS					
Self-certainty	8.43(3.20)	8.09(3.79)			
Self-reflectivity	15.77(4.67)	15.07(5.29)			
Faces Test	17.37(2.10)	17.74(1.68)			
Hinting task	1.54(0.41)	1.67(0.31)	0.031	[-0.25, -0.01]	0.35
IPSAQ					
Personalising bias					
Externalising bias	0.72(3.82)	1.52(3.99)			
WSCT					
Total errors	44.96(12.53)	44.37(13.32)			
Perseverative errors	46.38(12.15)	44.8(13.73)			
Non-perseverative errors	44.32(12.54)	44.52(13.40)			
Stroop test (T) - interference	54.84(11.25)	53.18(10.86)	0.05	[-6.24, 0.081]	0.14
WAIS-III (T)					
Digits	43.65(9.37	44.36(9.13)			
Vocabulary	92.13(20.20)	93.83(20.90)			
Attention (T)	46.74(12.16)	48.74(13.64)			
TMT (seconds)					
TMT-A	65.48(18.63)	65.79(22.09)			
TMT-B	80.68(49.82)	68.27(19.27)			
Tavec					
Immediate recall	39.45(9.52)	43.98(12.30)	0.009	[-7.90, -1.149]	0.43
Short-term memory	34.29(13.44)	40.03(14.31)	0.011	[-10.14, -1.33]	0.41
Long-term memory	33.29(15.92)	38.93(14.36)	0.026	[-10.59, -0.69]	0.36

* Categorical variables are presented in % and comparisons were computed using chi squared tests.

SUPPLEMENTARY RESULTS TO STUDY 4:

SUPPLEMENTAL METHOD

Regarding the two versions of the Empathic Accuracy task, we did not find any significant difference between participants who were administered the newer version of the Empathic Accuracy task and participants who were administered the older version (patients, mean=.52 (SD=.17) and mean=.59 (SD=.17) for the newer and older versions, respectively; controls, mean=.61 (SD=.10) and mean=.70 (SD=.10) for the newer and older versions, respectively).

SUPPLEMENTAL RESULTS

To better understand the sex difference on MASC and RFS total, we examined sex difference on subscales of MASC and RFS separately. For MASC, we found significant sex effects on all three subscales of MASC (MASC Verbal, $F_{(1,236)}$=9.46, p<.01, η^2_p=.039; MASC Nonverbal, $F_{(1,236)}$=6.31, p<.05, η^2_p=.026; MASC Effectiveness, $F_{(1,236)}$=9.09, p<.01, η^2_p=.037). We found a significant sex difference on RFS work ($F_{(1,331)}$=7.62, p<.01, η^2_p=.023) and RFS social functioning ($F_{(1,331)}$=7.28, p<.01, η^2_p=.022) and a marginally significant effect on RFS family functioning ($F_{(1,331)}$=3.08, p=.08, η^2_p=.009). A sex effect was not significant on RFS Independent living. Female patients with schizophrenia showed better work functioning, social functioning, and family functioning.

Supplementary table 13. Performance in objective and subjective social cognitive tasks.

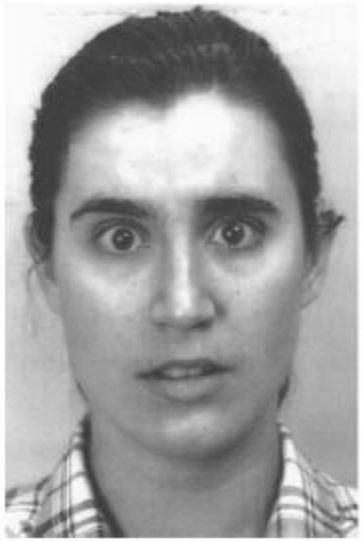
Objective Social Cognition					
	Patients		Controls		Statistics
	Female	*Male*	*Female*	*Male*	
Facial Affect Recognition	.77 (.14)	.75 (.13)	.82 (.08)	.82 (.08)	Group $F_{(1,329)}$=20.14, p<.001, h^2_p=.058
					Sex $F_{(1,329)}$=1.88, p=.17, h^2_p=.006, n=1303
					Group by Sex $F_{(1,329)}$=.001, p=.98, h^2_p=.000, n=19617
Emotion in Biological Motion	.70 (.12)	.67 (.13)	.77 (.11)	.76 (.09)	Group $F_{(1,323)}$=21.76, p<.001, h^2_p=.063
					Sex $F_{(1,323)}$=1.19, p=.27, h^2_p=.004, n=1957
					Group by Sex $F_{(1,323)}$=.57, p=.44, h^2_p=.002, n=3919
Self-referential Memory					
Physical	.84 (.66)	.68 (.57)	.66 (.55)	.57 (.61)	Group $F_{(1,325)}$=1.98, p=.15, h^2_p=.006 n=1303
					Sex $F_{(1,325)}$=2.82, p=.09, h^2_p=.009, n=867
					Group by Sex $F_{(1,325)}$=.10, p=.75, h^2_p=.000, n=19617
					Condition $F_{(2,650)}$=227.04, p<.001, h^2_p=.411
					Condition by Group $F_{(2,650)}$=21.08, p<.001, h^2_p=.061
Other	1.17 (.80)	1.07 (.69)	1.33 (.66)	1.21 (.56)	Condition by Sex $F_{(2,650)}$=.46, p=.62, h^2_p=.001, n=7843
Self	1.32 (.81)	1.22 (.73)	1.73 (.67)	1.47 (.63)	Condition by Group by Sex $F_{(2,650)}$=1.41, p=.24, h^2_p=.004, n=2403
Empathic Accuracy	.59 (.17)	.55 (.15)	.66 (.12)	.67 (.09)	Group $F_{(1,316)}$=24.13, p<.001, h^2_p=.071
					Sex $F_{(1,316)}$=.71, p=.40, h^2_p=.002, n=3919
					Group by Sex $F_{(1,316)}$=2.15, p=.14, h^2_p=.007, n=1116
MSCEIT Branch 4	39.48 (11.76)	36.04 (11.79)	52.26 (8.04)	48.39 (10.30)	Group $F_{(1,326)}$=69.03, p<.001, h^2_p=.175
					Sex $F_{(1,326)}$=5.83, p<.05, h^2_p=.018
					Group by Sex $F_{(1,326)}$=.02, p=.88, h^2_p=.000, n=19617

Subjective social cognition					
	Patients		Controls		Statistics
	Female	*Male*	*Female*	*Male*	
IRI Fantasy	13.6 (5.2)	13.4 (5.0)	14.8 (5.3)	12.1 (4.8)	Group $F_{(1,329)}$=.00, p=.99, h^2_p=.00, n=19617
					Sex $F_{(1,329)}$=4.46, p<.05, h^2_p=.013
					Group by Sex $F_{(1,329)}$=3.25, p=.07, h^2_p=.010, n=779
IRI Empathic Concern	20.1 (4.8)	18.7 (4.7)	22.1 (3.3)	19.2 (4.2)	Group $F_{(1,329)}$=4.18, p<.05, h^2_p=.013
					Sex $F_{(1,329)}$=11.43, p<.01, h^2_p=.034
					Group by Sex $F_{(1,329)}$=1.42, p=.23, h^2_p=.004, n=1957
IRI Perspective Taking	16.9 (4.7)	15.9 (4.8)	19.3 (5.2)	17.9 (4.3)	Group $F_{(1,329)}$=11.32, p<.01, h^2_p=.033
					Sex $F_{(1,329)}$=3.32, p=.06, h^2_p=.010, n=779
					Group by Sex $F_{(1,329)}$=.73, p=.78, h^2_p=.000, n=19617
IRI Personal Distress	13.3 (4.9)	11.7 (5.1)	7.5 (3.4)	7.3 (4.3)	Group $F_{(1,329)}$=61.78, p<.001, h^2_p=.158
					Sex $F_{(1,329)}$=1.98, p=.16, h^2_p=.006, n=1303
					Group by Sex $F_{(1,329)}$=1.20, p=.29, h^2_p=.003, n=2611
IRI Total	64 (13.96)	59.8 (12.1)	63.7 (11.0)	56.7 (11.4)	Group $F_{(1,329)}$=1.03, p=.31, h^2_p=.003, n=2611
					Sex $F_{(1,329)}$=11.58, p<.01, h^2_p=.034
					Group by Sex $F_{(1,329)}$=.77, p=.38, h^2_p=.002, n=3919

ANNEXES

ANNEX 1: BARON COHEN'S FACE TEST, TRANSLATED AND ADAPTED TO SPANISH POPULATION.

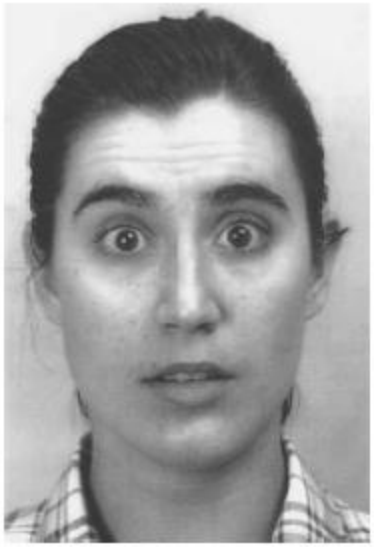
SORPRENDIDA

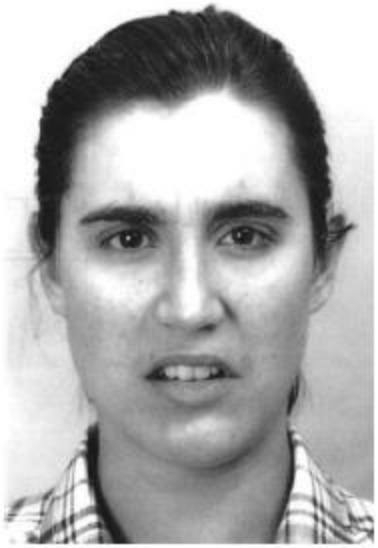


CONTENTA

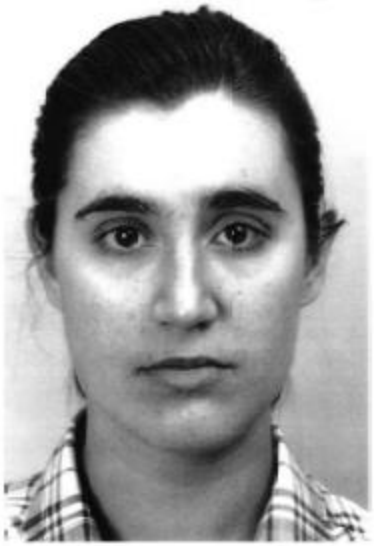
ENFADADA

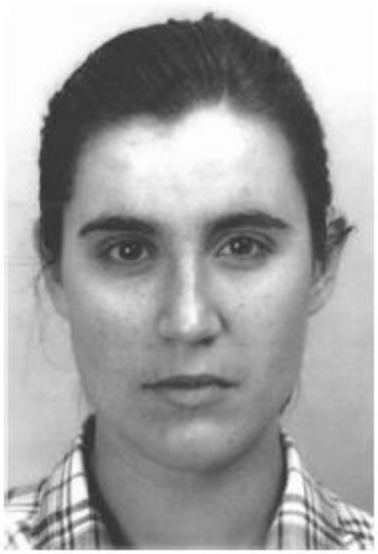
ASUSTADA





CONTENTA SORPRENDIDA ASQUEADA TRISTE





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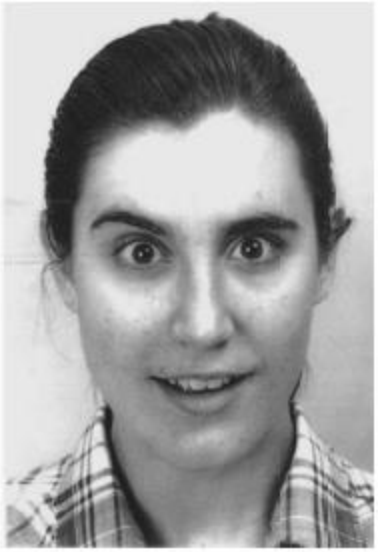
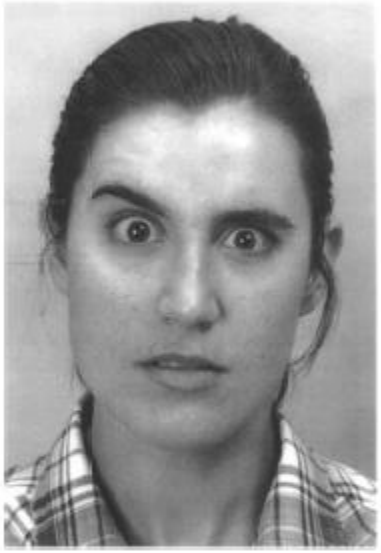


CONTENTA

SORPRENDIDA

ANGUSTIADA

TRISTE



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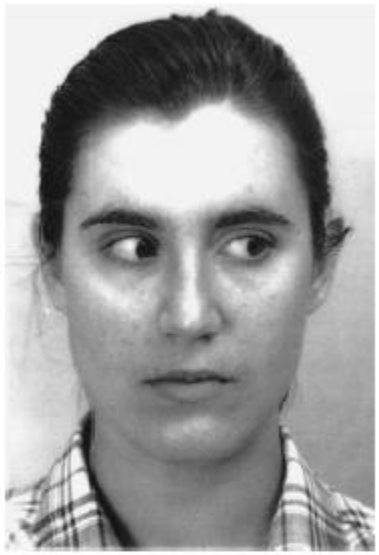
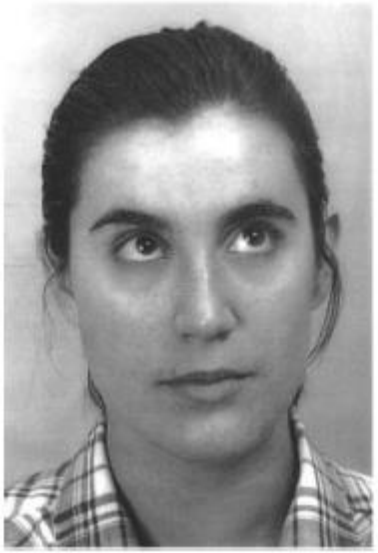


CALCULADORA ARROGANTE ARROGANTE CULPABLE



PENSATIVA ARROGANTE SORPRENDIDA ADMIRADA

INCRÉDULA CULPABLE CONTENTA COQUETA

ABURRIDO SOMNOLIENTA DESINTERESADA INTERESADA

INTERESADA DESINTERESADA CULPABLE ARROGANTE

ANNEX 2: INFORMED CONSENT FILES

Figure 2. Informed consent file for study 1

Parc Sanitari Sant Joan de Déu

Unidad de Investigación

Adaptación, validación y normalización del test de reconocimiento facial de emociones en personas con esquizofrenia y sujetos controles sanos

Nombre Apellidos

DNI Edad _____

Nombre Apellidos

Edad DNI

en calidad de *

***Pariente/a del/de la paciente, representante legal.**
***El orden de la relación para la autorización es el siguiente: paciente, cónyuge, padres, hijos/as, hermanos/as, parientes/as más próximos/as y tutores/oras.**

DECLARO: que el investigador/la investigadora_____
colegiado/a número_____ me ha propuesto participar en el estudio de investigación: *Adaptación, validación y normalización del test de reconocimiento facial de emociones en personas con esquizofrenia y sujetos controles sanos*
y después de recibir la información correspondiente, manifiesto que:

1. He recibido la hoja informativa y he comprendido la información sobre el estudio en el que participaré.

2. He sido informado/a de las implicaciones derivadas de la participación.

3. Soy consciente que mi participación es voluntaria y me puedo retirar en el momento que decida sin tener que dar explicaciones y sin que repercuta en mi atención.

4. De acuerdo con la Ley 15/1999 de Protección de Datos de Carácter Personal (LOPD) y el artículo 3, punto 6 del Real Decreto 223/2004, declaro haber sido informado/a de que mis datos formarán parte de un fichero de titularidad del Parc Sanitari Sant Joan de Déu (PSSJD) y de que su finalidad es la utilización para investigación clínica. Parc Sanitari le informa que puede ejercer los derechos de acceso, rectificación, cancelación y oposición previstos en la LOPD, por ejemplo: solicitar sus datos personales, rectificarlos si fuera necesario, así como revocar la autorización de inclusión en el estudio. Su petición será atendida de forma inmediata.

5. Autorizo al equipo investigador del estudio a consultar los datos de salud necesarios para dicho proyecto y que estén en la Historia Clínica de Parc Sanitari Sant Joan de Déu.

He entendido las explicaciones que me han facilitado en un lenguaje claro y sencillo, y el facultativo que me ha atendido me ha permitido realizar todas las observaciones y me ha aclarado todas las dudas que he planteado.

☐ **SI** ☐ **NO**

DOY MI CONSENTIMIENTO para participar en el estudio de investigación *Adaptación, validación y normalización del test de reconocimiento facial de emociones en personas con esquizofrenia y sujetos controles sanos*
Sant Boi de Llobregat,_____d_____de 20_____

CODI TIPUS CT-307 Protegim les Vostres Dades Personals de Salut

Camí Vell de la Colònia, 25 - 08830 Sant Boi de Llobregat (Barcelona) - Tel. 936615208 - Fax. 936306175
www.pssjd.org/pssjd@pssjd.org

Figure 3. Informed consent for studies 2 and 3

CONSENTIMIENTO INFORMADO PARA LA INTERVENCIÓN DEL ENTRENAMIENTO META-COGNITIVO (EMC) SOBRE LOS SÍNTOMAS, LA METACOGNICIÓN, Y EL FUNCIONAMIENTO NEUROPSICOLÓGICO .

Yo, el Sr. / Sra. ... ... doy consentimiento para participar en la intervención "Eficacia del Entrenamiento Meta-Cognitivo (EMC) sobre los síntomas, la metacognición, y el funcionamiento neuropsicológico en personas con psicosis de breve evolución" y manifiesto que:

1. He recibido y comprendido la información sobre la intervención en la que participaré.
2. He recibido una hoja informativa que explica las características del estudio.
3. He sido informado de las implicaciones derivadas de la participación.
4. Soy consciente de que mi participación es voluntaria y puedo retirar en el momento que decida sin tener que dar explicaciones y sin que repercuta en mi atención.
5. De acuerdo con la L.O. 15/1999, de 13 Diciembre y de Protección de Datos de Carácter Personal (artículo 3, punto 6 del Real Decreto 223/2004), declaro haber sido informado del registro de datos de Parque Sanitario San Juan de Dios y de su utilización por investigación por parte de la investigadora de la intervención.

Estoy de acuerdo en mi participación.

Nombre del/la paciente: Nombre del investigador/a

Firma: Firma:

En ... ..., a ... ... de ... ... de 201 ... ...

ANNEX 3: APPROVAL OF THE ETHICS COMMITTEE.

Figure 2. Approval of the ethics committee for Study 1.

Parc Sanitari Sant Joan de Déu

La Comissió de Recerca del Parc Sanitari Sant Joan de Déu, ha revisat i aprovat el projecte titulat "Adaptación, validación y normalización del test de reconocimiento facial de emociones de Baron-Cohen en población general" Dra. Huerta.

El projecte té el recolzament de la Comissió de Recerca. El tema es pertinent dintre de les línies de recerca de la Institució i el protocol es pot realitzar als termes proposats. El nivell de formació, experiència i dedicació dels investigadors garanteixin a la nostra opinió el desenvolupament del projecte.

Sant Boi de Llobregat, 1 de desembre de 2015

Signat: Josep Maria Haro Abad
President Comissió Recerca

Figure 3. Approval of the ethics committee for the first substudy that composes studies 2 and 3.

Fundació Sant Joan de Déu

CEIC Fundació Sant Joan de Déu

Informe Dictamen Favorable
Proyecto Investigación Biomédica

C.I. PIC-81-14

5 de marzo de 2015

Dr. Pablo Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

CERTIFICA

1º. Que el CEIC Fundació Sant Joan de Déu en su reunión del día 26/02/2015, ha evaluado la propuesta del promotor referida al estudio:

Título: "Eficacia del Entrenamiento Metacognitivo Individualizado (EMC+) en personas con psicosis de breve evolución"
Código Interno: PIC-81-14
IP: Dra. Susana Ochoa Güerre (PSSJD. Psiquiatría)

2º. Considera que:

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

3º. Por lo que este CEIC emite un **DICTAMEN FAVORABLE**.

4º. Este CEIC acepta que dicho estudio sea realizado en los siguientes CEIC/Centros por los Investigadores:

CEIC Fundació Sant Joan de Déu	**Dra. Susana Ochoa Güerre** *Parc Sanitari Sant Joan de Déu*

Lo que firmo en Esplugues de Llobregat, a 5 de marzo de 2015

Fdo:

Fundació Sant Joan de Déu

Dr. Pablo Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

Edifici Docent Sant Joan de Déu · c. Santa Rosa, 39-57, 3a planta, 08950 Esplugues de Llobregat / Barcelona
Telèfon +34 93 600 97 61 · Fax +34 93 600 97 71 · e-mail: info@fsjd.org · web: www.fsjd.org

Figure 4. Approval for the second substudy that composes studies 2 and 3.

Fundació Sant Joan de Déu

INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Dr. Pablo Ferrer Salvans, Secretario del Comité Ético de Investigación Clínica Fundació Sant Joan de Déu Esplugues de Llobregat (Barcelona)

CERTIFICA

Que en la reunión del Comité Ético de Investigación Clínica de la Fundació Sant Joan de Déu celebrada el día 22 de diciembre de 2011 se valoró la respuesta a las aclaraciones solicitadas para la realización del protocolo de estudio titulado **"Eficacia del Entrenamiento Meta-Cognitivo (EMC) sobre los síntomas, la metacognición, el funcionamiento social y neuropsicologico en personas con psicosis de breve evolución"**, Código **CEIC PIC-73-11**, cuya investigadora principal es la **Dra. Susana Ochoa Güerre** y se informó **favorablemente**.

Lo que firmo en Esplugues de Llobregat (Barcelona), a 10 de enero de 2012

Firmado:

Fundació Sant Joan de Déu

Dr. Pablo Ferrer Salvans
Secretario CEIC Fundación SJD