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Neuropsychological and neuroimaging markers and their potential use for schizophrenia diagnosis

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“Science and everyday life cannot

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Rosalind Franklin

“Cause it’s a long road to wisdom

but it’s a short one to being ignored”

The Lumineers

Contents

Foreword

The present thesis has been presented to obtain the degree of Doctor by the University of Deusto, and it is the result of four studies carried out at the Research Group of Neuropsychology of Severe Medical Conditions, at the Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto. The following articles have been published in international journals, as a result of the work performed, with a global impact factor (IF) of 9.22 (ISI Web of Science, Journal Citation Reports).

Paper I

Gómez-Gastiasoro, A., Peña, J., Zubiaurre-Elorza, L., del Pino, R., Ibarretxe-Bilbao, N., Ojeda, N. (2019). Cognitive scores as a potential diagnostic tool in schizophrenia: the use of raw and discrepancy scores. *Clinical Psychologist,* 1-9. DOI: 10.1111/cp.12191 [IF: 1.293, Q3 Psychology, Clinical].

Paper II

Gómez-Gastiasoro, A., Peña, J., Zubiaurre-Elorza, L., Ibarretxe-Bilbao, N., Ojeda, N. (2018). Spanish adaptation and validation of the Situational Feature Recognition Test 2 (SFRT-2) in patients with schizophrenia and healthy controls. *Psychiatry research*, *270*, 225-231. DOI: 10.1016/j.psychres.2018.09.051. [IF: 2.208, Q2 Psychiatry].

Paper III

Gómez-Gastiasoro, A., Peña, J., Zubiaurre-Elorza, L., Ibarretxe-Bilbao, N., Ojeda, N. (2019). Equivalent short forms of the Situational Feature Recognition Test 2: psychometric properties and analysis of inter-form equivalence and test-retest reliability. *International Journal of Methods in Psychiatric Research,* e1802. DOI: 10.1002/mpr.1802 [IF: 2.276, Q2 Psychiatry].

Paper IV

Gómez-Gastiasoro, A., Zubiaurre-Elorza, L., Peña, J., Ibarretxe-Bilbao, N., Rilo, O., Schretlen, D. J., & Ojeda, N. (2019). Altered frontal white matter asymmetry and its implications for cognition in schizophrenia: A tractography study. *NeuroImage: Clinical*, 101781. DOI: 10.1016/j.nicl.2019.101781 [IF: 3.943, Q1 Neuroimaging].

Glossary of abbreviations

AD = Axial Diffusivity

ANCOVA = Analysis of Covariance

AS = Attributional Style

ASQ = Attributional Style Questionnaire

AUC = Area Under the Curve

bCC = body of the Corpus Callosum

BET = Brain Extraction Tool

CC = Corpus Callosum

CIFA = Calibrated Ideational Fluency Assessment

DSM-III = Diagnostic and Statistical Manual of Mental Disorders 3rd Edition

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th Edition-Revised

DSM-V = Diagnostic and Statistical Manual of Mental Disorders 5th Edition

DTI = Diffusion Tensor Imaging

DWI = Diffusion Weighted Imaging

EP = Emotion Perception

FA = Fractional Anisotropy

FSL = FMRIB Software Library

GAF = Global Assessment of Functioning Scale

gCC = genu of the Corpus Callosum

HC = Healthy Controls

HVLT-R = Hopkins Verbal Learning Test, Revised

ICD-11 = International Classification of Diseases 11th Edition

MANCOVA = Multivariate Analysis of Covariance

MD = Mean Diffusivity

MO = Mode of Anisotropy

MRI = Magnetic Resonance Imaging

MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test

NART = National Adult Reading Test

NPV = Negative Predicted Values

PANSS = Positive and Negative Syndrome Scale

PPV = Positive Predicted Values

RD = Radial Diffusivity

ROC = Receiver-Operating Characteristic

ROI = Region Of Interest

SC = Social Cognition

sCC = splenium of the Corpus Callosum

SCID-I = Structured Clinical Interview for DSM

SCWIT = Stroop Color-Word Interference Test

SFRT-2 = Situational Feature Recognition Test, version 2

SP = Social Perception

SPSS = Statistical Software Package for Social Sciences

TBSS = Tract-Based Spatial Statistic

TFCE = Threshold-Free Cluster Enhancement

TMT-A = Trail Making Test, part A

TMT-B = Trail Making Test, part B

ToM = Theory of Mind

UCSD = University of California San Diego

UPSA = Performance-Based Skills Assessment

WAT = Word Accentuation Test

WM = White Matter

I. Abstract

1. Abstract

Basic cognitive processes and social cognition (SC) have been identified as being impaired in patients with schizophrenia. However, nowadays, these variables are not included in the commonly used diagnostic manuals for identifying the disease. Using cognitive impairment as a diagnostic marker for schizophrenia presents different challenges such as: 1) the difficulties when accounting for patient's premorbid functioning in order to establish the presence of cognitive impairment and 2) the lack of adapted and reliable measures for assessing cognition in these patients, mainly in Spanish-speaking samples. This last challenge is particularly problematic in the case of SC and especially regarding social perception (SP), one of the most impaired social cognitive domains in schizophrenia. Together with cognition, brain abnormalities might also be relevant and useful when establishing the diagnosis of schizophrenia. Specifically, white matter (WM) integrity, and more concretely WM asymmetry, has shown abnormalities in these patients. However, up to date, no study has assessed the role of WM integrity asymmetry in cognition in schizophrenia.

The present thesis is composed by four scientific contributions. The *first study* assessed the discriminant capability of both raw and discrepancy (controlling for sociodemographic and premorbid characteristics) cognitive scores when comparing patients and healthy controls (HC). The *second study* aimed to adapt and validate a well-known SP test (the Situational Feature Recognition Test 2, SFRT-2) into Spanish-speaking patients with schizophrenia and HC. The *third study* presented two shortened and equivalent forms of the SFRT-2 as well as their psychometric properties. The *fourth study* investigated the WM asymmetry abnormalities in two frontal and occipital WM tracts as well as their relationship with cognition in patients with schizophrenia.

Results showed that verbal memory and processing speed raw scores discriminated better than discrepancy scores between patients and HC, being verbal memory the best classifier. Moreover, the Spanish adaptation and validation of the SFRT-2 as well as the obtained shortened forms showed satisfactory psychometric characteristics. Finally, patients with schizophrenia showed an abnormal asymmetry pattern of a frontal WM tract showing greater integrity in the right compared to the left hemisphere. WM integrity of the right frontal tract showed a significant correlation with verbal memory performance in patients with schizophrenia.

This thesis provides an adapted and validated SP measure as well as its two shortened forms for Spanish-speaking patients with schizophrenia allowing establishing a reliable SP impairment profile in these patients. In addition, results support the inclusion of cognitive impairment, especially verbal memory alterations, and frontal WM asymmetry abnormalities as potential diagnostic markers for schizophrenia diagnosis.

Keywords: schizophrenia, verbal memory, diagnosis, cognition, social cognition, social perception, assessment, neuroimaging, white matter, brain asymmetry.

Resumen

Los procesos cognitivos básicos y la cognición social (CS) se encuentran alterados en pacientes con esquizofrenia. Sin embargo, hoy en día, estas variables no están incluidas en los manuales diagnósticos comúnmente utilizados para diagnosticar la enfermedad. Emplear el deterioro cognitivo como un marcador diagnóstico para la esquizofrenia presenta diferentes retos, como son: 1) las dificultades a la hora de discernir el funcionamiento premórbido del paciente y el deterioro cognitivo asociado al progreso de la enfermedad y 2) la falta de medidas adaptadas y fiables para evaluar la cognición en estos pacientes, sobre todo en muestras castellanohablantes. Este último reto es particularmente problemático en el caso de la CS y especialmente en relación con la percepción social (PS), uno de los dominios de la CS más afectados en la esquizofrenia. Junto con la cognición, las alteraciones cerebrales pueden ser también relevantes y útiles a la hora de establecer el diagnóstico de esquizofrenia. Específicamente, la integridad de la sustancia blanca (SB), y más concretamente la asimetría de la SB, se encuentra alterada en pacientes con esquizofrenia. Sin embargo, a día de hoy, ningún estudio ha evaluado el papel de la asimetría de la integridad de la SB en la cognición en la esquizofrenia.

Esta tesis está compuesta por 4 contribuciones científicas. El *primer estudio* evaluó la capacidad de discriminación de las puntuaciones cognitivas directas y de discrepancia (controlando por las características sociodemográficas y premórbidas) a la hora de comparar pacientes y controles sanos (CoS). El *segundo estudio* tuvo como objetivo adaptar y validar un conocido test de PS (el "Situational Feature Recognition Test 2", SFRT-2) en pacientes castellanohablantes con esquizofrenia y CoS. El *tercer estudio* presentó dos formas reducidas y paralelas del SFRT-2 así como sus propiedades psicométricas. El *cuarto estudio* investigó las anomalías en la asimetría de la integridad

de la SB en dos tractos frontales y occipitales y su relación con la cognición en pacientes con esquizofrenia.

Los resultados mostraron que las puntuaciones directas en memoria verbal y velocidad de procesamiento discriminaron mejor que las puntuaciones de discrepancia entre pacientes y CoS, siendo la memoria verbal el mejor clasificador. Además, la adaptación y validación del SFRT-2 así como las versiones reducidas mostraron unas características psicométricas satisfactorias. Finalmente, los pacientes con esquizofrenia mostraron un patrón de asimetría anómalo en un tracto frontal de SB que mostraba una mayor integridad en el hemisferio derecho comparado con el hemisferio izquierdo. La integridad de la SB del tracto frontal derecho mostró una correlación significativa con el desempeño en memoria verbal en pacientes con esquizofrenia.

Esta tesis facilita una herramienta adaptada y validada para la evaluación de la PS, así como sus dos formas abreviadas para pacientes castellanohablantes con esquizofrenia, permitiendo establecer un perfil de deterioro de la PS fiable en estos pacientes. Además, los resultados apoyan la inclusión del deterioro cognitivo, especialmente las alteraciones en memoria verbal, y las anomalías en la asimetría de la SB frontal como potenciales marcadores para el diagnóstico de la esquizofrenia.

Palabras clave: esquizofrenia, memoria verbal, diagnóstico, cognición, cognición social, percepción social, evaluación, neuroimagen, sustancia blanca, asimetría cerebral.

II. Introduction

2. Introduction

2.1. Short History of Schizophrenia

Schizophrenia is a chronic mental disorder characterized by the presence of hallucinations, delusions, cognitive impairment, and functional alterations among other symptoms. Since Emil Kraepelin first described the disease as *dementia praecox* (Kraepelin, 1899), schizophrenia conceptualization has undergone different stages across the years. In Kraepelin's words, *dementia praecox* was a disorder that included positive and negative symptoms along with cognitive and behavioral decline, identifying nine different clinical forms. However, it was Eugen Bleuler who first used the term *schizophrenia* in 1908 (Fusar-Poli & Politi, 2008) and recognized it as a thought, emotion, and behavior disorder. Bleuler also introduced a distinction between basic (thought and speech derailment, volitional indeterminacy, affective incongruence, and withdrawal from reality) and accessory (positive) symptoms. Later on, Schneider proposed the nine first-rank symptoms based on Bleuler's theory, which were eventually included in the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition [DSM-III; (American Psychiatric Association, 1980)] for the diagnosis of schizophrenia (Jablensky, 2010). Nowadays, both the DMS-V (American Psychiatric Association, 2014) and the International Classification of Diseases 11th Edition (ICD-11, World Health Organization, 2018) diagnose schizophrenia based on the commonly known positive and negative symptoms, but also taking into account subject's functioning in different areas.

Moreover, in the specific case of the ICD-11, cognitive impairment is included as a diagnostic criterion (see tables 1 and 2 for the complete diagnostic guidelines).

Table 1

Criteria for Schizophrenia Diagnosis Described in DSM-V (American Psychiatric Association, 2014).

DSM-V Schizophrenia 295.90 (F20.9)
A. Two (or more) of the following for at least a one-month (or longer) period of time, and at least one of them must be 1, 2, or 3: 1) Delusions 2) Hallucinations 3) Disorganized speech 4) Grossly disorganized or catatonic behavior 5) Negative symptoms, such as diminished emotional expression.
B. Impairment in one of the major areas of functioning for a significant period of time since the onset of the disturbance: work, interpersonal relations, or self-care.
C. Some signs of the disorder must last for a continuous period of at least 6 months. This six-month period must include at least one month of symptoms (or less if treated) that meet criterion A (active phase symptoms) and may include periods of residual symptoms. During residual periods, only negative symptoms may be present.
D. Schizoaffective disorder and bipolar or depressive disorder with psychotic features have been ruled out: 1) No major depressive or manic episodes occurred concurrently with active phase symptoms.

2) If mood episodes (depressive or manic) have occurred during active phase symptoms, they have been present for a minority of the total duration of the active and residual phases of the illness.

E. The disturbance is not caused by the effects of a substance or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder (childhood onset), the diagnosis of schizophrenia is only made if prominent delusions or hallucinations, along with other symptoms, are present for at least one month.

Table 2

Criteria for Schizophrenia Diagnosis Described in ICD-11 (World Health Organization, 2018).

ICD-11 Schizophrenia 6A20
Schizophrenia is characterized by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganization in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behavior are under the control of an external force), cognition (e.g., impaired attention, verbal memory, and social cognition), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behavior (e.g., behavior that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organization of behavior). Psychomotor disturbances, including catatonia, may be present. Persistent delusions, persistent hallucinations, thought disorder, and experiences of influence, passivity, or control are considered core

symptoms. Symptoms must have persisted for at least one month in order for a diagnosis of schizophrenia to be assigned. The symptoms are not a manifestation of another health condition (e.g., a brain tumor) and are not due to the effect of a substance or medication on the central nervous system (e.g., corticosteroids), including withdrawal (e.g., alcohol withdrawal).

2.2. Epidemiology

According to latest studies, schizophrenia's overall incidence varies from 13.1 per 100,000 person/year to 32.8 per 100,000 person/year depending on the population included (first contact studies vs. population registers) (Jongsma, Turner, Kirkbride, & Jones, 2019). Global prevalence was estimated to be 0.28% in 2016 with a prevalence peaking at around 40 years old and no sex differences, which entails around 21 million people diagnosed with schizophrenia worldwide. However, and even though schizophrenia is a low prevalence disorder, this pathology was ranked the 12th most disabling disorder in 2016 (Charlson et al., 2018), with the consequent costs assumed by the patient and social services.

2.3. Etiology

Even nowadays, and despite all the scientific advances, little is known about the etiology of schizophrenia. Overall, both genetic and environmental factors seem to have a decisive role when developing schizophrenia. On the one hand, genetic aspects of the disease have been supported by different sources of evidence such as: a) polygenic models; b) loci studies and c) heritability studies among others. Thus, genetic research has pointed out that schizophrenia is not derived from a major gen effects but from polygenic models (a), making it a complex genetic disorder (Harrison & Weinberger, 2005). One of the first confirmed genetic variations associated with schizophrenia was the deletion at chromosome 22q.11.2 (Karayiorgou et al., 1995). Most recent studies have

also described different locus (b) containing protein-code genes for dopamine (e.g.: DRD2) and glutamate (e.g.: GRIA1) receptors, and genes involved in calcium-ion channel (e.g.: CACNA1) and synaptic plasticity which might be involved in the onset of the disease (Kavanagh, Tansey, O'Donovan, & Owen, 2015). Genetic influence on developing schizophrenia has also been confirmed by means of heritability studies (c). These studies point to a complex heritability character of the disease due to its polygenic model. Thus, it is well known that family history of schizophrenia increases the risk for the disease in monozygotic twins (50-70% average relative risk), children with both parents affected (40-60% average relative risk) or first degree relatives (9-18% average relative risk) (Tandon, Keshavan, & Nasrallah, 2008). On the other hand, added to this genetic risk, both biological and psychosocial environmental factors also play a relevant role in the development of schizophrenia. Prenatal, perinatal and obstetric complications as well as sociodemographic factors such as poverty, living in a lower social class or coming from a minority ethnic group among others, have been described to increase the risk for schizophrenia (Insel, 2010; Lewis & Lieberman, 2000; Mueser & McGurk, 2004). Given that neither the genetic risk nor the environmental factors independently lead to develop schizophrenia *per se*, a more appropriated model to understand this disease suggests an interaction between genetic vulnerability and environmental factors (Mueser & McGurk, 2004).

2.4. Neurodevelopmental vs. Neurodegenerative Hypothesis

Although nowadays schizophrenia is well recognized to be a neurodevelopmental disease, neurodevelopmental and neurodegenerative hypothesis for schizophrenia have been opposed through years. Based on one of the first descriptions of schizophrenia as *dementia praecox*, a neurodegenerative character was presupposed to this pathology. According to this, schizophrenia would be an adult-onset disease with a progressive

course. However, nowadays, studies supporting neurodegenerative hypothesis for schizophrenia are inconclusive and controversial since some relevant features for neurodegeneration such as gliosis have not been found in patients with schizophrenia (Gupta & Kulhara, 2010). On the contrary, neurodevelopmental hypothesis proposes that illness onset is the final stage of an abnormal neurodevelopment that starts even in the prenatal phase. Most robust evidences supporting the neurodevelopmental hypothesis are the following: a) obstetric complications; b) clinical signs of impaired neurodevelopment (neurological signs and social and intellectual alterations); c) premorbid cognitive and neurologic deficits; d) results obtained by means of neuroimaging studies of first-episode psychosis and childhood onset schizophrenia; e) postmortem neuropathological studies, and f) genes, as some of the schizophrenia susceptibility genes are related to neurodevelopment (Gupta & Kulhara, 2010; Weinberger, 1996). Thus, adverse conditions would interfere with normal brain development, leading to abnormalities that eventually might be clinically manifested in early adulthood. This hypothesis is supported by transversal neuroimaging studies that identify brain abnormalities even in neonates at risk of schizophrenia who present gray matter abnormalities and ventricles enlargement (Gilmore et al., 2010; Li et al., 2016). Longitudinal neuroimaging studies also add evidence to this hypothesis showing no accelerated brain age-related decline in patients with schizophrenia in comparison with healthy controls (HC) (Voineskos et al., 2010; Zipursky, Reilly, & Murray, 2013). This pattern is also described in longitudinal studies that assess the course of cognitive impairment of these patients. As described in those studies, cognitive alterations show a stable course over time since their appearance in first psychotic episodes (Heilbronner, Samara, Leucht, Falkai, & Schulze, 2016; Zipursky et al., 2013).

2.5. Cognitive Impairment in Schizophrenia

2.5.1. Basic cognitive processes impairment.

Cognitive impairment has been identified as a core feature in patients with schizophrenia since Kraepelin's first description of the disease (Kraepelin, 1899). However, it has been considered a controversial area of research through years (Palmer et al., 1997; Wilk et al., 2005). Cognitive decline has been detected years before the disease's onset in individuals at high clinical risk for psychosis (see Brewer et al., 2006 for a review), highlighting its potential role when predicting transition to psychosis (Brewer et al., 2006). Interestingly, cognitive impairment has been described even in first-degree relatives without a diagnosis of schizophrenia (see Snitz, MacDonald, & Carter, 2006 for a review). This fact supports the idea of considering cognitive impairment as a disease's endophenotype. Overall, cognitive domains impaired before the onset of the disease include general IQ, verbal memory, language and attention (Brewer et al., 2006; Keefe & Harvey, 2012). In addition, offspring of patients with schizophrenia usually show abnormal motor skills that might be understood as indicators of the possible future development of the disease (Keshavan, Diwadkar, Montrose, Rajarethinam, & Sweeney, 2005). Within unaffected first-degree relatives, similar domains seem to be affected even when not suffering the disease, including language, spatial ability, executive functions, and attention (Snitz et al., 2006).

Regarding patients diagnosed with schizophrenia, cognitive decline has been described since the first phases of the disease as it has been shown with first psychotic episode patients (see Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009 for a review). In this phase of the disease, alterations have been described in numerous cognitive domains such as processing speed, verbal memory, attention, non-verbal memory and overall cognition (McCleery et al., 2014; Mesholam-Gately et al., 2009). Greatest impairments have been pointed out for processing speed and verbal memory,

which showed the largest effect sizes when comparing patients with normal controls (Mesholam-Gately et al., 2009). Cognitive impairment seems to maintain stable over years (Bozikas & Andreou, 2011; Napal et al., 2012), leading to a similar cognitive profile in chronic patients (Fioravanti, Bianchi, & Cinti, 2012; Heinrichs & Zakzanis, 1998). Thus, chronic patients with schizophrenia show a global cognitive decline involving different domains such as general IQ, processing speed, verbal ability, fluency, working memory, verbal and visual memory, reasoning, executive functioning, and attention (Heinrichs & Zakzanis, 1998; Keefe & Harvey, 2012; Schaefer, Giangrande, Weinberger, & Dickinson, 2013). As in previous stages of the disease, processing speed and verbal memory show the highest level of impairment among patients (Heinrichs & Zakzanis, 1998; Schaefer et al., 2013), highlighting again their relevance on this pathology independently of disease stage.

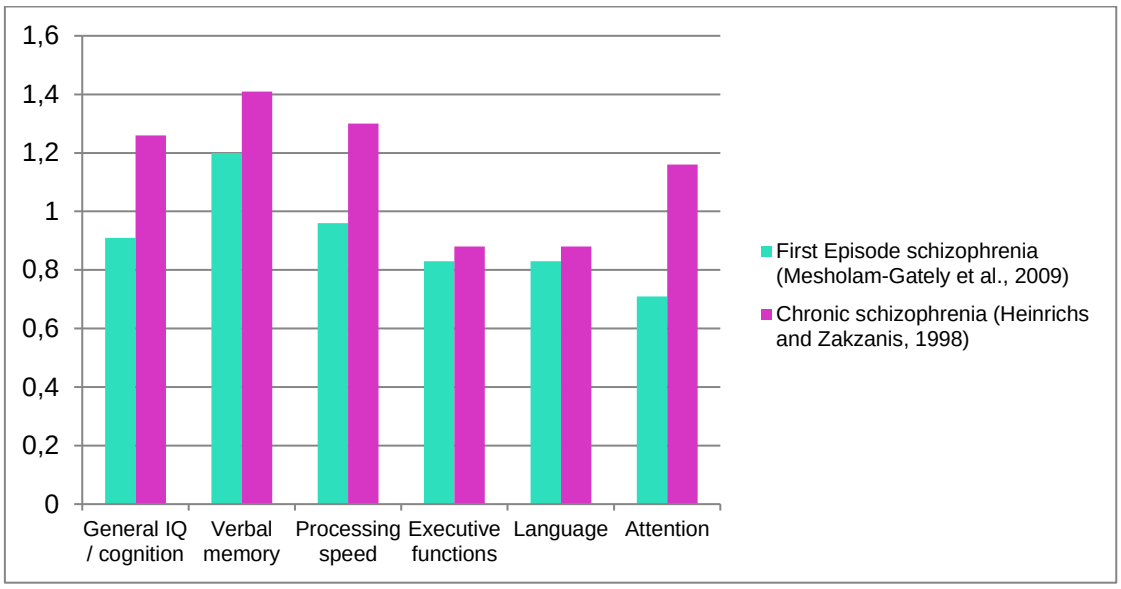

Figure 1. Mean effect sizes (Cohen's d) for cognitive impairment in first episode and chronic schizophrenia (figure made with the effect sizes' values extracted from Mesholam-Gately et al's., 2009 and Heinrichs and Zakzani's 1998 meta-analyses).

Therefore, cognitive impairment seems to be present in all patients and through all stages of the disease. However, some authors have relied on the idea that it is possible

to be diagnosed with schizophrenia and still not show cognitive impairment (Palmer et al., 1997). Nevertheless, these theories have been largely refuted by most of the available bibliography about schizophrenia and cognitive impairment (Keefe & Harvey, 2012; Wilk et al., 2005). The hypothesis supporting intact cognition in some patients with schizophrenia could come from methodological aspects related to how cognitive decline is measured nowadays. One of the most commonly used methods for identifying the presence of cognitive impairment in patients with schizophrenia is to compare their performance to a HC group's performance or to normative data (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997; Reichenberg, 2010; Reichenberg et al., 2009; Schretlen et al., 2007). Using this approach, patients with schizophrenia can appear as subjects with non-impaired cognition (Palmer et al., 1997) in comparison with a normative group. However, patients' cognitive performance can be worse than expected from their premorbid cognitive performance or by the expected level of performance based on their sociodemographic variables (Kremen et al., 2000). In addition, using this methodology, the percentage of patients with schizophrenia classified as cognitively impaired can vary from 54% to 84% depending on the criteria applied when establishing a cut off (Reichenberg et al., 2009). To respond to this issue, some authors have suggested that cognitive impairment should be studied relative to each patient's predicted performance taking into account their premorbid functioning or sociodemographic variables (Wilk et al., 2005). In order to achieve this aim, different approaches have been suggested. One of the most plausible ones is the use of regression-based norms (Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008; Testa, Winicki, Pearlson, Gordon, & Schretlen, 2009). This methodology controls for subjects premorbid cognitive functioning as well as for sociodemographic variables such as sex, years of education or age in order to obtain predicted cognitive performance scores. This allows establishing

cognitive impairment based on patient's own functioning by means of creating a discrepancy score that compares the predicted (expected) cognitive score and the obtained one. Regression-based norms have been used in order to study cognitive impairment in both pathological (Harnett, Godfrey, & Knight, 2004; Knight, McMahon, Green, & Murray Skeaff, 2006) and non-pathological samples (Schretlen et al., 2008; Testa et al., 2009) samples. However, up to date, and although some preliminary attempts have been performed (Testa & Schretlen, 2006), the discriminant capability of cognitive discrepancy scores has not been tested for patients with schizophrenia.

2.5.2. Social cognition impairment.

Social cognition (SC) is defined as the capability of perceiving, interpreting and generating responses to others' beliefs, thoughts and intentions and it includes those mental processes that are necessary to interpret social clues that are used to make those inferences (M. F. Green et al., 2008; Savla, Vella, Armstrong, Penn, & Twamley, 2013). This domain is conceptualized as formed by four different subdomains: a) theory of mind (ToM): the capability of represent others mental states and make inferences about others' beliefs; b) social perception (SP): the capability of perceive, decode and interpret others' social cues; c) emotion perception/processing (EP): the capability of perceive and using emotional information, and d) attributional style (AS): the manner in which one subject interprets and explains positive and negative social events (Pinkham et al., 2014). SC deficits have been described in patients with schizophrenia (Savla et al., 2013). Despite having received more attention in literature during last years, this field is not yet as developed as in the case of other basic cognitive domains. Nevertheless, SC impairment has been identified even in non-affected relatives of patients with schizophrenia in subdomains such as SP, AS and mentalizing (Lavoie et al., 2013). SC impairment has been described to be present also at early phases of the disease and it has been detected

in patients with a first episode of psychosis (Healey, Bartholomeusz, & Penn, 2016; Ludwig, Pinkham, Harvey, Kelsven, & Penn, 2017). However, not all SC subdomains (e.g.: ToM, EP, SP, and AS) present the same magnitude of impairment and some of them seem to be more affected than others in early phases (Healey et al., 2016; Ludwig et al., 2017). First episode psychosis patients show the largest impairments regarding ToM (both verbal and non-verbal) and EP when compared to HC (Healey et al., 2016; Ludwig et al., 2017). SP deficits have been also found in these patients (Healey et al., 2016). However, according to a recent review, SP has been less studied than EP and ToM in first episode psychosis (Healey et al., 2016). Finally, results are more inconclusive for AS deficits, and worse performance has been described in these patients for some but not all of its dimensions (Healey et al., 2016). Therefore, and following the rationale proposed with other cognitive domains, SC impairment has been suggested as a possible additional endophenotype of this disease (M. F. Green, Horan, & Lee, 2015).

SC impairment has shown to be stable across time and at different stages of the disease. Therefore, these deficits are also present in the chronic phase of this pathology. Patients with chronic schizophrenia showed similar SC impairment profile to first episode patients (Savla et al., 2013). However, given that SC impairment in chronic schizophrenia has been more studied than in first episode psychosis, evidences are more robust for some of the subdomains. Greatest deficits are observed in ToM and SP followed by EP (see Savla et al., 2013 for a meta-analysis). On the contrary, and according to the cited meta-analysis, patients do not seem to show significant deficits in AS (Savla et al., 2013), possibly due to a lack of studies assessing its impairment in schizophrenia. Especially, and although less studied than other subdomains, SP is described as the most impaired subdomain in these patients at least in the chronic phase of the disease (Savla et al., 2013), highlighting its role in the pathology.

However, and according to the previously mentioned meta-analysis and other researches, many measures usually used to study SC impairment in schizophrenia present critical limitations (Pinkham et al., 2014; Savla et al., 2013). These limitations are mainly related to the lack of adaptation and validation of those measures in schizophrenia population (Pinkham et al., 2014; Savla et al., 2013). In addition, many drawbacks have been detected when studying SC impairment in these patients. Most of the shortcomings are related with the scarce research available about SC measures' psychometric properties. These complications are more pronounced when using these measures in longitudinal studies and clinical trials (Grant, Lawrence, Preti, Wykes, & Cella, 2017; Pinkham et al., 2014; Pinkham, Penn, Green, & Harvey, 2016). In order to assess and address this issue, the Social Cognition Psychometric Evaluation (SCOPE) initiative was created in 2013 (Pinkham et al., 2014) with the aims of select and define the central social cognitive subdomains and assess the psychometric properties of some of the most used SC measures (Pinkham et al., 2014). Studies carried out in the context of this initiative have described different psychometric adequacy for the assessment tools of each of the SC subdomains. While selected ToM and EP tools showed good psychometric properties in both the first and the second studies (Pinkham, Harvey, & Penn, 2018; Pinkham et al., 2016), assessment tools regarding SP and AS domains showed poor psychometric properties in the first study (Pinkham et al., 2016). After changing the selected tools for assessing both domains, AS instrument showed better properties in the second study (Pinkham et al., 2018). However, on the second study of the initiative, measures used to assess SP still showed weak psychometric properties (Pinkham et al., 2018). Given this, these measures were not further recommended for their use in clinical trials and longitudinal studies in schizophrenia (Pinkham et al., 2018, 2016). These results have left the SP subdomain without any representative measure, which in authors' words

"underscores the need to continue improving existing measures and to develop new ones" (Pinkham et al., 2018). In addition, and according to the consulted literature, only three of the available SP measures present equivalent forms: The Social Attribution Test – Multiple Choice (SAT-MC) (Bell, Fiszdon, Greig, & Wexler, 2010), The Awareness of Social Inferences Test (TASIT) (McDonald et al., 2006), and The Trustworthiness/Approachability Task (Adolphs, Tranel, & Damasio, 1998). Moreover, up to date, there is only one SP measure available to assess this domain in Spanish-speaking patients with schizophrenia [The Social Perception Scale (SPS) (García, Fuentes, Ruíz, Gallach, & Roder, 2003)]. This lack of reliable SP tools hinders the assessment of this domain especially in Spanish-speaking patients with schizophrenia, mainly in longitudinal studies and clinical trials.

2.5.3. Functional outcome and the role of cognition and social cognition.

Both cognition and SC impairment have shown to be related to functional outcome in patients with schizophrenia (Fett et al., 2011; Fu, Czajkowski, Rund, & Torgalsbøen, 2017; M. F. Green, 2016; Hoe, Nakagami, Green, & Brekke, 2012; Schmidt, Mueller, & Roder, 2011). Within basic cognitive processes, social functioning has been related to attention, verbal learning and memory, verbal working memory, and reasoning and problem solving (Fett et al., 2011; Fu et al., 2017). More precisely, verbal learning and memory seem to be related to social behavior, while reasoning and problem solving show a relationship with social problem solving as well as attention and vigilance with social skills (Fett et al., 2011). However, and according to the last meta-analysis available, SC (mainly ToM) seems to be related to community functioning to a greater extent than basic cognitive processes (Fett et al., 2011). Other SC subdomains that are highly related to functional outcome in patients with schizophrenia are SP and EP, which show a relationship with social behavior and social skills respectively (Fett et al., 2011).

Nevertheless, in order to explain deeper the relationship between cognition, SC and functionality in schizophrenia, some authors also defend a more complex model in which the relationship between cognition and functionality would be mediated by SC (Schmidt et al., 2011). These findings support the idea that, although basic cognitive processes have been reported to underlie SC (Hoe et al., 2012), both are separate entities that interact in some way with social functioning in these patients. In fact, attending to latest studies, and taking into account the strong relationship showed between SC and functionality in schizophrenia, SC should be a crucial target when designing and implementing interventions for these patients (Fett et al., 2011; Hoe et al., 2012; Schmidt et al., 2011).

2.5.4. Cognitive impairment as diagnosis criterion for schizophrenia.

Even though cognitive impairment among patients with schizophrenia has been well described through most of the existing literature, nowadays this feature is not included as diagnostic criterion on diagnostic manuals, such as the DSM-V (American Psychiatric Association, 2015). Reservations regarding the inclusion of cognitive impairment as a diagnosis criterion for schizophrenia come, in part, from the lack of information about cognitive measures' capability to discriminate between patients and normal population (Barch & Keefe, 2010; Keefe, 2008; Keefe & Fenton, 2007). Doubts also come from the unassessed capability of cognitive impairment to establish the point of rarity between schizophrenia and other diagnosis such as schizoaffective disorder (Barch & Keefe, 2010; Keefe, 2008; Keefe & Fenton, 2007). Some authors have argued in the past years about the importance of including cognitive impairment as a diagnostic criterion. According to these authors, two main challenges can be identified when assessing cognitive impairment in order to include it in diagnostic manuals (Barch & Keefe, 2010; Keefe, 2008; Keefe & Fenton, 2007). The first one refers to the cognitive assessment methods available nowadays. Time constrictions when assessing patients with

schizophrenia in clinical environments highlight the need of brief and well validated cognitive assessment tools or batteries (Barch & Keefe, 2010; Keefe, 2008; Keefe & Fenton, 2007). The second one makes reference to the collection of historical information (e.g.: educational history, premorbid IQ or parental educational level) in order to establish the possible cognitive decline based on subject's premorbid functioning (Barch & Keefe, 2010; Keefe, 2008; Keefe & Fenton, 2007). This challenge is especially relevant in those cases in which patients present a high performance before the onset of the disease that declines after the appearance of the pathology, but it is still in the normal range. That classification as "normal functioning" can be prejudicial for the patient, who may not receive the necessary cognitive intervention. This second challenge emphasizes the importance of identifying the presence of cognitive impairment inherent to the pathology and not caused by other confounding variables in these patients (Keefe, 2008; Keefe & Fenton, 2007). Due to the frequently used methods for establishing the presence of cognitive impairment previously mentioned (comparison with a HC or a normative group), this challenge highlights the need of using approaches such as regression-based norms when assessing cognitive impairment in schizophrenia.

2.5.5. Diagnostic tools available for cognitive impairment in Spanish-speaking patients with schizophrenia.

Overall, there is a lack of available cognitive measures that overcome the two previously mentioned challenges for including cognitive decline as diagnostic criterion for patients with schizophrenia. Different initiatives have been carried out to establish a consensus about the cognitive batteries used for patients with schizophrenia regarding both cognition and SC measures, with good outcomes for English-speaking patients (M. F. Green & Nuechterlein, 2004; Pinkham et al., 2014). However, and as mentioned, the inclusion of premorbid and historical information in the cognitive assessment of these

patients is not well established. This situation is even more complicated regarding Spanish-speaking patients with schizophrenia due to two main reasons. First, many of the most used cognitive and SC measures are not adapted and validated into Spanish. This implies that some of the used tools might present cultural adaptation flaws and lack of adapted normative data, mainly regarding SC measures. This first shortcoming points out the necessity of culturally adapted and validated cognitive and SC tools for their use with Spanish-speaking patients with schizophrenia.

The second reason refers to the lack of use of measures corrected by patient's sociodemographic and premorbid variables when establishing the existence of an impairment. As previously mentioned, approaches such as regression-based norms and discrepancy scores have just been preliminary used in English-speaking patients with schizophrenia (Testa & Schretlen, 2006). Preliminary attempts have also been carried out in relation to Spanish-speaking samples but only regarding other pathologies than schizophrenia, such as dementia (Del Ser, González-Montalvo, Martínez-Espinosa, Delgado-Villapalos, & Bermejo, 1997). Therefore, the reliability and usage of these cognitive discrepancy scores when classifying patients with schizophrenia and HC still need further investigation in Spanish samples.

2.6. Magnetic Resonance Imaging as Diagnostic Tool for Schizophrenia

Since the first image of a human head was obtained by means of magnetic resonance imaging (MRI) back in 1978 (Geva, 2006), clinical use of this neuroimaging technique has been widely developed and implemented also in the schizophrenia field. The usage of MRI in the study of schizophrenia allows searching for the neuroanatomical and neurofunctional correlates of the disease. Given the fast advances developed in neuroimaging, it is possible nowadays to search for both macro- and microstructural brain abnormalities in patients with schizophrenia. The course of these abnormalities can also

be assessed across different stages of the disease. In addition, combining neuroimaging with cognitive data allows studying the relationship between cognitive performance and different brain areas in these patients. Focusing on neuroanatomical alterations, brain volumetric decreases in different brain areas such as the frontal, the temporal, and the parietal lobe as well as in subcortical brain areas such as the hippocampus and the amygdala have been found in patients with schizophrenia (Shenton, Dickey, Frumin, & McCarley, 2001; Van Erp et al., 2016; Wright et al., 2000). All these volumetric changes are accompanied by the enlargement of the ventricles, possibly one of the most characteristic brain anatomical signs of this pathology (Shenton et al., 2001; Van Erp et al., 2016).

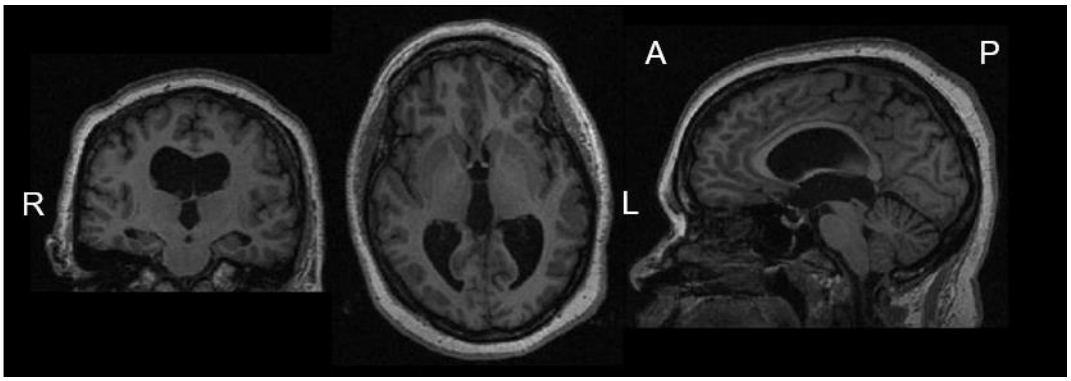

Figure 2. Increased size of the lateral ventricles in a patient with schizophrenia (T1 image corresponds to the brain of one of the patients recruited for the study). R: right; L: left; A: anterior; P: posterior.

2.6.1. White matter abnormalities (diffusion weighted imaging).

Along with the development of advanced neuroimaging techniques, new findings regarding the neuroanatomical basis of the pathology have been found highlighting the importance of white matter (WM) in this disease (Ellison-Wright & Bullmore, 2009). One of the neuroimaging techniques developed for studying WM abnormalities during the last two decades is diffusion tensor imaging (DTI), which uses diffusion-weighted images

(DWI) in order to assess brain WM integrity. DTI technique allows the study and measurement of macroscopic axonal organization by means of the random movement of water molecules (called Brownian motion) along axons (Le Bihan et al., 2001; Mori & Zhang, 2006). In order to study WM integrity, color maps are generated indicating the type of fiber depending on the connected areas namely: a) interhemispheric fibers: connecting both hemispheres; b) longitudinally associative fibers: connecting areas within the same hemisphere, and c) projective fibers: connecting subcortical and cortical brain areas (Oishi, Faria, van Zijl, & Mori, 2010).

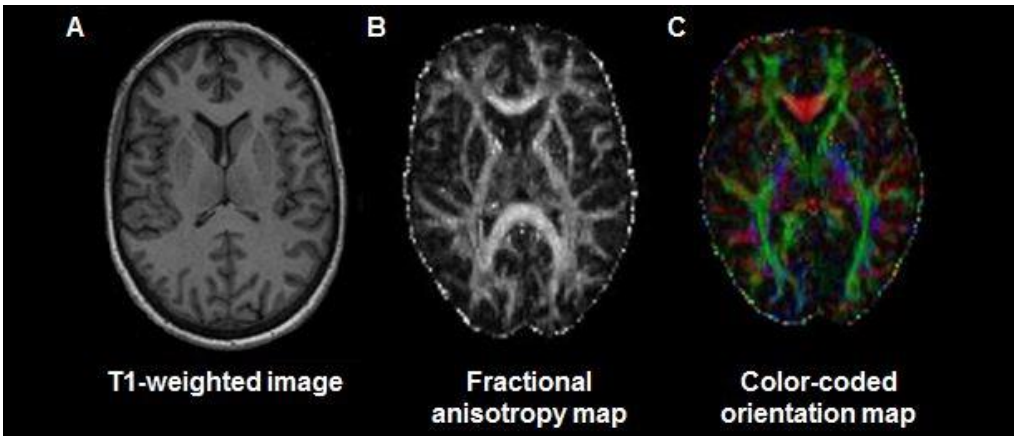

Figure 3. Examples of (A) conventional MRI T1-weighted image; (B) fractional anisotropy map and (C) color-coded orientation map. For the color-coded images, the intensity (brightness) is proportional to the anisotropy information (same as in anisotropy map, B) and the different colors, red, green, and blue, represent fibers running along the right-left, anterior-posterior, and inferior-superior axes, respectively [figure created using brain images of one of the participants recruited for the study, based on Oishi et al., (2010)].

Using this technique, different WM integrity indices can be obtained. Mean fractional anisotropy (FA) is the most commonly reported one and reflects the directionality of the water molecules' diffusion along the axons (Mori & Zhang, 2006). However, other WM integrity indices can also be obtained by means of DTI, namely:

mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and mode of anisotropy (MO). These measures allow to infer information about WM integrity, myelin loss, axonal damage, or the existence of crossing fibers among others (Ennis & Kindlmann, 2006; Jones, Knösche, & Turner, 2013; Le Bihan et al., 2001; Mori & Zhang, 2006). By means of DTI two main different approaches can be distinguished: a) a whole brain approach: including tract-based spatial statistics (TBSS). This approach assesses WM integrity alterations by means of registering FA images of different patients into a common anatomical space. To this extent, a whole brain fibers representation common to the whole group is created. This technique allows performing group whole brain WM integrity comparisons or correlation analyses; and b) a tract specific approach: including probabilistic tractography. This approach allows individual WM fibers representation in order to study one subject's structural connectivity in her/his own anatomical space. Thus, a specific WM tract can be isolated by means of reconstructing the fibers that connect different brain areas (seed and target). In this way, WM abnormalities in specific tracts can be studied. In addition, obtained tracts can be normalized into a common space in order to perform group analyses. Tractography has shown to be more specific than other approaches when studying WM brain abnormalities in schizophrenia (Kanaan et al., 2006). These two approaches have identified the presence of brain WM integrity alterations and anatomical disconnection in patients with schizophrenia by means of the study of both whole brain WM fibers and specific WM tracts. Thus, patients with schizophrenia show anatomical connectivity alterations in widespread brain areas including both intra- and interhemispheric fibers (Kelly et al., 2018), but these alterations seem to be mainly present in medial frontal circuits (Buchsbaum et al., 2006; Ellison-Wright & Bullmore, 2009; Ellison-Wright et al., 2014; Kelly et al., 2018; Mamah et al., 2010; Wheeler & Voineskos, 2014). Specifically, WM fibers of two left brain areas have

been described to be altered in patients with schizophrenia (see Ellison-Wright & Bullmore, 2009 for a meta-analysis). The first one includes left frontal WM and comprises WM interhemispheric fibers traversing the genu of the corpus callosum (gCC) as well as the cingulum, the anterior thalamic radiation, the corticobulbar tract, and the inferior fronto-occipital fasciculus. The second one involves the left temporal WM and includes inter-hemispheric fibers via the splenium of the corpus callosum (sCC) as well as the fornix, the inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus (Ellison-Wright & Bullmore, 2009). Other WM fibers that have shown altered integrity in schizophrenia are the anterior corona radiata, the internal and external capsule, the superior longitudinal fasciculus, the uncinated fasciculus or the fornix (Kelly et al., 2018; Skudlarski et al., 2013).

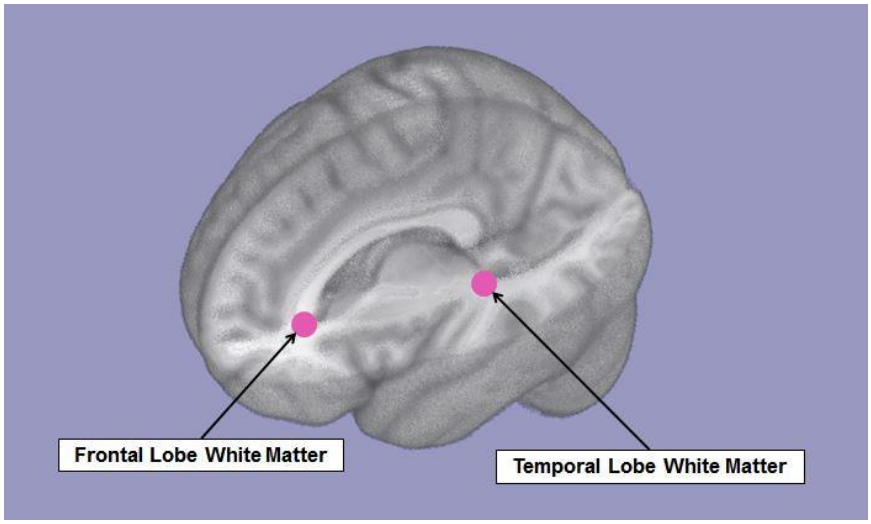

Figure 4. WM regional FA reductions in schizophrenia. Temporal and frontal areas (figure created based on Ellison-Wright and Bullmore, 2009).

2.6.1.1. White matter asymmetry in schizophrenia

As it can be inferred from Ellison-Wright and Bullmore's meta-analysis, interhemispheric fibers, and the corpus callosum (CC) specifically, are mainly affected in schizophrenia (Ellison-Wright & Bullmore, 2009; Ellison-Wright et al., 2014; Knöchel

et al., 2012; Kubicki et al., 2008). Brain interhemispheric fibers alteration might cause aberrant connectivity between both hemispheres in patients with schizophrenia (Choi et al., 2011; Ellison-Wright et al., 2014; Pol et al., 2004; Wheeler & Voineskos, 2014). This interhemispheric alteration has also been described to account for alterations of the normal brain asymmetry seen in these patients (Innocenti, Ansermet, & Parnas, 2003; Park et al., 2004; Ribolsi, Daskalakis, Siracusano, & Koch, 2014). As first stated by Crow in 1989, brain asymmetry alterations and schizophrenia might be two very related entities (Crow et al., 1989). This author proposed that altered development of brain asymmetry could be on the basis of the disease's onset and that genes involved in both brain asymmetry and schizophrenia could be related (Crow et al., 1989). Crow (1997) also stated that language, one of the most representative impaired domains in schizophrenia, might result of an incomplete hemispheric specialization. This idea has been supported by other studies that have found a relationship between human brain asymmetries and language (Catani et al., 2007; Crow, 1997; Mitchell & Crow, 2005; Pearlson & Folley, 2008).

Abnormal asymmetry in patients with schizophrenia is mainly characterized by a reduced leftward asymmetry compared to HC. That is, while HC show a greater WM integrity in left hemisphere compared to the right hemisphere, this asymmetry is reduced or even inversed in patients with schizophrenia (see Ribolsi et al., 2014 for a review). In fact, this pattern of abnormal asymmetry has been found regarding WM anisotropy of the gCC in patients with schizophrenia (Park et al., 2004). However, the opposite alterations (reduced right greater than left hemisphere asymmetries) have also been described among patients with schizophrenia regarding some WM tracts such as the sCC (Park et al., 2004). Although these WM integrity asymmetry alterations have not been widely studied in schizophrenia, some specific tracts have been identified as impaired. Thus, asymmetry

abnormalities have been described in these patients regarding the uncinate fasciculus, the inferior fronto-occipital fasciculus, the superior fronto-occipital fasciculus, and the anterior cingulum bundle (see Ribolsi et al., 2014 for a review). However, asymmetry alterations in patients with schizophrenia have not been well described. Specifically, there is a lack of studies focused on assessing fibers connecting anterior and posterior parts of the CC with frontal and occipital lobes respectively (anterior/frontal cortical projections of the gCC and posterior/occipital cortical projections of the sCC).

2.6.1.2. Abnormal white matter and cognition in schizophrenia

The study of the neuroanatomical correlates of cognition in patients with schizophrenia has been widely studied. Specifically, the role of WM integrity in cognition in patients with schizophrenia has been a focus of study through the last decade. Researches have described the relationship between different WM fibers and different cognitive domains (Dwork, Mancevski, & Rosoklija, 2007; A. E. Green, Croft, Maller, & Fitzgerald, 2016; Karbasforoushan, Duffy, Blackford, & Woodward, 2015; Karlsgodt et al., 2008). Thus, regarding two of the most altered cognitive domains in schizophrenia, processing speed and verbal memory, studies have found a relationship between those and commissural and associative WM fibers mainly (A. E. Green et al., 2016; Karbasforoushan et al., 2015). Processing speed performance has been related to the cingulum, the CC, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the fornix, and WM fibers traversing the superior and inferior frontal gyrus (Dwork et al., 2007; Karbasforoushan et al., 2015; Liu et al., 2013). Neuroanatomical correlates of verbal memory have been described regarding the uncinate fasciculus, the inferior longitudinal fasciculus, the fronto-occipital fasciculus, the fornix, the cingulum, and WM fibers adjacent to the hippocampus (Dwork et al., 2007; M. F. Green, 2016; Liu et al., 2013). Regarding other cognitive functions, and more generally, attention,

executive functioning and working memory performance seem to be related to WM integrity of fronto-temporal and interhemispheric fibers such as the uncinate fasciculus, the cingulum or the CC (Dwork et al., 2007; Karlsgodt et al., 2008; Voineskos et al., 2013).

Implications of abnormal brain asymmetries on cognition in schizophrenia have been studied predominantly in relation to volumetric and brain morphometric characteristics (see Antonova, Sharma, Morris, & Kumari, 2004 for a review). These studies have identified alterations in length of the lateral sulcus, width of Sylvian fissure, and anterior frontal and occipital asymmetries to be related to performance on measures of expressive language, attention or verbal memory in schizophrenia (DeLisi et al., 1997; Hoff et al., 1992). However, up to date, no study has assessed the implications of the alterations in cerebral WM integrity asymmetry of the anterior/frontal cortical projections (gCC) and posterior/occipital cortical projections (sCC) in cognitive dysfunction in persons with schizophrenia.

III. Approach to the present study and objectives

3. Approach to the present study and objectives

The present thesis includes four studies that aim to improve the identification and diagnosis of schizophrenia based on both neuropsychological and neuroimaging variables. The comprised studies present: 1) the comparison of raw and predicted cognitive scores as discrimination indices in schizophrenia; 2) an Spanish adaptation and validation of a SP assessment tool for patients with schizophrenia and HC; 3) two short equivalent forms of a SP assessment tool for Spanish speaking patients with schizophrenia, and 4) the characteristics and correlates of brain asymmetry with cognition in patients with schizophrenia.

Paper I

"Cognitive scores as a potential diagnostic tool in schizophrenia: the use of raw and discrepancy scores"

Background

Cognitive scores could be a useful tool when discriminating between patients with schizophrenia and non-psychiatric population. However, whether these scores can contribute to the accurate diagnosis of the disease is still unclear.

Objectives

- The main objective was to test the usefulness of cognitive raw scores to discriminate between patients with schizophrenia and HC and their diagnostic utility.
- The second objective was to assess the discrimination ability of cognitive discrepancy scores, obtained after controlling for sociodemographic and premorbid characteristics by means of regression-based norms, when comparing patients with schizophrenia and HC.

Hypothesis

- Raw cognitive scores will optimally discriminate between patients with schizophrenia and HC.
- Cognitive discrepancy scores will discriminate and classify patients with schizophrenia and HC better than raw cognitive scores, after taking into account subject's sociodemographic and premorbid characteristics.

Paper II

"Spanish adaptation and validation of the Situational Feature Recognition Test 2 (SFRT-2) in patients with schizophrenia and healthy controls"

Background

SP impairment is common among patients with schizophrenia. However, nowadays only one measure of SP is available in Spanish and none of the existing SP measures have been adapted to native Spanish-speaking population. The scarce number of SP tests available highlights the need of reliable instruments in Spanish.

Objectives

- The main objective was to adapt and validate the Situational Feature Recognition Test 2 (SFRT-2) (a SP assessment tool) by using a sample of both native Spanish-speaking patients with schizophrenia and HC.

Hypothesis

- The Spanish adaptation of the SFRT-2 will show an adequate reliability by means of high internal consistency indices.
- The Spanish adaptation of the SFRT-2 will show good concurrent validity when assessing its relationship with other social cognitive measures.
- The Spanish adaptation of the SFRT-2 will show good discriminant validity when classifying patients with schizophrenia and HC.

Paper III

"Equivalent short forms of the Situational Feature Recognition Test 2: psychometric properties and analysis of inter-form equivalence and test-retest reliability"

Background

Equivalent forms of SP measures are useful for longitudinal studies with patients with schizophrenia. However, up to date, few equivalent forms are available for assessing this domain. In addition, SP measures are usually time consuming, compromising patients' performance.

Objectives

- The main objective was to develop two equivalent short forms of the original SFRT-2 in a sample of native Spanish-speaking patients with schizophrenia.
- The second aim was to assess the psychometric properties of the short forms from a classical test theory perspective, in terms of (1) internal consistency, (2) inter-form equivalence, (3) sensitivity to change, (4) test-retest reliability, (5) convergent and discriminant validity in relation to other SC measures and cognition scores respectively, and (6) convergent validity in relation to functional impairment and symptom severity.

Hypothesis

- (1) short forms would have medium to high internal consistency, (2) both short forms would be equivalent in both test and re-test times, (3) short forms' scores would show sensitivity to change after a cognitive rehabilitation intervention, (4) both forms would present medium to high test-retest reliability scores, (5) both forms would correlate with other SC measures and, to a lesser extent, to basic cognitive processes' measures, and (6) both forms would show a medium to high relationship with functional outcome and symptom severity scores.

Paper IV

"Altered frontal white matter asymmetry and its implications for cognition in schizophrenia: A tractography study"

Background

WM alterations are well documented in schizophrenia. Abnormalities in interhemispheric fibers appear to account for altered WM asymmetry. However, the regional specificity (e.g., frontal versus occipital) of these alterations and their potential contribution to cognitive dysfunction in schizophrenia remain unknown.

Objectives

- The main objective was to assess the whole brain WM integrity differences between patients with schizophrenia and HC.
- The second objective was to examine cerebral asymmetry in anterior frontal cortical projections of the genu of the corpus callosum and posterior occipital cortical projections of the splenium of the corpus callosum in patients and HC by means of probabilistic tractography.
- The third objective was to determine whether any observed differences in WM integrity asymmetry contribute to cognitive dysfunction in schizophrenia.

Hypothesis

- Patients with schizophrenia would show reduced WM integrity compared to HC specifically in fronto-temporal and occipital areas.
- WM asymmetry of patients would be altered compared to HC.
- WM asymmetry alterations would correlate with cognitive dysfunction in patients with schizophrenia.

IV. Methods

4. Methods

4.1. Studies Sample

This thesis includes different pathological and non-pathological samples depending on the study. Patients with schizophrenia for studies I, II and III came from the same dataset recruited from the Osakidetza Public Mental Health Services in Biscay (Spain). However, HC for studies I and II came from different datasets. Study III has no HC sample. Finally, whole data (schizophrenia and HC) of study IV came from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) dataset. This recruitment as well as samples' characteristics will be further and widely explained in the following section.

4.1.1. Patients with schizophrenia.

4.1.1.1. Studies I, II and III.

Patients with schizophrenia were recruited from the Osakidetza Public Mental Health Services in Biscay (Spain). Patients were enrolled in a clinical trial which assessed the efficacy of the REHACOP cognitive rehabilitation program for psychosis (Peña et al., 2016). For papers I and II, only those scores obtained before the implementation of the cognitive rehabilitation program were used. For study III, both pre- and post-intervention scores were used.

Inclusion criteria:

a) Being diagnosed with schizophrenia based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2000), using the Structured Clinical Interview for DSM-IV (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997).

Exclusion criteria:

a) Having evidence of alcohol or drug abuse in the previous 30 days.

b) Having a previous episode of loss of consciousness.

c) Mental retardation.

d) Substance dependence.

e) Having any relevant neurological or medical condition.

4.1.1.2. Study IV.

Patients were recruited from the Baltimore site of the B-SNIP study.

Inclusion criteria:

a) Having schizophrenia diagnosis based on clinical data and the SCID-I for DSM-IV (First et al., 1997).

b) Being clinically stable.

Exclusion criteria:

a) A known neurological illness.

b) Current substance use detected or verified by urine toxicology screens.

4.1.2. Healthy controls.

4.1.2.1. Study I.

A group of HC was recruited from the Normacog study (Del Pino, Peña, Schretlen, Ibarretxe-Bilbao, & Ojeda, 2015).

Exclusion criteria

a) Having a medical history of physical or mental illness.

b) Presenting severe cognitive impairment.

c) Presenting sensory limitations (visual or auditory) which could not be adequately compensated by corrections (glasses or hearing aids).

4.1.2.2. Study II.

A group of HC was recruited by means of word-of-mouth and snowball methods.

4.1.2.3. Study IV.

A group of HC was recruited from the Baltimore site of the B-SNIP study.

Inclusion criteria

a) No diagnosis in axis I based on the SCID-I (First et al., 1997).

Exclusion criteria

a) A known neurological illness.

b) Current substance use detected or verified by urine toxicology screens.

4.2. Cognitive, Social Cognition, Functional and Clinical Measures

4.2.1. Study I.

Patients with schizophrenia and HC underwent an exhaustive neuropsychological assessment which included measures of a) premorbid IQ [the Word Accentuation Test (WAT), the Spanish version of the National Adult Reading Test (NART), which consisted of 30 words to be read aloud with the correct accentuation by participants (Del Ser et al., 1997)]; b) verbal memory [the Hopkins Verbal Learning Test-revised (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998), which is included in the MATRICS Consensus cognitive battery as a recommended measure of verbal learning (Nuechterlein et al., 2008). Trials one, two and three were added and used as total recall verbal memory index, and the fourth trial was used as a delayed recall verbal memory index]; and c) processing speed [the Trail Making Test part A (TMT-A) (Reitan & Wolfson, 1985). TMT-A total time was used as a measure of processing speed].

4.2.2. Studies II and III.

Patients with schizophrenia and HC were assessed by means of the SFRT-2 (Corrigan, Silverman, Stephenson, Nugent-Hirschbeck, & Buican, 1996) as a measure of SP. In addition, patients were also assessed by means of other SC measures such as the Strange Stories Test for Theory of Mind (Happé, 1994) for ToM, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) for EP (Mayer, Salovey, & Caruso, 2002),

and the self-serving bias index of the Attributional Style Questionnaire (ASQ) for AS (Peterson et al., 1982; P. Sanjuan & Magallares, 2006). Patients were also assessed using other cognitive measures such as the Word Accentuation Test (WAT) (Del Ser et al., 1997) for assessing premorbid IQ, the HVLT-R for verbal learning and memory (Benedict et al., 1998), the Trail Making Test, parts A and B (TMT-A and TMT-B) for processing speed and cognitive flexibility (Reitan & Wolfson, 1985); the Stroop Color-Word Interference Test (SCWIT) for inhibition (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006), and the Calibrated Ideational Fluency Assessment (CIFA) (Schretlen & Vannorsdall, 2010) for verbal phonetic fluency. In addition, patients were also assessed using different functionality variables such as the University of California, San Diego (UCSD) Performance-Based Skills Assessment-UPSA (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001) to assess functional competence and the Global Assessment of Functioning Scale (GAF) (Frances, Pincus, & First, 1994) to assess global functioning and psychiatric symptom severity. For study II, recruited HC were assessed only with the SFRT-2 once. Given the aim of the study, no HC were included on study III.

4.2.3. Study IV.

Both patients and HC were assessed using a combination of learning and delayed recall from the HVLT-R (Benedict et al., 1998) in order to assess verbal memory whereas processing speed was assessed using the sum of letters (3 and 6) and patterns (3 and 6) of the Salthouse Perceptual Comparison Test (Salthouse & Babcock, 1991). In addition, the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used to assess patients' clinical symptoms.

4.3. Neuroimaging Acquisition

4.3.1. Diffusion weighted images.

Diffusion-weighted images were obtained from a scanner placed at Baltimore (USA) as described in Skudlarski, et al. (2013) (see specific characteristics of the image acquisition process in Table 3). The scanner used single-shot spin-echo planar imaging (EPI) with a twice-refocused balance echo sequence.

Table 3

Characteristics of DWI acquisition.

	Baltimore scanner (prior to machine change)	**Baltimore scanner (after machine change)**
Model	Siemens Magnetom Trio. 3T	Siemens Magnetom Trio. 3T
TR	6,700 ms	6,300 ms
TE	92 ms	86 ms
FOV	230 mm	220 mm
b value 2	1,000 s/mm^2	1,000 s/mm^2
Directions	25*	25*
Slices	48 contiguous	48 contiguous
Voxel size	1.8 x 1.8 x 3.0 mm^3	1.7 x 1.7 x 3.0 mm^3

TR, repetition time; TE, echo time; FOV, field of view; ms, milliseconds; cm, centimeters; s/mm^2, seconds per squared millimeters; mm^3, cubic millimeters.

*Due to a movement artifact, 5 directions were removed from the original 30 directions.

4.3.2. T1 brain images.

High resolution isotropic T1-weighted MP-RAGE sequences were acquired in a 3T scanner placed at Baltimore (see specific characteristics of the image acquisition process in Table 4). These images were only used for registration purposes, as it will be later described.

Table 4

Characteristics of T1 acquisition.

	Baltimore scanner
Model	Siemens Magnetom Trio. 3T
TR	2300 ms
TE	2.91 ms
Flip angle	9º
Slices	160
Matrix	256 x 240 mm
Voxel Size	1 x 1 x 1.2 mm

TR, repetition time; TE, echo time; ms, milliseconds; mm, millimeters.

4.4. Neuroimaging Pre-processing

FMRIB Software Library (FSL) software (Smith et al., 2004) was used in order to perform diffusion image processing. All images were visually inspected. Distortions were corrected using eddy current correction (Andersson & Sotiropoulos, 2016) and the non-diffusion image (B0) was extracted. Brain Extraction Tool (BET) (Smith, 2002), was used to remove non-brain tissue. After this, FA, MD, AD, RD and MO maps were generated using DTIFIT, implemented in the FMRIB's diffusion toolbox.

4.4.1. Tract-based spatial statistic.

Group differences in FA, MD, AD, RD and MO were assessed using TBSS (Smith et al., 2006). By means of TBSS, data were prepared to apply a nonlinear registration of all FA images into standard space. The mean FA image was created using a threshold of 0.2 and thinned to create a “mean FA skeleton” which represents the centers of all tracts common to the group. Non-FA (MD, AD, RD and MO) data were analyzed using “tbss non FA” script, applying the original non lineal registration to data and merging all

subjects' warped MD, AD, RD and MO data into a 4D file. This 4D file was then projected onto the original mean FA skeleton to create the 4D-projected data. The aforementioned process was also performed in a subsample of 10 patients with schizophrenia and 10 HC selected for tractography analyses. This subsample was selected based on the quality of their DWI and only images with satisfactory quality for tractography (i.e.: no artifacts) were included. The whole brain overall FA values as well as the mean FA, MD, AD, RD and MO values of the different areas of the CC were obtained by means of TBSS in this subsample. Regions of interest (ROIs) of the gCC, the sCC and the body of the CC (bCC) were obtained from the Johns Hopkins University (JHU) WM atlas implemented in FSL. The obtained values were exported to SPSS for further analyses.

4.4.2. Probabilistic tractography.

gCC and frontal area, seeds and waypoint masks respectively, were extracted from the JHU atlas (implemented in FSL) and Craddock atlas (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012) in order to perform tractography analyses. These were selected based on the whole brain results obtained after *randomise* was performed which pointed to a left fronto-temporal area of WM in which patients showed a lower mean FA than HC. Therefore, the rationale for performing probabilistic tractography was to assess the characteristics of some of the WM fibers that traversed that area. An automatic registration between the selected mask and the FA map was performed using the T1 image as a reference. Afterwards, gCC masks were manually corrected on each participant's color-coded FA maps based on the MRI Atlas of Human White Matter (Oishi et al., 2010). BedpostX and ProbtrackX (implemented in FSL) were applied in order to obtain WM pathways of interest. Probabilistic connectivity distributions were generated from every voxel in the seed masks, and only those paths that went through the waypoint masks and stopped there were used for analysis. All WM reconstructed trajectories were normalized

by dividing by the number of streamlines that went through the waypoint masks and then thresholded at 5%. Tract-specific FA, MD, AD, RD and MO were obtained for each participant and exported to SPSS. The same process was used to obtain the posterior occipital cortical projections of the sCC interconnecting the sCC and occipital areas. Seeds and waypoints used to obtain this second pathway were set based on the second main area of WM differences described in Ellison-Wright and Bullmore's meta-analysis (Ellison-Wright & Bullmore, 2009).

4.5. Statistical Analyses for Neuropsychological and Clinical Data

All the sociodemographic, neuropsychological and clinical data was assessed using SPSS v.23.

4.5.1. Study I.

Multiple linear regression analyses were performed on the HC group with the three cognitive variables (verbal memory total recall, verbal memory delayed recall and processing speed) as dependent variables and age, years of education and premorbid IQ as predictor variables. Participant's predicted scores were calculated based on the theoretical formula showed in Table 5. The discrepancy scores for each of the cognitive variables were obtained subtracting the predicted scores from the current scores of the participants, based on the methodology proposed by Testa et al., (2009).

Table 5

Theoretical formula applied for calculating predicted scores

Theoretical formula:
*Predicted score = (Age B * Age raw score) + (Years of education B * Years of education raw score) + (Premorbid IQ B * Premorbid raw score) + K*

B: standardized b obtained by means of linear regressions; K: constant.

The Kolmogorov-Smirnov test was used to assess the normality of the variables and the subsequent statistical analyses were performed depending on their normal or non-normal distributions. Differences in sex were assessed using the Chi-square test. Mann-Whitney *U*-tests were used to assess the differences in age, years of education, premorbid IQ and neuropsychological variables between groups. MANCOVA analyses were used to compare neuropsychological performance between patients and HC, adding sex, years of education and premorbid IQ as covariates. Spearman's correlations were performed in order to assess the relationship between cognitive and sociodemographic and premorbid variables. Differences between patients and HC in discrepancy scores were assessed using Student's *t*-test or Mann-Whitney *U*-test, as appropriate. The Receiver-Operating Characteristic (ROC) curve analysis was used to classify and discriminate between patients with schizophrenia and HC. Sensitivity and specificity indices were obtained. Positive Predicted Values (PPV), Negative Predicted Values (NPV) and accuracy were calculated based on the prevalence. Effect sizes were calculated.

4.5.2. Study II.

Distribution of the variables was studied using the Kolmogorov-Smirnov test and the following statistical analyses were therefore performed depending on their normal or non-normal distribution. Sociodemographic and SFRT-2 performance differences between groups were assessed using Mann-Whitney *U* and Chi-square analyses. Cohen's *d* effect sizes were obtained and then converted into Hedges's *g* effect sizes (0.2 = small; 0.5 = medium, and 0.8 = large). In order to assess reliability, Cronbach's alpha was used to obtain the internal consistency indices of the SFRT-2. Concurrent validity was assessed by means of Spearman's correlations in the schizophrenia group. Finally, ROC curve analysis was used to study the discriminant validity of the SFRT-2 when comparing patients with schizophrenia and HC. The area under the curve (AUC) values were also

obtained. Sensitivity and specificity were obtained based on Youden index. Accuracy was calculated.

4.5.3. Study III.

The Kolmogorov-Smirnov test was used to assess the distribution of the variables and, therefore, the subsequent statistical analyses were performed based on their normal or non-normal distribution. Internal consistency of the total action hits, goal hits, action false positives and goal false positives was assessed by means of Cronbach's alpha in order to study the reliability of the short forms of the SFRT-2. Inter-form equivalence between both short forms of the SFRT-2 was assessed by means of a) Spearman correlations for assessing the relationship between forms; b) Wilcoxon signed rank tests for assessing differences between forms and c) a repeated measures MANOVA to assess the interaction between forms and time factors. Two 2 (group) x 2 (time) repeated measures MANOVAs (one for each form) were performed in order to assess sensitivity to change. Spearman correlation analyses were performed to study test-retests reliability and convergent and discriminant validity. Spearman correlation analyses were also used in order to assess the relationship between short forms and functionality.

4.5.4. Study IV.

Normality of the variables was assessed with Shapiro-Wilk test and the following analyses were performed depending on the distribution of the variables. Chi-square analyses and Fisher's exact test were used in order to assess group differences in sex, race, handedness, and DWI sequence. Student *t*-tests were used to assess group differences in age and years of education. Differences between the 10 patients with schizophrenia and the 10 HC in gCC, bCC and sCC WM integrity were assessed by means of MANCOVA. Repeated measures ANCOVA (including group as inter-subjects factor and laterality as intra-subjects factor) was used to examine group differences in the

laterality of both anterior frontal cortical projections of the gCC and posterior occipital cortical projections of the sCC WM indices (FA, MD, AD, RD and MO). In order to assess the relationship between both right and left anterior frontal cortical projections of the gCC and posterior occipital cortical projections of the sCC WM indices and cognitive performance partial correlations were performed separately in patients with schizophrenia and HC. Whole brain overall FA values were entered as a covariate in all the analyses.

4.6. Neuroimaging Analyses

4.6.1. Study IV.

Whole WM brain differences in FA, MD, AD, RD and MO between 41 patients and 21 HC were tested by means of *randomise* tool (5000 permutations) with TFCE correction in FSL. Given that there was a MRI-software change during the project development DWI sequence along with age, sex and race was included as covariate. Significant regions were located and labelled anatomically with the MRI Atlas of Human White Matter (Oishi et al., 2010). Statistical threshold was set at $p < .05$ (FWE-corrected).

4.7. Ethics Statement

Studies I, II and III were reviewed and approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain and the Ethics Committee of the University of Deusto. Study IV was reviewed and approved by the institutional review boards of all participating institutions (Hartford Hospital/Yale University and the University of Maryland/Johns Hopkins University).

V. Results

5. Results

5.1. Paper I

"Cognitive scores as a potential diagnostic tool in schizophrenia: the use of raw and discrepancy scores"

5.2. Paper II

"Spanish adaptation and validation of the Situational Feature Recognition Test 2 (SFRT-2) in patients with schizophrenia and healthy controls"

5.3. Paper III

"Equivalent short forms of the Situational Feature Recognition Test 2: psychometric properties and analysis of inter-form equivalence and test-retest reliability"

5.4. Paper IV

"Altered frontal white matter asymmetry and its implications for cognition in schizophrenia: A tractography study"

VI. Discussion

6. Discussion

The present thesis aimed to contribute to improve the schizophrenia diagnosis by means of identifying new cognitive, SC and neuroimaging markers that could help to discriminate between pathological and non-pathological samples.

The *study I* aimed to assess the discriminant capability of both verbal memory and processing speed raw and discrepancy scores (controlling for age, years of education and premorbid IQ) when classifying patients with schizophrenia and HC. Results showed that verbal memory raw and discrepancy scores discriminated well between patients with schizophrenia and HC. However, raw cognitive scores showed to classify better patients and HC than discrepancy scores. Regarding processing speed, only raw scores showed to discriminate between both groups. Specifically, verbal learning and delayed recall were the two cognitive variables that best classified patients. Consistent with these results, verbal memory has been identified as one of the most affected cognitive domains in patients with schizophrenia when comparing their performance to that in HC (Aleman, Hijman, De Haan, & Kahn, 1999; Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Heinrichs & Zakzanis, 1998). Other study has also described the capability of both verbal memory and processing speed measures to discriminate well between patients with schizophrenia, bipolar disorder patients and HC with and without cognitive impairment (Rojo et al., 2010). Contrary to the findings presented in this thesis, the aforementioned study showed that processing speed (measured by a composite score using three different assessment tools) and not verbal memory was the measure that discriminated better between participants with and without cognitive impairment (Rojo et al., 2010). This might suggest that a more complex processing speed measure could perform better than a unique test when classifying patients with schizophrenia and HC in different groups. In addition, discriminant values obtained especially regarding verbal memory measures, are

very similar to those presented by the PANSS when discriminating between psychotic and mood disorder patients based on their clinical symptoms (Ritsner, Mar, Arbitman, & Grinshpoon, 2013). This, added to the fact that the PANSS is a well-recognized measure that is sometimes used in the diagnosis of schizophrenia, highlights the potential role of verbal memory raw scores in the diagnosis of this pathology. Contrary to what was expected, discrepancy scores did not discriminate better than raw scores between patients and HC. Therefore, although discrepancy scores would seem more accurate cognitive scores, taking into account subject's premorbid functioning, these did not classify better patients and HC than raw scores, as far as this sample is concerned. These findings contrast with some preliminary results obtained by other authors using a regression-based approach in order to classify patients with schizophrenia and HC which described cognitive discrepancy scores as good classifiers (Testa & Schretlen, 2006). The results obtained in the present thesis might be explained attending to the variables controlled when calculating discrepancy scores, particularly years of education and premorbid IQ. Thus, contrasting with neurodegenerative diseases, premorbid IQ might be impaired in patients with schizophrenia (Khandaker, Barnett, White, & Jones, 2011). Similarly, the onset of the disease usually truncates patients' educational achievements, leading to lower years of education compared to HC. These two facts support the neurodevelopmental theory for schizophrenia, describing alterations that appear from early live stages until the onset of the disease at young-middle ages. By eliminating the influence that these two factors might have in cognitive performance in order to obtain discrepancy scores, we might be favoring the reduction of differences in cognitive performance between patients and HC. Therefore, in light of the results obtained, raw and not discrepancy cognitive scores should be taken into account when trying to classify a person as a patient with schizophrenia. Hence, subject's premorbid and historical data should be considered by

means of other approach or in the context of a neurodevelopmental disorder rather than the obtaining of discrepancy scores, at least for diagnosing schizophrenia.

The objective of *study II* was to adapt and validate one of the most used SP measures among patients with schizophrenia: the SFRT-2 (Corrigan et al., 1996). Results obtained described good psychometric properties of the SFRT-2 Spanish adapted version in both patients with schizophrenia and HC. Regarding reliability, internal consistency indices of the SFRT-2 scores (actions and goals hits and false positives) ranged from moderate to high, similar to those obtained in the original version of the test in English (Corrigan et al., 1996). Reliability indices obtained were also in line with those presented by other SC measures that had been validated into Spanish such as the GEOPTE (J. Sanjuan et al., 2003), the MSCEIT (Extremera, Fernández-Berrocal, & Salovey, 2006) or the ASQ (P. Sanjuan & Magallares, 2006). The Spanish adaptation and validation of the SFRT-2 also showed good concurrent validity since both hits and false positives were related to other SC measures such as the GEOPTE and the MSCEIT. The magnitude of these correlations was from small to medium depending on the assessed index, similar to those reported by other studies when testing the association between different SC measures and domains in psychiatric samples (Bell et al., 2010; Mancuso, Horan, Kern, & Green, 2011). Finally, the SFRT-2 Spanish version showed to discriminate between patients with schizophrenia and HC with moderate-good discriminant validity when using a composite score including hits and false positives of both actions and goals. Concretely, the composite score showed to better identify patients with schizophrenia as having the pathology than to identify HC as not presenting the disease. Results regarding discriminant capability suggest that the SFRT-2 could be a useful SC measure that, along with cognitive and clinical measures, could help in the diagnosis of schizophrenia. To our knowledge, nowadays only another measure is available to assess SP in Spanish-speaking

patients with schizophrenia, namely the Social Perception Scale [SPS, (García et al., 2003)]. This scale was specifically designed to assess the three main goals of a particular SP rehabilitation subprogram (García et al., 2003), making it less generalizable to broader conceptions of SP. Therefore, the SFRT-2 adaptation and validation into Spanish could help to overcome the lack of available specific SP assessment measures for Spanish-speaking patients with schizophrenia, improving SC assessment in this population. Moreover, its use could allow clinicians to obtain a SP impairment profile of patients based on a reliable and valid measure and, eventually, to potentially improve the implementation of intervention programs in this pathology.

Following the results from study II, *study III* aimed to obtain two shortened and equivalent forms of the SFRT-2 as well as to test their psychometric properties. Two shortened forms were proposed including four situations each. Internal consistency of the two forms was good for both Time 1 and Time 2 of assessment. Both forms were related to each other and, when time interaction was assessed, no differences were found between forms. However, when time effects were not assessed, patients showed to perform better on Form 2 than on Form 1. Both forms showed good test-retest reliability and sensitivity to change, especially hits scores. In addition, hits and false positives of both forms showed a relationship with functional outcome and other SC measures. Internal consistency indices ranged from acceptable to excellent, in line with those obtained by other SC measures selected by the SCOPE study (Pinkham et al., 2016). These indices were also very similar to those presented by the original version of the test (Corrigan et al., 1996). Regarding the equivalence between forms, Form 1 and Form 2 showed inter-form equivalence in terms of inter-relationship reliability between forms and equivalence and stability when considering both assessment times. However, performance on Form 2 overtook that in Form 1 when Time 1 and Time 2 were considered separately,

compromising this type of interform equivalence. Studies such as the SCOPE have highlighted the need for standardized and validated equivalent forms of SC measures and especially for SP in schizophrenia (Pinkham et al., 2018, 2016). It is difficult to compare the obtained inter-form equivalence data of the SFRT-2 with other SP equivalent forms since, to our knowledge, nowadays only three SP assessment tools present alternative forms. One of those measures, the SAT-MC, also showed differences between forms when psychometric properties of the test were assessed in the SCOPE study (Pinkham et al., 2018). However, in the original manuscript presenting the alternative forms, both versions of the test were equivalent (Johannesen, Fiszdon, Weinstein, Ciosek, & Bell, 2018). In addition, hits but not false positives of both forms of the SFRT-2 detected changes after the implementation of an intervention. However, unlike the common expected pattern of sensitivity to change in any assessment tool, changes after the intervention were given due to stability on the SFRT-2 scores in the experimental group and a decrease in the control group. Given the lack of information about the common pattern of longitudinal changes registered by the SFRT-2 in patients with schizophrenia when no intervention is implemented, it is not possible to determine if the obtained changes followed the typical pattern or not. Concerning test-retest reliability of the SFRT-2 shortened forms, obtained indices were similar to those presented by different SC measures in the SCOPE study (Pinkham et al., 2018, 2016). These results point out the utility of these two forms of the SFRT-2 as repeated measures. In addition, both forms showed low to medium correlations with a SC composite score including other SC measures such as EP, ToM and AS. Lowest correlations were found for actions hits of the second form whereas highest correlations were found for goals false positives of the second form. These results concerning convergent validity are in line with other studies stating that whereas ToM and EP seem to be highly related to SP (Grant et al., 2017), AS

seems to present a weaker relationship with this domain (Benedict et al., 1998; Mancuso et al., 2011). This inconsistency could have led to the described low to medium relationship magnitudes between SP scores measured by the shortened forms of the SFRT-2 and the other SC measures' composite score. Regarding discriminant validity, effect sizes of the relationship between the short forms' scores and the neurocognition composite score were lower than those obtained for SC composite score. In this line, other studies have acknowledged the weaker relationship of SC measures and neurocognition compared to the interrelation among the SC domains themselves (Mancuso et al., 2011; Sergi et al., 2007). Moreover, both forms' scores were related to functional and symptom severity measures, mainly functional competence. Relationship to functional outcome has been highlighted as one of the most important features to take into account when choosing a SC measure for clinical trials (Pinkham et al., 2014, 2016). Magnitudes of the obtained correlations were moderate and similar to those obtained when testing the relationship between the SCOPE's SC measures and functional outcome (Pinkham et al., 2018, 2016). Finally, and as a noteworthy point, administration time was reduced from 15 minutes for the original version to 5 minutes for each of the reduced forms. All the obtained results emphasize the fact that short forms of the SFRT-2 might represent a practical and reliable SP measure to be used in clinical trials or within long cognitive batteries. The use of these shortened forms could help to better assess and understand longitudinal course of SP performance in patients with schizophrenia. Moreover, the inclusion of these shortened forms might be especially relevant in clinical trials, contributing to better understanding and testing interventions' efficacy.

Finally, *Study IV* aimed to assess whole brain WM integrity differences between patients with schizophrenia and HC. In addition, other objective was to study WM asymmetry differences between patients with schizophrenia and HC of both the anterior

frontal (gCC) and posterior occipital (sCC) cortical projections of the CC as well as their relationship with cognition. Whole brain WM analyses showed a well-defined left frontal area that presented a reduced integrity in patients compared to HC. This area included WM fibers such as the anterior corona radiata, anterior limb of the internal capsule (left anterior thalamic radiation and part of the left inferior fronto-occipital fasciculus), the gCC, the cingulum, and WM adjacent to the left inferior and superior frontal gyri. The described area overlaps with one of the two areas identified in the meta-analysis by Ellison-Wright and Bullmore (2009) as the two most impaired WM brain areas in schizophrenia. According to this meta-analysis, that area included WM fibers traversing the left frontal region such as inter-hemispheric fibers via the gCC, the cingulum bundle, the left inferior fronto-occipital fasciculus, and the left anterior thalamic radiation (Ellison-Wright & Bullmore, 2009). However, the present study failed to find abnormalities in the other abnormal brain area described in the mentioned meta-analysis comprising WM fibers traversing the sCC among others. This could be caused by our relatively small sample and methodological differences compared to the studies included in the meta-analysis. Concerning interhemispheric fibers specifically, WM abnormalities were identified in the gCC but not in the sCC or the bCC. This pattern of greater alterations in the gCC than in the sCC or the bCC is widely supported by different studies in schizophrenia (Knöchel et al., 2012; Kubicki et al., 2008; Price et al., 2007; Skudlarski et al., 2013). The larger damage of the gCC compared to the other subdivisions of the CC could be explained attending to the maturation course of the CC. Thus, within all its subdivisions, the gCC is the one whose peak maturation occurs later, making it vulnerable to be interrupted by the onset of the disease at mid-20s in many cases (Bartzokis et al., 2012; Häfner & An Der Heiden, 1997; Kochunov et al., 2013, 2012). However, the most remarkably finding was the altered WM asymmetry found in patients with schizophrenia

regarding the anterior frontal cortical projections of the gCC. As expected, HC showed higher mean FA and reduced mean RD in left than right hemisphere tract, pointing to a leftward asymmetry of this tract. On the contrary, patients showed the reverse pattern of asymmetry: higher mean FA and reduced mean RD in right than left hemisphere. In addition, these asymmetry abnormalities were related with a worse performance on verbal learning/memory – a hallmark of cognitive dysfunction in schizophrenia. Abnormalities in human brain asymmetry have been widely linked with language alterations in schizophrenia (Crow, 1997; Mitchell & Crow, 2005; Pearlson & Folley, 2008). In fact, these abnormalities have been directly related to the origin of the disease (Crow, 1997; Crow et al., 1989). Moreover, WM asymmetry abnormalities have been well documented in schizophrenia (Miyata et al., 2012; Park et al., 2004). However, this is, to the best of our knowledge, the first study to assess these abnormalities regarding the anterior frontal cortical projections of the gCC and their role in cognition in schizophrenia. Supporting the present results, common left greater than right asymmetry pattern observed in HC has shown to be reduced in patients with schizophrenia (Ribolsi et al., 2014). Abnormalities have been described especially regarding some WM fibers such as those traversing the anterior CC, the optic radiation, the uncinate fasciculus, the posterior limb of the internal capsule or the cingulum bundle (Kubicki et al., 2002; Miyata et al., 2012; Park et al., 2004; Ribolsi et al., 2014). Interestingly, asymmetry of some of the brain WM fibers has been attributed to genetic factors to a larger extent than to environmental factors (Jahanshad et al., 2010). Therefore, asymmetry alterations observed in those brain areas with high heritability rates could serve as endophenotypes to guide the study of new genes related to schizophrenia. Regarding the relationship between higher WM integrity of the right anterior frontal cortical projections of the gCC and a worse verbal memory performance in patients, this might result from an abnormal axonal pruning that could

affect cognitive development or even from an altered development of those brain areas related to verbal memory. Deficient axonal pruning has been previously related to altered information transmission due to the existence of redundant brain networks (Alba-Ferrara & de Erausquin, 2013). Thus, it could be hypothesized that a deficient pruning could contribute to higher WM integrity and to a decreased cognitive efficiency in this pathology. Attending to this, abnormalities observed in right frontal areas of the brain, as those found in the anterior frontal cortical projections of the gCC in the present study, could reflect a neuroanatomical substrate of verbal memory impairment in schizophrenia. In conclusion, findings suggest that abnormal WM asymmetry could contribute to both language processing and verbal memory dysfunction in schizophrenia. Combination of both reversed WM asymmetry, particularly in frontal areas, and impaired verbal learning/memory could serve as a useful marker of schizophrenia once its sensitivity and specificity for diagnosis were proved.

In conclusion, all the described studies attempt to contribute to identify possible pathological markers by means of reliable methods in order to improve schizophrenia diagnosis. The obtained results might serve as added scientific evidence supporting the inclusion of both cognitive and neuroimaging markers in the diagnosis of schizophrenia.

The present thesis emphasizes the importance of raw cognitive scores in schizophrenia and proposes that, supporting the neurodevelopmental character of the disease, some premorbid characteristics such as educational level are affected by the pathology itself even before its onset. Consequently, it seems reasonable to propose that altered cognition could be present when the disease is diagnosed. Therefore, cognitive alterations might be relevant when diagnosing schizophrenia and their inclusion as diagnostic criterion could be beneficial for the correct identification of the pathology. However, there is a lack of adapted and valid measures in Spanish for some cognitive

domains such as SP, which has been described to be altered and a potential endophenotype in schizophrenia. This, added to the lack of information about discriminant capability of most of the cognitive measures, might complicate the inclusion of SP and other cognitive domains alteration as diagnostic criterion. Nevertheless, derived from this thesis, two contributions have been made in order to overcome these problems. Firstly, an adapted and validated version of a well-known SP measure for Spanish-speaking patients is now available for its use when establishing the presence of SP impairment in patients with schizophrenia. In addition, two shortened and equivalent forms of this same measure are now also available in order to contribute to improve the assessment of this domain in longitudinal studies and clinical trials. Secondly, verbal memory raw scores have emerged as reliable discriminant measures when classifying patients with schizophrenia based on their cognitive performance, offering a potential marker and diagnostic tool for this pathology. In addition, this cognitive alteration has shown to be highly related with brain asymmetry abnormalities in these patients, which could be also proposed as a marker of the disease, highlighting its likely contribution to the schizophrenia diagnosis.

Therefore, even though a lot of work is still needed regarding the inclusion of cognitive alterations in schizophrenia diagnostic manuals, results of the present thesis suggest the use of verbal memory raw scores and SP scores obtained by means of the SFRT-2 as markers which might be potentially included as diagnostic tools.

VII. Conclusions

7. Conclusions

The main conclusions derived from the present thesis through the presented studies can be summarized as follows:

- Verbal memory and processing speed raw scores showed to discriminate between patients with schizophrenia and HC. Verbal memory raw cognitive scores were the best classifiers. Contrary to what was expected, cognitive discrepancy scores controlling for age, premorbid IQ and years of education did not discriminate better than raw scores between patients and HC. Obtained results highlight the potential role of cognitive raw scores when discriminating patients with schizophrenia and HC. This outcome supports previous attempts of including cognitive impairment as diagnosis criterion in diagnostic manuals.
- Spanish adaptation and validation of the SFRT-2 test for assessing SP in patients with schizophrenia showed good psychometric characteristics. Concretely, the SFRT-2 Spanish adaptation showed good reliability indices as well as good concurrent and discriminant validity. This adapted and validated measure could allow clinicians to obtain a SP impairment profile of patients with schizophrenia. This finding could help to overcome the complications derived from the use of non-adapted and non-validated SC measures for the assessment of patients with schizophrenia.
- Shortened forms of the SFRT-2 showed good psychometric properties. Both forms showed good reliability indices as well as good convergent and discriminant validity. When considering both assessment times, both forms showed to be equivalent. However, equivalence between forms should be carefully taken. In addition, both forms showed sensitivity to change after a cognitive rehabilitation was implemented. Moreover, both short forms showed a

relationship with functional measures. Obtained results suggest that shortened forms of the SFRT-2 could be used as reliable and practical SP measures especially in longitudinal studies and clinical trials with patients with schizophrenia.

- Patients with schizophrenia showed a well-defined left frontal WM area with decreased WM integrity compared to HC including the gCC but not the bCC or the sCC. In addition, when assessing specifically the anterior frontal cortical projections of the gCC in these patients, an abnormal WM asymmetry was found. Patients showed a right greater than left WM asymmetry, contrary to the pattern that was found in HC. This asymmetry abnormality was related to a worse verbal memory performance in patients with schizophrenia. Combination of abnormal frontal tracts asymmetry and verbal memory impairment might serve as a useful marker of schizophrenia.

Conclusiones

Las conclusiones principales derivadas de los estudios descritos en la presente tesis pueden resumirse como sigue:

- Las puntuaciones directas de memoria verbal y velocidad de procesamiento mostraron discriminar entre pacientes con esquizofrenia y CoS. Las puntuaciones directas en memoria verbal fueron los mejores clasificadores. Al contrario de lo esperado, las puntuaciones cognitivas de discrepancia controlando por edad, IQ premórbido y años de educación no discriminaron mejor que las puntuaciones directas entre pacientes y CoS. Los resultados obtenidos destacan el papel potencial de las puntuaciones cognitivas directas a la hora de discriminar entre pacientes con esquizofrenia y CoS. Este hallazgo podría apoyar intentos previos de incluir el deterioro cognitivo como un criterio diagnóstico en manuales diagnósticos.
- La adaptación y validación española del SFRT-2 para evaluar la PS en pacientes con esquizofrenia mostró buenas características psicométricas. Concretamente, la adaptación española del SFRT-2 mostró buenos índices de fiabilidad y validez concurrente y discriminante. Esta medida adaptada y validada podría permitir a los clínicos obtener un perfil del deterioro de la PS en pacientes con esquizofrenia. Esta herramienta podría ayudar a superar las complicaciones derivadas del uso de medidas de CS no adaptadas y no validadas en la evaluación de pacientes con esquizofrenia.
- Las formas abreviadas del SFRT-2 mostraron buenas propiedades psicométricas. Ambas formas mostraron buenos índices de fiabilidad así como buena validez convergente y discriminante. Cuando los dos tiempos de evaluación se tenían en cuenta, las dos formas mostraron ser equivalentes. Sin embargo, la equivalencia

entre formas debería tomarse con cautela. Además, ambas formas mostraron sensibilidad al cambio tras la implementación de una rehabilitación cognitiva. Por otro lado, ambas formas revelaron una relación con medidas funcionales. Los resultados obtenidos sugieren que las formas abreviadas del SFRT-2 podrían ser usadas como medidas de PS fiables y prácticas especialmente en estudios longitudinales y ensayos aleatorizados con pacientes con esquizofrenia.

- Los pacientes con esquizofrenia mostraron una zona frontal izquierda bien definida con una integridad de la SB reducida en comparación con los CoS incluyendo el genu del cuerpo calloso pero no el cuerpo o el splenium. Además, a la hora de evaluar las proyecciones fronto-corticales anteriores del genu del cuerpo calloso en estos pacientes se encontró una asimetría anómala. Los pacientes mostraron una mayor integridad de la SB en el hemisferio derecho comparado con el izquierdo, contario al patrón que se encontró en CoS. Esta anomalía en la asimetría se relacionó con un peor desempeño en memoria verbal en pacientes con esquizofrenia. La combinación de la asimetría anómala de los tractos frontales y el deterioro en memoria verbal podría servir como un marcador diagnóstico útil para la esquizofrenia.

VIII. References

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