Correlates of creativity and effects of integrative cognitive remediation in schizophrenia: a multimodal neuroimaging study

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Fundación Tatiana Pérez de Guzmán el Bueno

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University of Deusto

Resiliencia creativa

Esta ilustración representa la capacidad de adaptarse y de hacer frente a las adversidades de la vida. La capacidad de florecer, de crecer ante a las dificultades, de transformar los problemas en oportunidades; a través de un gran esfuerzo y aprendizaje y a través de nuestra capacidad de resiliencia creativa, que nos permite reimaginar, reinventar, crear nuevas posibilidades y cambiar el mundo que nos rodea.

Ilustradora: Naiara Zalbidea

Creative resilience

This illustration represents the ability to adapt and cope with life's adversities. The ability to flourish, to grow in the face of difficulties, to transform problems into opportunities; through great effort and learning and through our capacity for creative resilience, which allows us to reimagine, reinvent, create new possibilities and change the world around us.

Illustrator: Naiara Zalbidea

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Doctoral thesis presented by Agurne Sampedro Calvete,

To obtain the degree of Doctor of Psychology by the University of Deusto

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This thesis has been carried out in the Research Group of Neuropsychology of Severe Medical Conditions (https://neurolab.deusto.es), in the Department of Psychology, Faculty of Health Sciences, University of Deusto. This group has been qualified with the maximum research label awarded by the Basque Government (Category A-Excellence).

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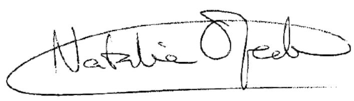
Dr. Javier Peña Lasa, coordinator of the Doctoral program in Psychology, member of the academic commission of the Doctoral program in Psychology, Assistant Professor of the Department of Methods and Experimental Psychology, director of the present thesis; and Dr. Natalia Ojeda del Pozo, principal investigator of the Neuropsychology of Severe Medical Conditions research team, head and tenured Professor of the Department of Methods and Experimental Psychology at the University of Deusto, director of the present thesis, certify that the present thesis entitled **"Correlates of creativity and effects of integrative cognitive remediation in schizophrenia: a multimodal neuroimaging study"** represents an original research work, which is presented by Agurne Sampedro Calvete in order to obtain the degree of Doctor.

Director

Dr. Javier Peña Lasa

Director



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"Meanwhile we all have problems

but have potential for

resilient creative response."

Ruth Richards

Contents

Foreword

The present thesis has been presented to obtain the degree of Doctor of Psychology by the University of Deusto and is the result of six studies carried out at the Research Group of Neuropsychology of Severe Medical Conditions, at the Department of Psychology, Faculty of Health Sciences, University of Deusto. Four of the following studies have been published in international journals, with a global impact factor (IF) of 18.019 (2020 Journal Citation Reports, published by Web of Science Group in 2020). The other two studies are currently in publication process in international journals.

Study I

Sampedro, A., Peña, J., Ibarretxe-Bilbao, N., Sánchez, P., Iriarte-Yoller, N., Ledesma-Gonzalez, S., Tous-Espelosin, M., & Ojeda, N. (2019). The mediating role of cognition and social cognition on creativity among patients with schizophrenia and healthy control: revisiting the Shared Vulnerability Model. *Psychiatry and Clinical Neurosciences, 74*(2), 1-7. https://doi.org/10.1111/pcn.12954 [IF: 3.351, 64/204, Q2, Clinical Neurology].

Study II

Sampedro, A., Peña, J., Ibarretxe-Bilbao, N., Sánchez, P., Iriarte-Yoller, N., Pavón, C., Hervella, I., Tous-Espelosin, M., & Ojeda, N. (2020). Neurocognitive, social cognitive, and clinical predictors of creativity in schizophrenia. *Journal of Psychiatric Research, 129*, 206-213. https://doi.org/10.1016/j.jpsychires.2020.06.019 [IF: 4.791, 26/143, Q1, Psychiatry].

Study III

Sampedro, A., Peña, J., Sánchez, P., Ibarretxe-Bilbao, N., Iriarte-Yoller, N., Pavón, C., Hervella, I., Tous-Espelosin, M., & Ojeda, N. (2021). The impact of creativity on functional outcome in schizophrenia: a mediational model. *npj Schizophrenia*, *7*(14), 1-8. https://doi.org/10.1038/s41537-021-00144-5 [IF: 5.200, 32/156, Q1, Psychiatry].

Study IV

Sampedro, A., Peña, J., Ibarretxe-Bilbao, N., Cabrera-Zubizarreta, A., Sánchez, P., Gómez-Gastiasoro, A., Iriarte-Yoller, N., Pavón, C., & Ojeda, N. (2020). Brain white matter correlates of creativity in schizophrenia: a diffusion tensor imaging study. *Frontiers in Neuroscience*, *14*(572), 1-10. https://doi.org/10.3389/fnins.2020.00572 [IF: 4.677, 87/273, Q2, Neurosciences].

Study V

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Study VI

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Glossary of abbreviations

ACIPS = Anticipatory and Consummatory Interpersonal Pleasure Scale

AD = Axial diffusivity

BET = Brain Extraction Tool

BLERT = Bell Lysaker Emotion Recognition Test

BNSS = Brief Negative Symptom Scale

BOLD = Blood oxygenation level dependent

CREW = Cognitive Remediation Experts Working

CFI = Comparative fit index

CRES = Consumer Reports Effectiveness Scale

DAN = Dorsal attention network

DMN = Default mode network

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

DTI = Diffusion Tensor Imaging

ECN = Executive control network

EHI = Edinburgh Handedness Inventory

EM = Expectation maximization

ENIGMA = Enhancing Neuro Imaging Genetics through Meta Analysis

FA = Fractional anisotropy

FDR = False discovery rate

fMRI = Functional Magnetic Resonance Imaging

FSL = FMRIB Software Library

FWE = Family-wise error

GSES = General Self-Efficacy Scale

HC = Healthy controls

HVLT-R = Hopkins Verbal Learning Test-Revised

ICD-11 = International Classification of Diseases 11th Edition

IQ = Intelligence quotient

LISREL = Linear Structural Relations

MATRICS = Measurement and Treatment to Improve Cognition in Schizophrenia

MD = Mean diffusivity

MNI = Montreal Neurological Institute

MO = Mode of anisotropy

M-WCST = Modified Wisconsin Card Sorting Test

NIMH = National Institute of Mental Health developed

NNFI = Non-normed fit index

PANSS = Positive and Negative Syndrome Scale

REHACOP = Cognitive Remediation Program for Psychosis

RD = Radial diffusivity

RML = Robust maximum likelihood

RMSEA = Root-mean-square error of approximation

SAT-MC = Social Attribution Task Multiple Choice

SCOPE = Social Cognition Psychometric Evaluation

SCWT = Stroop Color-and Word Test

SFS = Social Functioning Scale

sMRI = Structural Magnetic Resonance Imaging

SN = Salience network

SPM = Statistical Parametric Mapping

SPSS = Statistical Software Package for Social Sciences

SRMR = Standard residual mean square root

SUMD = Scale of Unawareness of Mental Disorder

TBSS = Tract-based spatial statistic

TFCE = Threshold-free cluster enhancement

TTCT = Torrance Test of Creative Thinking

UCSD = University of California San Diego

UPSA = UCSD Performance-Based Skills Assessment

VIF = Variance inflation factor

WAIS-III = Wechsler Adult Intelligence Scale-III

WAT = Word Accentuation Test

I. Abstract

1. Abstract

1.1. Abstract

The idea that there is a relationship between creativity and schizophrenia has been a research topic of great interest for centuries. It is now suggested that people with schizophrenia show an impaired creative capacity. Nevertheless, the cognitive, clinical and brain underpinnings of the relationship between creativity and schizophrenia, and the possible role of creativity in functional outcome remain almost unknown. Being one of the most disabling disorders in the world, the improvement of functional outcome is considered the main treatment target in this disease. Cognitive remediation has shown to be an effective intervention in improving functional outcome as well as cognition and clinical symptoms in schizophrenia. However, results among studies are still heterogeneous and little is known about the effectiveness of the combination of cognitive remediation with other trainings in improving creativity, primary negative symptoms, and brain structure and function in schizophrenia. Moreover, it is unclear which domains predict the improvement in functional outcome.

The present thesis is composed by six scientific contributions. The *first study* (Psychiatry and Clinical Neurosciences) aimed to analyze differences in creativity between patients with schizophrenia and healthy controls as well as the mediating role of cognitive flexibility, working memory, and theory of mind in the relationship between schizophrenia and creativity. The *second study* (Journal of Psychiatric Research) investigated simultaneously the specific contribution of multiple neurocognitive, social cognitive and clinical variables to creativity in schizophrenia. The *third study* (npj Schizophrenia) assessed the predictive role of creativity on functional outcome through a mediational model including sociodemographic, clinical, neurocognitive, and social cognitive variables among patients with schizophrenia. The *fourth study* (Frontiers in

Neuroscience) analyzed whole brain white matter correlates of different creativity dimensions in schizophrenia. The *fifth study* (accepted) evaluated the effectiveness of an integrative cognitive remediation program (REHACOP) that combined training in neurocognition, social cognition, as well as social and functional skills among patients with schizophrenia in multiple domains: creativity, neurocognition, social cognition, functional outcome, and clinical symptoms. An additional aim of the *fifth study* was to explore the mediators predicting improvement in functional outcome after the integrative cognitive remediation. Finally, the *sixth study* (under review) explored the structural and functional brain changes induced by the REHACOP program in patients with schizophrenia.

Results showed that patients with schizophrenia obtained lower scores in creativity compared to healthy controls and that this lower performance was partly due to an impairment in cognitive flexibility, working memory, and theory of mind. Moreover, creative performance of patients with schizophrenia was explained by multiple neurocognitive, social cognitive and clinical variables. In addition, creativity mediated the relationship between neurocognition and functional outcome as well as the relationship between negative symptoms and functional outcome in patients with schizophrenia. White matter mean fractional anisotropy adjacent to multiple brain regions, including frontal, temporal, subcortical, brain stem, and interhemispheric regions, correlated positively with creativity and specifically, with figural originality, among patients with schizophrenia. Furthermore, the integrative cognitive remediation was effective in producing significant changes in neurocognition, social cognition, creativity, functional outcome, and clinical symptoms. Besides, changes in verbal memory, inhibition, and emotion processing partially explained the effect of cognitive remediation on functional competence. Finally, the integrative cognitive remediation failed to produce structural and functional brain changes in patients with schizophrenia. However, the REHACOP group showed greater grey matter volume and cortical thickness in right temporal regions at post-treatment.

In conclusion, the present thesis provides on the one hand, a better understanding of the role of creativity on schizophrenia, through the interaction of multiple neurocognitive, social cognitive, clinical, functional outcome, and brain characteristics. On the other hand, this thesis reinforces the effectiveness of integrative cognitive remediation in multiple cognitive and functional outcome domains, and provides initial evidence of the effect of cognitive remediation in creativity and primary negative symptoms among patients with schizophrenia. Moreover, this thesis attempts to better understand the effects of integrative cognitive remediation in brain structure and function, suggesting that further research should clarify whether the temporal lobe may be a key area involved in neuroprotective processes of cognitive remediation.

Keywords: schizophrenia, creativity, neurocognition, social cognition, clinical symptoms, functional outcome, brain correlates, integrative cognitive remediation, neuroimaging, brain changes, brain plasticity, brain connectivity

1.2. Resumen

La idea de que existe una relación entre la creatividad y la esquizofrenia ha sido un tema de investigación de gran interés durante siglos. Actualmente se sugiere que las personas con esquizofrenia muestran una afectación en la capacidad creativa. Sin embargo, las bases cognitivas, clínicas y cerebrales que subyacen en la relación entre la creatividad y la esquizofrenia, así como el posible papel de la creatividad en la capacidad funcional siguen siendo casi desconocidos. Precisamente, siendo una de las enfermedades más incapacitantes del mundo, la mejora de la capacidad funcional se considera el objetivo de tratamiento principal de esta enfermedad. La rehabilitación cognitiva ha demostrado ser una intervención eficaz para mejorar la capacidad funcional, así como la cognición y los síntomas clínicos en la esquizofrenia. No obstante, los resultados entre los estudios son todavía heterogéneos y se sabe poco sobre la eficacia de la combinación de la rehabilitación cognitiva con otros entrenamientos en la mejora de la creatividad, los síntomas negativos primarios y la estructura y función cerebral en la esquizofrenia. Además, no está claro qué dominios predicen la mejora la capacidad funcional.

Esta tesis está compuesta por seis contribuciones científicas. El *primer estudio* (Psychiatry and Clinical Neurosciences) tuvo como objetivo analizar las diferencias en el desempeño de la creatividad entre pacientes con esquizofrenia y controles sanos, así como el papel mediador de la flexibilidad cognitiva, la memoria de trabajo y la teoría de la mente en la relación entre la esquizofrenia y la creatividad. El *segundo estudio* (Journal of Psychiatric Research) investigó simultáneamente el valor predictivo de múltiples variables de neurocognición, cognición social y clínicas en el desempeño de la creatividad en la esquizofrenia. El *tercer estudio* (npj Schizophrenia) evaluó el papel predictivo de la creatividad en la funcionalidad de los pacientes con esquizofrenia a través de un modelo de mediación que incluía variables sociodemográficas, clínicas, neurocognitivas y de

cognición social. El *cuarto estudio* (Frontiers in Neuroscience) analizó los correlatos de sustancia blanca cerebral de diferentes dimensiones de la creatividad en pacientes con esquizofrenia. El *quinto estudio* (aceptado) evaluó la eficacia de un programa de rehabilitación cognitiva integral (REHACOP) que combinaba el entrenamiento en neurocognición, cognición social y habilidades sociales y funcionales en pacientes con esquizofrenia en múltiples dominios: neurocognición, cognición social, creatividad, funcionalidad y síntomas clínicos. Un objetivo adicional del *quinto estudio* fue explorar los mediadores que explican la mejora en capacidad funcional tras de la rehabilitación cognitiva integral. Por último, el *sexto estudio* (en revisión) exploró los cambios de la estructura y función cerebral tras el programa REHACOP en pacientes con esquizofrenia.

Los resultados mostraron que los pacientes con esquizofrenia obtuvieron puntuaciones más bajas en creatividad en comparación con los controles sanos y que este menor rendimiento se debía en parte a un deterioro en la flexibilidad cognitiva, memoria de trabajo y teoría de la mente. Además, el rendimiento creativo de los pacientes con esquizofrenia fue explicado por múltiples variables de neurocognición, cognición social y clínicas. Asimismo, la creatividad medió la relación entre la neurocognición y la funcionalidad, así como la relación entre los síntomas negativos y la funcionalidad en pacientes con esquizofrenia. La anisotropía fraccional media de la sustancia blanca adyacente a múltiples regiones cerebrales, incluyendo regiones frontales, temporales, subcorticales, del tronco cerebral e interhemisféricas, se correlacionó positivamente con la creatividad y, específicamente, con la originalidad figurativa en los pacientes con esquizofrenia. Por otro lado, la rehabilitación cognitiva integral produjo cambios significativos en neurocognición, cognición social, creatividad, funcionalidad y los síntomas clínicos. Además, los cambios en memoria verbal, inhibición y el procesamiento de las emociones explicaron parcialmente el efecto de la rehabilitación cognitiva en la capacidad funcional. Por último, la rehabilitación cognitiva integral no logró producir cambios estadísticamente significativos en la estructura y función cerebral de los pacientes con esquizofrenia. Sin embargo, el grupo REHACOP mostró un mayor volumen de sustancia gris y grosor cortical en regiones temporales derechas en el post-tratamiento.

En conclusión, esta tesis proporciona, por un lado, una mejor comprensión del papel de la creatividad en la esquizofrenia, a través de la interacción de diferentes variables de neurocognición, cognición social, clínicas, funcionales, y características cerebrales. Por otro lado, esta tesis refuerza la eficacia de la rehabilitación cognitiva integral en múltiples dominios cognitivos y funcionales, y proporciona datos preliminares sobre el efecto de la rehabilitación cognitiva en la creatividad y los síntomas negativos primarios de las personas con esquizofrenia. Además, esta tesis ofrece una mayor comprensión de los efectos de la rehabilitación cognitiva integral en la estructura y función cerebral, sugiriendo que los futuros estudios deberían clarificar si el lóbulo temporal es una región clave implicada en los procesos neuroprotectores de la rehabilitación cognitiva.

Palabras clave: esquizofrenia, creatividad, neurocognición, cognición social, síntomas clínicos, funcionalidad, correlatos cerebrales, rehabilitación cognitiva integral, neuroimagen, cambios cerebrales, plasticidad cerebral, conectividad cerebral

II. Introduction

2. Introduction

2.1. Schizophrenia: a Brief Overview

Schizophrenia is a chronic severe psychiatric disorder characterized by a wide variety of symptoms including clinical symptoms, cognitive impairment and functional impairment as well as structural and functional brain alterations (Millan et al., 2016). This disease was first described by Emil Kraepelin as a *dementia praecox* and was later renamed with the term *schizophrenia,* as it is known today, by Eugen Bleuler (Hoenig, 1983).

This disorder affects over 20 million people worldwide (James et al., 2018). The global prevalence of schizophrenia in 2016 was estimated to be 0.28% (Charlson et al., 2018). More specifically in Spain, the global prevalence of schizophrenia spectrum disorders during the years 2008-2015 was 0.62% (Orrico-Sánchez et al., 2020). In addition, schizophrenia is considered one of the 15 most disabling disorders in the world (Vos et al., 2017). It is usually diagnosed between late teens and early thirties, with an earlier onset in men than in women (Ochoa et al., 2012). In spite that some studies have found no sex difference in prevalence (Charlson et al., 2018), others have found a higher prevalence in men than in women (McGrath et al., 2008; Orrico-Sánchez et al., 2020).

Although the etiology is still unknown, most evidence supports the idea that schizophrenia is a neurodevelopmental disease and that its origin may occur at early stages of development (Gupta & Kulhara, 2010; Rapoport et al., 2012). According to this idea, genetic and environmental risk factors interact during prenatal, perinatal, and early childhood and adolescence periods producing an abnormal brain development (Kochunov & Hong, 2014). This alteration in the development produces a state of vulnerability that in combination with other external or internal factors lead to the onset and manifestation of the psychiatric symptoms, usually during the adolescence and young adulthood (Pino et al., 2014). Less evidence supports the idea that schizophrenia is a neurodegenerative disease that starts in the early adulthood and in which a neurodegenerative process is given (Gupta & Kulhara, 2010).

Nowadays two types of diagnostic classification systems are used for the diagnosis of schizophrenia: the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) and the International Classification of Diseases, 11th Edition (ICD-11; World Health Organization, 2018). Although both classification systems have similarities, they also have some differences such as the inclusion of cognitive impairment (in ICD-11) or functional impairment (in DSM-5) as a diagnostic criterion.

The main pharmacological treatment in this disease is antipsychotic medication, which aims to reduce psychotic symptoms and preventing relapse (Millan et al., 2016). This pharmacological treatment has focused in several neurotransmitters including dopamine and serotonin, and more recently, additional neurotransmitters such as glutamate, acetylcholine, and gamma-aminobutyric acid have been proposed for novel treatments (Patel et al., 2014; Yang & Tsai, 2017). Nevertheless, antipsychotic medication is not effective in improving other symptoms such as negative symptoms, cognitive deficits and functional impairment. Therefore, non-pharmacological treatments, such as cognitive remediation, which will be addressed later in this thesis, have gained importance in the last decades (Green et al., 2019).

2.2. Clinical Symptoms in Schizophrenia

Clinical symptoms in schizophrenia are usually divided in two main categories: positive symptoms and negative symptoms. Regarding positive symptoms, these are referred to the excess or distortions of normal functions (American Psychiatric Association, 2000). The most common positive symptoms include delusions, hallucinations, disorganized thinking and speech (formal thought disorder), and disorganized or abnormal motor behavior (including catatonia) (American Psychiatric Association, 2013).

With respect to negative symptoms, these are characterized by the blunting or loss of normal functions (American Psychiatric Association, 2000). Some of the most common negative symptoms are abulia (loss of motivation), alogia (poverty of speech), anhedonia (incapacity to experience pleasure), apathy (lack of interest), avolition (lack of initiative), diminished emotional expression, and asociality (lack of interest in social interactions) (American Psychiatric Association, 2013; Tandon et al., 2009). It is important to note that some of these symptoms may be produced by other factors such as the antipsychotic medication (American Psychiatric Association, 2000; Patel et al., 2014).

Although this is one of the most commonly used classification systems, there are other classification systems and categories for clinical symptoms. For example, in addition to positive and negative symptoms, a disorganization syndrome has also been suggested (Peralta et al., 1992), which includes the aforementioned disorganized speech and behavior.

2.3. Cognitive Impairment in Schizophrenia

Despite not being included in all current diagnostic classification systems, cognitive impairment has been considered a core feature of schizophrenia for more than a century (Bleuler, 1911; Kraepelin, 1913). This means that cognitive deficits are not caused by other symptoms or by the treatment received, but represent a central aspect of the disorder (Green et al., 2004). Moreover, it is thought that multiple structural and brain abnormalities could underlie this cognitive impairment (Kronbichler et al., 2017; Minzenberg et al., 2009; Penadés et al., 2019).

Cognitive deficits have been explored across different phases of schizophrenia by a large number of studies (Green et al., 2019). Specifically, various meta-analyses have found that cognitive impairment is present among individuals who are at high risk for developing psychosis (Lee et al., 2015; Zheng et al., 2018), individuals in their first episode of psychosis (Bora & Murray, 2014; Mesholam-Gately et al., 2009), as well as among individuals with chronic schizophrenia (Bora et al., 2009a). Moreover, there is evidence supporting the idea that these deficits in cognition are present even before the onset of clinical symptoms (MacCabe, 2008; MacCabe et al., 2013; Reichenberg et al., 2010; Woodberry et al., 2008). Interestingly, some studies indicate that first-degree relatives of patients with schizophrenia who have not developed psychosis also show cognitive deficits compared to healthy controls (HC; Asarnow et al., 2002; de Achával et al., 2010; Huepe et al., 2012).

In general, longitudinal studies have shown that cognitive impairment remains stable after the first psychotic episode and throughout the course of the disease over 5 (Mccleery et al., 2017), 6 (Friedman et al., 2001) and 10 years (Rund et al., 2016). However, in the 6-year longitudinal study of Friedman et al. (2001), cognitive impairment started showing a decline at later ages (above age 65). Furthermore, the degree of impairment does not vary significantly depending on the stability of the patient's psychotic symptoms, that is, it remains similar under a psychotic episode as when symptoms are under control or in full remission (Nuechterlein et al., 2014).

Patients with schizophrenia experience a significant impairment in a large variety of cognitive domains (Green et al., 2019). In fact, the first meta-analysis conducted on cognitive impairment in schizophrenia found moderate to large raw effect sizes across a wide range of cognitive domains, including 22 different neurocognitive measures (Heinrichs & Zakzanis, 1998). In a study carried out by Bilder et al. (2000), patients with a first-episode schizophrenia also showed an impairment in multiple cognitive domains with a 1.5 standard deviation compared to HC. Specifically, a greater impairment was found in executive functions and memory, and a lower impairment in language (Bilder et al., 2000). Although there is some heterogeneity in the severity and cognitive domains that are affected among patients (Hajdúk et al., 2018; Joyce & Roiser, 2007), there is a typical profile that is different from the pattern of other disorders such as dementia (Kazui et al., 2011) or bipolar disorder (Bora & Pantelis, 2015). The main cognitive deficits affected in schizophrenia can be classified in two branches: nonsocial cognition (or neurocognition) and social cognition (Green et al., 2019). In an attempt to improve research about cognition and treatment in schizophrenia, the National Institute of Mental Health (NIMH) developed the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) initiative (Green & Nuechterlein, 2004; Marder & Fenton, 2004). The MATRICS identified seven cognitive domains that are impaired in this disease: processing speed, attention and vigilance, verbal learning and memory, visual learning and memory, working memory, reasoning and problem solving or executive functions, and social cognition (Nuechterlein et al., 2004). The nonsocial and social cognitive domains most impaired in schizophrenia are explained in more detail in the following sections.

2.3.1. Nonsocial Cognitive Impairment

Some of the most affected neurocognitive domains include processing speed, attention, working memory, learning and memory (verbal and visuospatial), language, and executive functions (Green et al., 2019; Nuechterlein et al., 2004).

Processing Speed. Processing speed refers to the ability to develop a response quickly and accurately when performing a relatively simple perceptual, motor or cognitive task (Green et al., 2019). A meta-analysis carried out with almost 2,000 patients with schizophrenia showed that this cognitive domain is more impaired than other neurocognitive domains (Dickinson et al., 2007). In addition, processing speed is essential for the adequate performance of other cognitive functions and has shown to explain most of the cognitive differences found between patients with schizophrenia and HC (Ojeda, Peña, Schretlen, et al., 2012).

Attention. Attention is the ability to focus and maintain a concentration over a prolonged period of time on a stimuli for a given cognitive process (Green et al., 2019). This cognitive domain is crucial and underlies any other higher cognitive function. Different types of attention (focused attention, sustained attention, selective attention, alternating attention, divided attention) are highly impaired in schizophrenia (Galaverna et al., 2012).

Working Memory. Working memory consists of the capacity to hold and manipulate information online over a relatively short period of time to perform a given cognitive process (Green et al., 2019). This capacity is usually impaired in schizophrenia, particularly verbal working memory (Bowie & Harvey, 2006).

Learning and Memory. Learning and memory involves the initial encoding and subsequent recall and recognition of verbal (e.g., words) or non-verbal (e.g., shapes) information (Green et al., 2019). This ability and more specifically, verbal memory, is highly impaired in schizophrenia (Bowie & Harvey, 2006).

Language. Patients with schizophrenia have many difficulties in the organization, comprehension, and producing of language (Bowie & Harvey, 2006; Mitchell & Crow, 2005). In particular, verbal fluency is highly impaired in this disease (Bowie & Harvey, 2006). Although language has not been included in the MATRICS, this may be due to the fact that verbal fluency is usually classified within the dimension of processing speed instead of within the language dimension (Nuechterlein et al., 2004).

Executive Functions. Executive functions involve the generation, maintenance, and adjustment of strategies aimed at achieving the goals of a given task (Barkley, 2012). It is a complex construct that comprises a wide range of cognitive processes such as cognitive flexibility, inhibitory control, planning and problem solving (Orellana & Slachevsky, 2013). Patients with schizophrenia have significant difficulties in performing tasks that require this higher-order cognitive function (Orellana & Slachevsky, 2013).

2.3.2. Social Cognition Impairment

Social cognition is a broad concept that encompasses the mental processes necessary to perceive, interpret and process social information for adaptive social interactions (Green et al., 2019). The interest in social cognition impairment in this disease has grown dramatically in the last two decades (Green et al., 2019). Such has been the growing interest in this area that the Social Cognition Psychometric Evaluation (SCOPE) project has been developed to improve the measurement of social cognition in schizophrenia (Pinkham et al., 2018). In fact, patients with schizophrenia experience difficulties in multiple social cognitive domains such as theory of mind, emotion processing, social perception, and attributional style (Green et al., 2019; Savla et al., 2013).

Theory of Mind. Theory of mind is the capacity to infer intentions, dispositions, emotions, and beliefs of others (Green et al., 2019). Various meta-analyses have found large effect sizes for an impairment in theory of mind in patients with schizophrenia (Bora et al., 2009b; Savla et al., 2013).

Emotion Processing. Emotion processing is defined as the capacity to perceive and use emotional information adaptively (Green et al., 2019). The emotion processing ability that most has been studied in this disease is facial emotion perception (Green et al., 2019). Although not as studied as theory of mind, a large effect size have also been found for an impairment in emotion processing (Savla et al., 2013).

Social Perception. Social perception involves the ability to identify social roles, social rules, and social contexts from non-verbal cues such as voice or body language (Green et al., 2019). As with the previous social cognition domains, the meta-analysis of Savla et al. (2013) found a significant impairment in social perception in patients with schizophrenia.

Attributional Style. Attributional style refers to the manner in which individuals infer the causes of the positive and negative events encountered (Green et al., 2019). Less evidence has been found for an impaired attributional style in schizophrenia, probably due to the kind of assessment tool employed (Buck et al., 2017). For instance, the aforementioned meta-analysis of Savla et al. (2013) found no differences in this capacity between patients with schizophrenia and HC.

Taken together, the literature makes clear the multidimensional severe cognitive impairment in schizophrenia and the need for research on interventions that are effective in improving all these cognitive domains.

2.4. Creative Impairment in Schizophrenia

Another domain that seems to be impaired in schizophrenia is creativity (Acar et al., 2017). Creativity is the capacity to generate something original or novel and appropriate or useful for a task (Sternberg & Lubart, 1995). This ability is considered a key factor for real-life problem solving (Plucker et al., 2015). One of the most important components of creativity is divergent thinking. Divergent thinking refers to the ability to simultaneously establish remote associations between unrelated ideas from different categories, as well as to generate multiple alternative and novel answers to a problem (Guilford, 1967). It is a multifaceted concept composed of multiple dimensions including originality, fluency or flexibility (Guilford, 1967) and it can be expressed in diverse modalities, such as in verbal or figural forms.

The assumption that psychopathology is associated with creativity dates back several centuries (Thys et al., 2013). In fact, this relationship has been considered the oldest and most controversial topic in the behavioral sciences (Becker, 2014). Nevertheless, nowadays the debate about whether creativity and psychopathology are related to each other remains open (Simonton, 2019). The idea that schizophrenia is positively related to creativity has been mainly reinforced by case studies (Lauronen et al., 2004; Payne, 2014), such as those of famous geniuses who suffered from schizophrenic symptoms (*e.g.,* Vincent Van Gogh and John Nash; Abraham et al., 2007). On the contrary, the majority of the empirical studies available have reported poorer performance in creative tasks among people with schizophrenia compared to HC (Abraham et al., 2007; Jaracz et al., 2012; Rodrigue & Perkins, 2012). Very few empirical studies have found a better creative performance in schizophrenia (Glicksohn et al., 2001). Additionally, in an epidemiological study carried out by Kyaga et al. (2011), people with schizophrenia, in comparison with controls, did not show an higher rate of creative occupations. Moreover, a recent meta-analysis from Acar et al. (2017) concluded that people with schizophrenia show a lower performance in creative tasks. However, interestingly, people with bipolar disorder and healthy relatives of individuals with schizophrenia or bipolar disorder seem to be overrepresented in creative professions (Kyaga et al., 2011). This is congruent with the idea that creativity and psychopathology have an inverted-U shape relationship. According to this idea, some minor schizotypal symptoms (such as those present in some relatives of people with schizophrenia or bipolar disorder) could promote creative thinking, whereas a greater severity of symptoms (such as symptoms present in schizophrenia) could impede it (Abraham, 2014).

Altogether, although there may be a relationship between psychopathology and creativity, most evidence suggests that patients with schizophrenia have impaired creative abilities. In an attempt to better understand this controversial relationship, multidimensional models that take into account other domains such as cognition or clinical symptomatology have been developed. This will be explained in the following section.

2.4.1. The Role of Cognition and Clinical Symptoms in Creativity

In an effort to understand the association between psychopathology and creativity, Carson (2011) developed the Shared Vulnerability Model. According to this model, creativity and psychopathology share several genetic vulnerability factors, which would promote accessibility to the associational ideas that are normally processed out of consciousness. This enhanced accessibility could promote creativity, or instead constitute a risk for psychopathology, depending on the presence of several risk factors (Carson, 2011). Low intelligence quotient (IQ), impaired working memory, and impaired cognitive flexibility are the risk factors that would encourage psychopathology instead of creativity (Carson, 2011). This model suggests that the worse creative performance found in people with schizophrenia could be partly explained by their impairment in diverse neurocognitive functions. In fact, this approach goes in line with the Creative Cognition Approach, which is one of the most widely used models for understanding human creative ability (Ward, 2007). This approach states that creativity arises from the application of basic cognitive processes to already existing knowledge structures (Ward, 2007).

As previously mentioned, one of the domains that seems to be crucial for creativity according to the Shared Vulnerability Model is working memory (Carson, 2011). This domain enables a large amount of associational material to be held in the mind without being overwhelmed by it (Carson, 2011). However, the role of working memory in creative performance of people with schizophrenia has scarcely been studied (Abraham et al., 2007). In contrast, more research has been carried out with healthy people, suggesting a positive relationship between creativity and working memory (Benedek, Jauk, Sommer, et al., 2014; de Dreu et al., 2012; Oberauer et al., 2008).

With respect to cognitive flexibility, this ability seems necessary to produce new ideas, because it enables switching from concept to concept (Nijstad et al., 2010; Pan & Yu, 2016). Two previous studies found that people with schizophrenia had lower cognitive flexibility and creativity compared to healthy people and that these domains were related to each other (Abraham et al., 2007; Jaracz et al., 2012). Specifically, Abraham et al. (2007) found that cognitive flexibility mediated the relationship between being a patient with schizophrenia vs a HC and creativity performance. Studies carried out on healthy people, in general, report a positive association between cognitive flexibility and creativity (Krumm et al., 2018; Nusbaum & Silvia, 2011; Pan & Yu, 2016; Wang et al., 2017; Zabelina & Robinson, 2010), though non-significant associations have also been found (Benedek, Jauk, Sommer, et al., 2014).

Besides these cognitive domains suggested by the Shared Vulnerability Model, other neurocognitive functions highly impaired in schizophrenia may be relevant for creative thinking. For instance, in order to suppress salient and less original ideas and focus on innovative information, inhibitory control may be necessary (Edl et al., 2014). A positive correlation between creativity and inhibitory control in healthy people has been found by multiple studies (Benedek et al., 2012; Benedek, Jauk, Sommer, et al., 2014;

Edl et al., 2014; Groborz & Necka, 2003), although a negative association has also been found (Carson et al., 2003; Radel et al., 2015). Studies carried out with healthy people have suggested that processing speed is also related to creativity (Forthmann et al., 2018; Rindermann & Neubauer, 2004; Vartanian et al., 2009). This may be because higher processing speed provides a faster access to memory during the performance of a given task and, consequently, this could improve creativity (Preckel et al., 2006). Another cognitive function that could underlie creativity is verbal memory. In fact, memory retrieval has shown to be relevant for the generation of creative ideas in healthy people (Benedek, Jauk, Fink, et al., 2014; Gilhooly et al., 2007). A controlled retrieval seems important in order to access the internal knowledge representations and recombine this stored knowledge to generate novel ideas (Benedek, Jauk, Fink, et al., 2014). However, very few studies have analyzed the association between the performance in a memory retrieval task (e.g., short verbal memory task) and creativity, and both positive (Polner et al., 2018) and non-significant associations (Moreno et al., 2017) have been found.

In addition to these neurocognitive domains, it has been suggested that social cognition could also be crucial for creativity (Abraham, 2019). Nevertheless, to date there have been few studies examining the role of social cognition in creativity and none of these studies included individuals with schizophrenia. Specifically, some studies have found a positive association between theory of mind and creativity in healthy people (Sigirtmac, 2016; Suddendorf & Fletcher-Flinn, 1997, 1999). According to Suddendorf and Fletcher-Flinn (1997), while a theory of mind task requires knowing what others know, a divergent thinking task requires actively searching one's knowledge and therefore, knowing what one knows. These two skills (*i.e.,* knowing what one knows and knowing what others know) involve meta-representational thinking (Suddendorf & Fletcher-Flinn, 1997). Suddendorf and Fletcher-Flinn (1997) suggested that the meta-representational skills required for theory of mind may not only be needed to understand other people's minds, but also to understand one's own mind. These meta-representational skills may allow individuals to consider information from multiple perspectives, and thus to conceive different representations of the same object simultaneously and to consider multiple alternative solutions for a problem. It seems that no previous study has explored whether other social cognitive domains that are also impaired in schizophrenia, such as social perception and emotion processing, are related to creativity.

Finally, in addition to all these neurocognitive and social cognitive domains, clinical symptomatology may also influence creativity performance in people with schizophrenia. Nevertheless, inconsistent results have been found among studies carried out with people with schizophrenia (Abraham et al., 2007; Jaracz et al., 2012; Son et al., 2015). For instance, Abraham et al. (2007) found that thought disorder was significantly associated with lower creativity. In contrast, Son et al. (2015) did not find any significant association between creativity and positive symptoms. Regarding negative symptoms, Jaracz et al. (2012) found significant associations between creativity and negative symptoms, but Abraham et al. (2007) did not find any significant relationship.

Considering the important role of creativity on daily life (Plucker et al., 2015), the understanding of which domains underlie creativity seems relevant. In fact, studying the creativity underpinnings could give us clues for the improvement of this capacity through non-pharmacological interventions, such as cognitive remediation. Therefore, more research is needed in order to understand the creative impairment found in this disorder.

2.5. Functional Outcome in Schizophrenia

As mentioned previously, schizophrenia is considered to be one of the most disabling disorders in the world (Vos et al., 2017). Individuals with schizophrenia have a high level of dependency in multiple daily life functional domains at very early ages (Conus et al., 2007; Harvey, 2014). Some of the most impaired functional domains are independent living, occupational functioning, and social functioning (Harvey, 2014). This functional disability not only has a major impact on the quality of life of patients, but also has indirect effects on the quality of life of relatives and caregivers (Fleischhacker et al., 2014). Moreover, this functional impairment causes a very high financial cost (Harvey & Strassnig, 2012). Since pharmacological treatment has not proven to be effective in improving functional outcome (Green et al., 2019), this impairment remains one of the most challenging treatment target in schizophrenia. For all these reasons, identifying the factors that hinder functional outcome in this disease is crucial for establishing better potential treatment targets. In fact, alternative non-pharmacological interventions such as cognitive remediation could focus on those factors that difficult an adequate functional outcome in order to improve this domain. The following section provides a brief overview of some of the factors that have been associated with functional outcome to date.

2.5.1. Factors Predicting Functional Outcome in Schizophrenia

Over the last two decades, there has been a great interest in studying the factors underlying functional impairment in schizophrenia (Harvey & Strassnig, 2012). Two main factors have been proposed, which are severity of clinical symptoms and cognitive impairment (Bowie et al., 2008; Fu et al., 2017; Green, 2016; Lepage et al., 2014; Ojeda et al., 2019).

With respect to clinical symptoms, both negative and positive symptoms have been related to functional outcome (Fervaha et al., 2014; Galderisi et al., 2014; Leifker et al., 2009). Nevertheless, studies suggests that negative symptoms have a greater influence on functional outcome than positive symptoms (Lin et al., 2013; Milev et al., 2005; Ojeda et al., 2019; Ventura et al., 2009). Primary negative symptoms influence functional outcome even after controlling for secondary negative symptoms, such as those caused by medication (Fervaha et al., 2014). In particular, it seems that motivational deficits are the negative symptoms that most have been related to functional impairment (Fervaha et al., 2015). Disorganization is an additional clinical factor that has also shown to influence functional outcome, which is closely related to neurocognition (Galderisi et al., 2014).

Regarding cognition, impairment in both neurocognition and social cognition has shown to be a strong predictor of functional outcome in this disease (Fu et al., 2017; Galderisi et al., 2014; Green, 1996; Green et al., 2000; Lepage et al., 2014; Ojeda et al., 2019; Peña et al., 2018; Strassnig et al., 2015). Specifically, a meta-analysis carried out by Fett et al. (2011) indicated that social cognition showed a stronger association with functional outcome than neurocognition did. Other studies have suggested that social cognition could act as a mediator between neurocognition and functional outcome (Galderisi et al., 2014; Green et al., 2015; Schmidt et al., 2011; Sergi et al., 2006). Furthermore, other studies have also suggested that clinical symptoms, mainly negative symptoms, mediate between cognition and functional outcome (Lin et al., 2013; Ojeda et al., 2019; Ventura et al., 2009).

In addition to these clinical and cognitive factors, it has been suggested that other kinds of personal resources could also be relevant predictors of functional outcome (Galderisi et al., 2014; Leifker et al., 2009). Specifically, a personal resource that could be important for functional outcome in schizophrenia is creativity (Nemoto et al., 2007). As Richards (2010) states, *creative resilience* may serve as a healthy compensatory advantage for schizophrenia or other mental disorders. Creativity is considered a relevant capacity for real-life problem solving (Plucker et al., 2015) and for adaptation and coping with daily life adversities (Flood & Scharer, 2006; Russ, 1998). This ability may help performing everyday activities through the application of creative problem solving skills to daily life problems (Richards, 1993). Several authors have suggested that this capacity applied to our daily life could improve people's physical and psychological health and could be beneficial for self-competency, life satisfaction, social life, civil participation, and academic and job performance (Conner et al., 2018; Fisher & Specht, 1999; Grebennikova et al., 2019; Richards, 2010; Rindermann & Neubauer, 2004; Silvia et al., 2014). For instance, a study carried out with healthy people (Silvia et al., 2014), showed that psychological health and specifically, feeling active and happy, was related to being more creative in daily life. With regard to studies carried out in schizophrenia, Nemoto et al. (2007) found that higher creativity was associated with better functional outcome in this disease. In a study carried out by Jolly (2000) with people with schizophrenia spectrum and bipolar disorder, creativity was associated with several coping strategies. Additionally, in a pilot study carried out by Nemoto et al. (2009), a creativity intervention improved negative symptoms, creativity, general psychopathology, global functioning, and interpersonal relations in individuals with schizophrenia. It has been suggested that creativity may also act as a compensatory advantage for better daily functioning and well-being in other populations, such as the elderly or people with bipolar disorder (Grebennikova et al., 2019; Richards, 2010). Overall, previous literature suggests that individuals with schizophrenia with better creative skills may benefit from this capacity for a more adaptive daily life functioning.

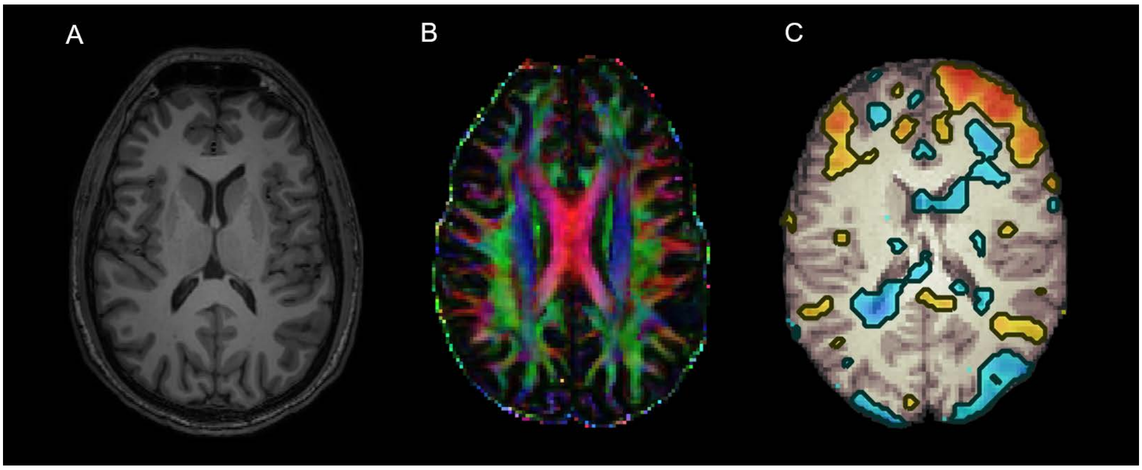
As a whole, the literature suggests that functional outcome in schizophrenia may be explained not only by factors such as clinical symptoms and cognitive impairment, but also by other factors like creativity. Nonetheless, more research is needed to clarify the specific role of creativity, in conjunction with cognitive and clinical factors, in functional outcome. This better understanding of the factors hindering functional outcome could be crucial for the development of more efficient interventions. In fact, training on creative skills, directly through creative training interventions (Nemoto et al., 2009) or indirectly through cognitive remediation, may be beneficial for the improvement of functional outcome.

2.6. Structural and Functional Brain Abnormalities in Schizophrenia

Over the last years, different neuroimaging techniques to assess brain structure and function have been developed, enabling a more reliable and exact measure of the brain. Some of these techniques include functional Magnetic Resonance Imaging (fMRI) and structural Magnetic Resonance Imaging (sMRI; see Figure 1). Neuroimaging techniques are particularly interesting in the field of schizophrenia, since these can provide a better understanding of the neural underpinnings of the complex symptomatology of this disease. In fact, the multiple cognitive deficits that suffer patients with schizophrenia, are thought to be consequence of brain alterations (Kronbichler et al., 2017; Minzenberg et al., 2009; Penadés et al., 2019). The Schizophrenia Working Group within the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) project has made possible in the recent years the investigation of brain alterations in schizophrenia through large-scale imaging meta-analyses. A brief overview of the different structural and functional abnormalities found in schizophrenia is presented in the following sections.

Figure 1

Examples of different magnetic resonance imaging (MRI) techniques



Note. Examples of (A) conventional MRI T1-weighted image; (B) colored fractional anisotropy map in which the green, red, and blue represent fibers running along the anterior-posterior, right-left, and inferior-superior axes, respectively; and (C) fMRI image showing connectivity between different regions (figure created using brain images of a participant recruited for the study).

2.6.1. White Matter Structural Abnormalities

Disrupted white matter integrity is thought to be a core characteristic of schizophrenia that may be present before the onset of the symptoms (Di Biase et al., 2020). In fact, it has been suggested that the multiple clinical, behavioral and cognitive symptoms of patients with schizophrenia may be due to an abnormal functional integrity or a disconnection between different brain structures (Friston, 1998). The microstructural integrity of white matter fiber tracts is usually estimated by Diffusion Tensor Imaging (DTI), a neuroimaging technique that uses diffusion-weighted images (Basser et al., 1994). This technique analyses the direction and anisotropy of the diffusion of water molecules along axons (Basser et al., 1994). By means of DTI, several white matter integrity indices can be obtained, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and mode of anisotropy (MO). FA is the most commonly used scalar measure (Di Biase et al., 2020) and is scaled from 0 (isotropic) to 1 (anisotropic; Mori & Zhang, 2006). While higher values represent an anisotropic movement of water molecules, greater directionality and coherent fiber tract, lower values indicate an isotropic movement of water molecules, that is, greater random movement of water and, consequently, reduced directionality of the fiber tract, indicating a possible demyelination and axonal injury (Mori & Zhang, 2006). All these indexes are thought to reflect an estimate of the properties of the white matter fiber tracts, such as fiber density, axonal diameter, and myelination of white matter (Di Biase et al., 2020; Wheeler & Voineskos, 2014).

Numerous empirical studies and meta-analysis have reported white matter alterations and mainly, a decreased FA in patients with schizophrenia (Bora et al., 2011; Ellison-Wright and Bullmore, 2009; Stämpfli et al., 2019; Wheeler and Voineskos, 2014). These white matter abnormalities predominate in frontal and temporal regions including interhemispheric (corpus callosum), intrahemispheric (e.g., thalamic radiation, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinated fasciculus, cingulum, and fornix), and projective fibers (corticospinal tract; Bora et al., 2011; Ellison-Wright & Bullmore, 2009; Kubicki et al., 2005; Pettersson-Yeo et al., 2011; Stämpfli et al., 2019; Wheeler & Voineskos, 2014). Nevertheless, white matter alterations have also been reported in other regions including the parietal and occipital lobes (Wheeler & Voineskos, 2014; White et al., 2011). White matter abnormalities have been found in both patients with chronic schizophrenia and individuals with first episode psychosis, although evidence is less consistent with the later (Di Biase et al., 2020). In addition, there is also some evidence of an abnormal white matter integrity in individuals at high risk for developing psychosis (Di Biase et al., 2020).

2.6.2. Grey Matter Structural Abnormalities

Brain grey matter structural abnormalities, measured through sMRI, have been widely reported in schizophrenia (van Erp et al., 2018). Grey matter alterations in schizophrenia consist mainly in slight but widespread reductions in cortical thickness as well as in cortical and subcortical grey matter density and volume (Frangou & Kahn, 2020). These grey matter reductions are more notable in certain regions, including the temporal (inferior, middle and superior temporal, hippocampus, amygdala, parahippocampal and fusiform gyrus) and the frontal (lateral orbitofrontal and inferior frontal gyrus) lobe, the posterior cingulate cortex, and the insula (Frangou & Kahn, 2020; van Erp et al., 2018). In contrast, some grey matter areas within the motor (precentral gyrus), somatosensory (postcentral gyrus), and parietal (superior and inferior parietal cortex and paracentral lobule) cortex (Frangou & Kahn, 2020) as well as some subcortical regions such as pallidum and lateral ventricle may be enlarged in this disorder in comparison to healthy people (van Erp et al., 2016). These grey matter alterations are also present at the time of the first psychotic episode (Lesh et al., 2015) and at individuals at clinical high risk for psychosis (Cannon et al., 2016). Although the association is complex, there is evidence suggesting that whole-brain grey matter reductions are related to a more severe symptomatology including a worse functional outcome (Frangou & Kahn, 2020).

2.6.3. Functional Brain Abnormalities

Within functional neuroimaging techniques, fMRI is the most widely used technique (Arnold Anteraper et al., 2020). fMRI relies on a mechanism called the blood oxygenation level dependent (BOLD) change during a task performance or at resting-state (Arnold Anteraper et al., 2020). An increase in the BOLD signal is thought to reflect higher brain activation (Ogawa et al., 1990). In schizophrenia, functional connectivity abnormalities have been found in both task-based and resting-state fMRI (Pearlson, 2020). Moreover, these alterations have not only been found in patients with chronic schizophrenia, but also in individuals with first episode psychosis as well as individuals at high risk for psychosis (Cooper et al., 2014; Mwansisya et al., 2017; Radua et al., 2012; Shim et al., 2010).

Resting-state fMRI assesses the brain activity while being in a resting and awake state. It is supposed to reflect intrinsic neural activity and involves low-frequency BOLD signal fluctuations that correlate at a time scale of seconds (Pearlson, 2020). The default mode network (DMN) is the network that tends to be more involved during resting state and that decreases its activation during the performance of cognitive tasks (Pearlson, 2020). The DMN is comprised by multiple brain regions including the medial prefrontal cortex, posterior cingulate cortex, the precuneus, the medial temporal lobe, and the lateral parietal cortex (Alves et al., 2019; Buckner et al., 2008; Raichle et al., 2001). In addition to the DMN, other "cognitive" networks, namely the frontal-parietal or executive control network (ECN), dorsal attention network (DAN), and salience network (SN), also show a coherent activity during resting-state (Karbasforoushan & Woodward, 2013).

The most frequently reported finding in resting-state studies in schizophrenia is a hyper-connectivity of the DMN (Karbasforoushan & Woodward, 2013; Pearlson, 2020), although findings are inconsistent since hypo-connectivity of this network has also been reported (Sheffield & Barch, 2016). Additional abnormalities have been reported in this disease, such as a reduced activity in the dorsolateral prefrontal cortex (Karbasforoushan & Woodward, 2013; Sheffield & Barch, 2016), reduced prefrontal-thalamic connectivity and increased motor and somatosensory connectivity with the thalamus (Giraldo-Chica & Woodward, 2017). Moreover, in a study carried out by Woodward et al. (2011), patients with schizophrenia, in comparison with HC, showed an increased functional connectivity in the DMN, but a reduced connectivity in the DAN and the ECN, as well as no differences in the SN. Other studies have reported a reduced connectivity also in the SN (Orliac et al., 2013; Shao et al., 2018).

Cognitive task-based fMRI studies can be relevant for understanding the neural circuits underlying the cognitive deficits in this disease (Gur & Gur, 2010). Studies carried out with patients with schizophrenia have found an abnormal neural activity in multiple neural systems and during the performance of different tasks or cognitive processes including motor tasks, executive functions, working memory, attention, verbal learning, and emotion processing (Galderisi et al., 2019; Gur & Gur, 2010). It seems that patients with schizophrenia tend to activate similar brain areas as HC during task performance, but with a different magnitude of activation (Galderisi et al., 2019; Minzenberg et al., 2009). These abnormalities usually consist on a decreased activation in some regions and a compensatory overactivation of other regions when performing a particular task (Gur & Gur, 2010). For instance, in a meta-analysis of functional neuroimaging during an executive function task performance, reduced activation in the left dorsolateral prefrontal cortex, rostral and dorsal anterior cingulate cortex, and left thalamus and an increased activation in several midline cortical areas was found in patients with schizophrenia in comparison to HC (Minzenberg et al., 2009). Regarding learning or memory tasks as well as working memory tasks, in general, a decreased activation mainly in prefrontal and temporal regions has been found (Achim & Lepage, 2005; Gur & Gur, 2010; Kraguljac et al., 2013). With respect to functional studies of social cognition, such as emotion recognition, patients with schizophrenia tend to show an abnormal activation in regions from the limbic system, particularly in the amygdala (Gur & Gur, 2010; Taylor et al., 2012). Interestingly, in a meta-analysis carried out with individuals with first episode psychosis, it was found that the brain areas with an abnormal activation were usually the same brain areas in which structural abnormalities have been found (Radua et al., 2012).

2.6.4. Brain Correlates of Creativity in Schizophrenia

The interest to understand the underlying neuroanatomical substrates of human creativity has grown dramatically in the last decade (Kenett et al., 2018). Despite the significant increase in the number of studies analyzing this issue, the brain correlates of creativity still remain inconclusive (Arden et al., 2010; Sawyer, 2011; Takeuchi & Kawashima, 2018). Specifically, prefrontal, parietal, temporal, and subcortical areas are some of the main brain regions that have been associated with creativity among healthy people (Abraham et al., 2018; Arden et al., 2010; Beaty et al., 2014, 2015, 2018; Boccia et al., 2015; Japardi et al., 2018; Shi et al., 2018; Sun et al., 2019; Vartanian et al., 2018; Wu et al., 2015). Nevertheless, most of these findings have come from fMRI studies.

With respect to structural brain correlates of creativity in healthy people, contradictory and inconclusive findings have been reported (Takeuchi & Kawashima, 2018). Moreover, few studies have explored the relationship between white matter structural connectivity and creativity. Among studies examining white matter FA, both positive (Takeuchi et al., 2010) and negative associations (Jung, Grazioplene, Caprihan, Chavez, & Haier, 2010), as well as non-significant associations (Takeuchi et al., 2016) have been found. For instance, in the study of Jung et al. (2010), a negative association between creativity (including both verbal and figural creativity tasks) and FA was found mainly within the left inferior frontal white matter. On the contrary, in the study of Takeuchi et al. (2010), positive associations between verbal creativity and FA from the bilateral prefrontal cortex, corpus callosum, cingulate cortex, bilateral basal ganglia, bilateral temporo-parietal junction, and the right inferior parietal lobe were found.

Findings from Takeuchi et al. (2010) suggest that multiple brain regions could underlie creativity.

Regarding the neuroanatomical substrates of creativity in schizophrenia, very few studies have been carried out (Folley, 2006; Son et al., 2015). Besides, these studies only focused on specific brain areas and the fluency dimension rather than analyzing the whole brain correlates of different dimensions of creativity, such as originality or flexibility (Folley, 2006; Son et al., 2015). Furthermore, no significant brain associations with creativity were found in these studies (Folley, 2006; Son et al., 2015).

Interestingly, brain white matter regions that have been related to creativity in healthy people (Jung et al., 2010; Takeuchi et al., 2010) are regions that seem to be impaired in schizophrenia (Bora et al., 2011; Ellison-Wright and Bullmore, 2009; Stämpfli et al., 2019). Therefore, it may be possible that the creativity impairments found in this disorder are due, at least in part, to abnormalities in white matter.

2.7. Cognitive Remediation in Schizophrenia

Due to the lack of effectiveness of pharmacological treatment in improving cognitive impairment and functional outcome in individuals with schizophrenia, cognitive remediation began to gain importance a few decades ago (Wykes et al., 2007). Cognitive remediation was defined by the Cognitive Remediation Experts Working (CREW) Group as an intervention based on behavioral training that has the aim to improve cognitive processes in order to generalize them and make them endure (Wykes et al., 2011). Although this intervention was designed with the aim of improving cognition, it was expected that functional outcome would also be indirectly improved (Wykes et al., 2007). Cognitive remediation is based on three main principles: compensation, substitution, and direct training (Zangwill, 1947).

There is a great variety of cognitive remediation programs, as these can be based on different methods or approaches (e.g., drill and practice vs drill plus strategy, or computerized vs paper and pencil; Wykes et al., 2011). In addition, cognitive remediation can be implemented in conjunction with other interventions or trainings, such as social or functional skill training programs. This is the case of the REHACOP program, an integrative group-based cognitive remediation program that combines training in neurocognition, social cognition, social skills and functional skills (Ojeda & Peña, 2012). In the next section, an overview of effectiveness of cognitive remediation in multiple domains among patients with schizophrenia is presented.

2.7.1. Cognitive, Creative, Clinical, and Functional Improvements after Cognitive Remediation

The effectiveness of cognitive remediation in improving different impaired domains in schizophrenia has been supported by multiples meta-analyses (Cella et al., 2017, 2020; Green et al., 2000; McGurk et al., 2007; Revell et al., 2015; Wykes et al., 2011). Specifically, cognitive remediation has shown to improve not only neurocognition and social cognition, but also clinical symptoms and functional outcome of people with this disease (Cella et al., 2017, 2020; Revell et al., 2015; Wykes et al., 2011). Nevertheless, it should be mentioned that previous studies analyzing the effects of cognitive remediation on clinical symptoms did not assess primary negative symptoms separately, but primary and secondary symptoms together.

As mentioned before, cognitive remediation can be implemented in combination with additional trainings. In fact, it has been suggested that the combination of different types of interventions enhances the effect that individual treatments have on each other and, therefore, can produce greater improvements than the application of cognitive remediation alone (Cella et al., 2015). Evidence on the benefits of combining cognitive remediation with other trainings is more limited than that of implementing cognitive remediation alone, but in the last decade, the number of studies exploring this idea has been increasing slightly. Nevertheless, this evidence still comes from a heterogeneous and small number of studies. For instance, several studies have employed a combination of cognitive remediation with social cognitive training (Bechi et al., 2015; Fernandez-Gonzalo et al., 2015; Fisher et al., 2017; Hooker et al., 2012; Lindenmayer et al., 2018; Mueller et al., 2015). Other studies have combined cognitive remediation with social skill training (Galderisi et al., 2010), with functional skill training (Bell et al., 2008) or with both social and functional skill training (Bowie et al., 2012; Sánchez et al., 2014). In addition, there is evidence for the effectiveness of applying a combination of cognitive training, social cognitive training as well as social and functional skill training (Peña et al., 2016). It is worth mentioning that some of these authors have suggested that future research should improve several methodological issues (Bechi et al., 2015; Galderisi et al., 2010; Lindenmayer et al., 2018; Mueller et al., 2015; Peña et al., 2016), such as the assessment tools for social cognition, functional outcome or negative symptoms and the inclusion of an active control group.

Finally, considering the role of cognitive capacity in the creative performance of people with schizophrenia (Abraham et al., 2007; Jaracz et al., 2012), it may be possible that training cognition could indirectly improve the creative capacity. Taking into account that creativity has been shown to influence functional outcome among patients with this disease (Nemoto et al., 2007), the possibility of improving creativity through cognitive remediation could be relevant. It seems that only one study (Kiritsis, 2018) to date has explored whether cognitive training could improve creative capacity in people with schizophrenia, but this study did not include a patient control group. Therefore, more research is needed to explore whether cognitive remediation could be an effective intervention in improving creativity in this disease.

2.7.2. Mediating Mechanisms of Functional Improvement

Although there is a large body of literature indicating that cognitive remediation is effective in improving functional outcome, still multiple questions remain unanswered (Barlati et al., 2019). The Medical Research Council and the National Institute of Mental Health highlighted that it is necessary to clarify which mechanisms can lead to a greater benefit from these kind of interventions (Wykes et al., 2012). Identifying mediating mechanisms of improvement would allow the development of more personalized treatment plans (Seccomandi et al., 2020) as well as the proper management of health-care resources (Cella et al., 2015).

However, some recent reviews indicate that very few studies have analyzed which characteristics of patients with schizophrenia could predict functional outcome improvement after cognitive remediation (Barlati et al., 2019; Seccomandi et al., 2020). Baseline cognitive performance and functioning, age, clinical symptoms, premorbid adjustment, and cognitive change after cognitive remediation are some of the identified individual characteristics associated with functional response to cognitive remediation (Barlati et al., 2019). In a systematic review carried out by Seccomandi et al. (2020), no high-quality replicated evidence was found of any reliable moderator predicting improvement after cognitive remediation. Research on the cognitive changes induced by cognitive remediation that have been related to functional improvement has been scarce (Barlati et al., 2019). Specifically, executive functioning (Eack et al., 2011; Wykes et al., 2012), working memory (Rispaud et al., 2016), verbal memory (Fiszdon et al., 2008; Peña et al., 2018), processing speed (Peña et al., 2018; Rispaud et al., 2016), and emotion management (Eack et al., 2011) are some of the cognitive domains where changes have been related to an improvement in functional outcome. Fewer studies have looked at cognitive changes related to functional improvement following cognitive remediation combined with social cognition or social and functional skill training (Eack et al., 2011; Peña et al., 2018; Sánchez et al., 2014). Due to the lack of studies and the mixed findings, further investigation of possible predictors is needed (Barlati et al., 2019; Reser et al., 2019; Seccomandi et al., 2020).

2.7.3. Brain Changes after Cognitive Remediation in Schizophrenia

In addition to cognitive, clinical, and functional improvements, recent literature suggests that cognitive remediation could also produce brain structural and functional changes in patients with schizophrenia (Hegde et al., 2020). Moreover, brain changes tend to correlate with cognitive changes after cognitive remediation (Eack et al., 2010; Penadés et al., 2013, 2016). Nevertheless, the underlying neural mechanisms of cognitive remediation in schizophrenia are not yet well understood (Penadés et al., 2017). Two main neuroimaging techniques that have been used in order to analyze this issue are fMRI and sMRI.

Regarding both task-based and resting-state fMRI studies, the most commonly reported finding is an increased activation mainly in prefrontal regions (Eack et al., 2016; Edwards et al., 2010; Fan et al., 2017; Haut et al., 2010; Keshavan et al., 2017; Subramaniam et al., 2012; Vianin et al., 2014; Wykes et al., 2002). In fact, as indicated in a systematic review of Penadés et al. (2017), the first studies in this field focused in the hypofrontality hypothesis, suggesting that frontal hypoactivation was the main underlying mechanisms of cognitive impairment and that cognitive remediation could increase this activation. In addition to prefrontal cortex, greater activation in other brain regions including inferior and superior parietal lobe, middle occipital cortex, anterior and middle cingulate cortex, and thalamic regions have also been reported in several studies (Bor et al., 2011; Donohoe et al., 2018; Edwards et al., 2010; Fan et al., 2017; Habel et al., 2010; Ramsay, Nienow, et al., 2017; Ramsay & Macdonald, 2015; Vianin et al., 2014; Wei et al., 2016). Furthermore, a recent meta-analysis concluded that brain effects of cognitive remediation were widely distributed across subcortical and cortical regions, with no specific brain regions showing consistent effects across studies (Mothersill & Donohoe, 2019).

More recently, studies have begun to examine additional aspects such as the functional connectivity in different brain networks at task-based and resting-state fMRI (Penadés et al., 2017). It is now suggested that increased brain activation does not necessarily involve a better cognitive functioning (Penadés et al., 2017). Specifically, it may be possible that cognitive remediation could produce a more efficient connectivity in different networks, activating or deactivating brain regions when necessary (Penadés et al., 2017). For instance, diverse interconnected regions that should be active during resting-state (e.g. the DMN), should be deactivated during the performance of cognitive tasks (Penadés et al., 2017). This was the case of the study of Penadés et al. (2013), in which patients with schizophrenia showed a decreased activation of several areas from the DMN during the performance of a cognitive task after a four-month cognitive remediation, achieving activation patterns similar to those of HC.

With respect to structural changes after cognitive remediation in schizophrenia, less literature is available (Eack et al., 2010; Matsuoka et al., 2019; Morimoto et al., 2018; Penadés et al., 2013; Ramsay, Fryer, et al., 2017). Results from these studies suggest that cognitive remediation could have a neuroprotective effect on the brain (Hegde et al., 2020; Penadés et al., 2017). Two studies have found significant changes in grey matter volume, mainly in temporal regions (Eack et al., 2010; Morimoto et al., 2018). Specifically, Eack et al. (2010) found greater preservation of grey matter volume in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and increased left amygdala grey matter volume after a two-year cognitive remediation. More recently, Morimoto et al. (2018) found increased grey matter volume in the right hippocampal region after 12 weeks of cognitive remediation. In addition, Ramsay, Fryer, et al. (2017) found that the cognitive remediation group who had improved cognitive functioning showed increases in left thalamic volume, although they did not find a significant group x time effect.

To date, very few studies have analyzed the effect of cognitive remediation on white matter integrity in schizophrenia (Matsuoka et al., 2019; Penadés et al., 2013). Penadés et al. (2013) found increased FA in the anterior part of the genu of the corpus callosum and in the right posterior thalamic radiations after cognitive remediation. Matsuoka et al. (2019) also found increased FA as well as decreased RD and MD after cognitive remediation, although these changes were located in the posterior lobe of the left cerebellum.

Altogether, literature indicates that cognitive remediation may produce structural and functional brain changes mainly in frontal and temporal regions in patients with schizophrenia and that these changes may be related to cognitive improvements (Matsuda et al., 2019; Penadés et al., 2017). However, results are still heterogeneous and inconclusive. Moreover, evidence for brain changes induced by integrative cognitive remediation combined with other trainings comes from a small number MRI studies (Eack et al., 2010; Eack et al., 2016; Keshavan et al., 2017; Subramaniam et al., 2014). Therefore, further research is needed to better understand the neural mechanisms of cognitive remediation.

III. Approach to the present study and objectives

3. Approach to the present study and objectives

The present thesis includes six studies examining on the one hand, the association between creativity and different neuropsychological, clinical, functional and brain characteristics in schizophrenia and on the other hand, the effect of a cognitive remediation program in cognition, creativity, functional outcome, clinical symptoms, and brain structure and function. The objectives and hypotheses for each study are described below.

3.1. Study I

"Mediating role of cognition and social cognition on creativity among patients with schizophrenia and healthy control: revisiting the Shared Vulnerability Model"

Background

As suggested by the Shared Vulnerability Model, impairment in cognitive flexibility and working memory could lead to worse creative performance among individuals with schizophrenia. Another impaired function in schizophrenia, previously related to creativity in healthy people, is theory of mind. However, little is known about the effect of theory of mind in creativity in schizophrenia.

Objectives

- The first objective was to analyze differences in various dimensions of creativity in patients with schizophrenia and HC.
- The second aim was to assess whether cognitive flexibility, working memory, and theory of mind mediate the relation between schizophrenia and different creative abilities.

Hypotheses

- Patients with schizophrenia would obtain lower scores in creativity compared to HC.
- The poorer creative performance among patients with schizophrenia would be at least partially due to deficits in cognitive flexibility, working memory and theory of mind.

3.2. Study II

"Neurocognitive, social cognitive, and clinical predictors of creativity in schizophrenia"

Background

It has been suggested that impairment in working memory, cognitive flexibility, and theory of mind could lead to lower creativity in schizophrenia. Additionally, other neurocognitive and social cognitive domains, as well as clinical symptoms could play a role in this relationship. However, the extent to which each of these domains influences creativity in schizophrenia remains unknown.

Objective

- The aim was to simultaneously investigate the specific contribution of neurocognitive, social cognitive, and clinical variables to creativity in schizophrenia.

Hypothesis

- Creativity of patients with schizophrenia would be partly explained by different factors including clinical, neurocognitive, and social cognitive variables. Regarding clinical symptoms, these would be negatively associated with creativity. With respect to neurocognitive and social cognitive variables, these would be positively related to creativity.

3.3. Study III

"The impact of creativity on functional outcome in schizophrenia: a mediational model"

Background

Functional impairment remains one of the most challenging issues for treatment in schizophrenia. However, previous studies have mainly focused on the negative impact of symptoms excluding variables that could positively impact functional outcome, such as creativity, which is considered an adaptive capacity for real-life problem solving.

Objective

- The aim was to analyze the predictive role of creativity on functional outcome in patients with schizophrenia through a mediational model including sociodemographic, clinical, neurocognitive, and social cognitive variables.

Hypothesis

- Creative capacity would be associated with functional outcome, mediating the association between neurocognition, social cognition, negative symptoms, and functional outcome in schizophrenia

3.4. Study IV

"Brain white matter correlates of creativity in schizophrenia: a diffusion tensor imaging study"

Background

The relationship between creativity and psychopathology has been a controversial research topic for decades. Specifically, it has been shown that people with schizophrenia have an impairment in creative performance. However, little is known about the brain correlates underlying this impairment.

Objective

- The aim was to analyze whole brain white matter correlates of several creativity dimensions in people with schizophrenia.

Hypothesis

- Creativity would be positively associated mainly with the frontal lobe as well as with interhemispheric white matter fibers.

3.5. Study V

"Cognitive, creative, functional, and clinical symptom improvements in schizophrenia after an integrative cognitive remediation program: a randomized controlled trial"

Background

The combination of cognitive remediation with other trainings has shown to improve cognition, functional outcome, and clinical symptoms in schizophrenia. However, results among studies are still heterogeneous and little is known about predictors of functional outcome improvement. Moreover, the possible effectiveness of integrative cognitive remediation in improving primary negative symptoms and creative capacity, which has been related to functional outcome, remains unknown.

Objectives

- The first objective was to analyze the effectiveness of an integrative cognitive remediation program, REHACOP, which combines training in neurocognition, social cognition, social skills and functional skills, in improving cognition, creativity, functional outcome, and clinical symptoms in patients with schizophrenia.

- The second objective was to explore the possible mediators predicting improvement in functional outcome after the integrative cognitive remediation program.

Hypotheses

- Patients who attend the integrative cognitive remediation would improve cognition, creativity, functional outcome, and clinical symptoms in comparison to patients from the active control group.
- Improvement in cognition would mediate between receiving integrative cognitive remediation and improvement in functional outcome.

3.6. Study VI

"Analyzing structural and functional brain changes related to an integrative cognitive remediation program in schizophrenia: a randomized controlled trial"

Background

Brain changes after cognitive remediation in patients with schizophrenia have been demonstrated in previous studies. However, results among studies are still heterogeneous and little is known about the structural as well as functional changes after the combination of cognitive remediation with other trainings in schizophrenia.

Objectives

- The aim was to assess the structural and functional brain changes related to an integrative cognitive remediation program, REHACOP, in patients with schizophrenia.

Hypotheses

- Patients who attend the integrative cognitive remediation would show functional and structural brain changes in comparison to patients from the active control group.

IV. Methods

4. Methods

4.1. Studies Sample

All the studies of the present thesis include patients with schizophrenia from the same dataset. Additionally, Study I includes a HC sample. A more detailed explanation about the recruitment and characteristics of the sample is provided in the following section.

4.1.1. Patients with schizophrenia

Patients with schizophrenia were recruited from the Psychiatric Hospital of Álava and the Mental Health Network in Álava (Spain). All patients with schizophrenia met the following inclusion and exclusion criteria.

Inclusion criteria:

a) Adults between 18 and 65 years.
b) Meeting the diagnostic criteria for schizophrenia according to the DSM-5 (F20.9) (American Psychiatric Association, 2013).
c) More than two years since the onset of the disease.

Exclusion criteria:

a) Clinical instability, which consisted on meeting the relapse criteria of Csernansky et al. (2002).
b) Significant changes in the antipsychotic treatment in the previous three months.
c) Cognitive impairment secondary to another medical condition (e.g., dementia or brain injury).
d) Diagnosis of an active Major Affective Disorder.

e) Diagnosis of Substance Use Disorder according to the DSM-5 (American Psychiatric Association, 2013) and including alcohol during the six months prior to study inclusion (with the exception of nicotine).
f) Patients undergoing a cognitive remediation program (different from the REHACOP) already started.
g) Incompatibilities with MRI (e.g., claustrophobia, metal implants in the body, or patients who were undergoing deep brain stimulation). This criterion was only applied to patients who underwent a MRI acquisition.

4.1.2. Healthy controls

HC for Study I were recruited in Biscay (Spain). The HC group met the following inclusion and exclusion criteria.

Inclusion criteria:

a) Adults between 18 and 65 years.

Exclusion criteria:

a) Presenting of severe cognitive impairment.
b) Having a medical history of psychiatric or systemic disease.
c) Previous history of substance abuse.

4.2. Procedure

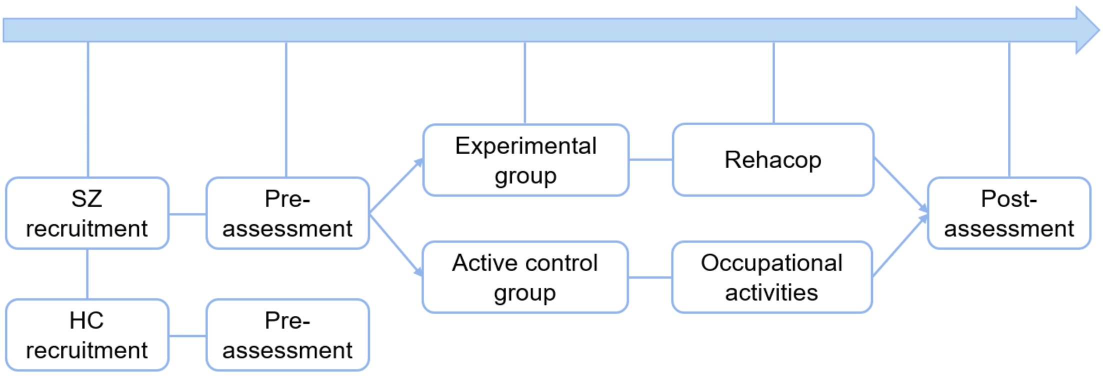
The study design was a parallel-group randomized trial. The patients' psychiatrists gave them the opportunity to participate in the study. Recruitment and enrollment were conducted between June 2017 and June 2020. The present thesis included two arms: a cognitive remediation group and an active control group. This study is part of a larger project that has been later expanded to include an additional arm (a group receiving intense physical exercise). The cognitive remediation arm has been completed, while the physical exercise arm is ongoing. Therefore, the physical exercise arm has not been included in this thesis. Patients were randomly assigned to each study condition using an online computer-generated randomization. All patients underwent a neuropsychological and psychiatric assessment at baseline and after 5-month follow-up. Additionally, some of these patients underwent a MRI acquisition at baseline and after 5-month follow-up. Post-treatment assessment (finished by November 2020) was performed within the first three weeks after completing the intervention. All raters were blind to the experimental treatment condition and had no other role in the study that could undermine the trial blinding. The design of the study is summarized in Figure 2.

Studies I, II, III and IV include cross-sectional data from the pre-treatment assessment and Studies V and VI include longitudinal data from the pre- and post-treatment assessments.

The sample of HC used in study I was recruited in 2018 for another project. For this reason, this HC sample only underwent a neuropsychological assessment of some specific domains (specified later).

Figure 2

Summary of study design



Note. SZ = Patients with schizophrenia; HC = Healthy controls; REHACOP = Cognitive Remediation Program for Psychosis.

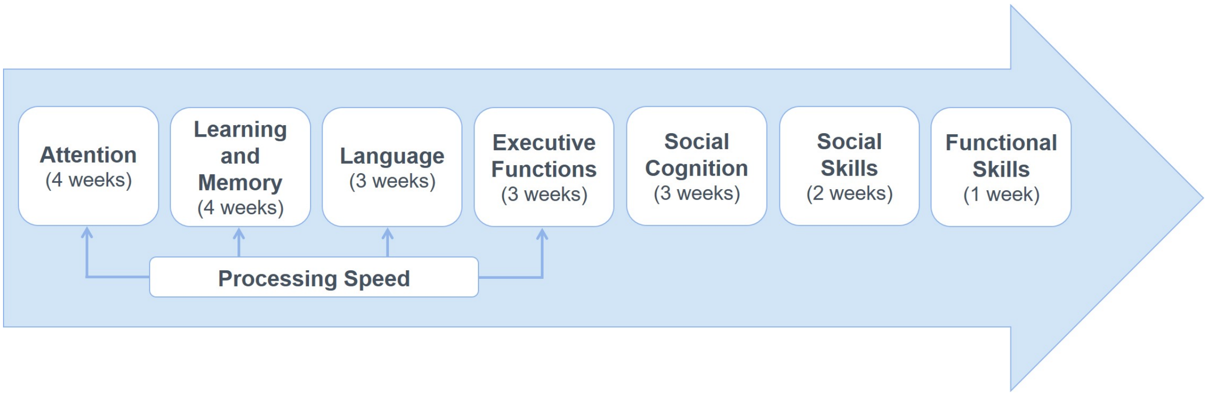
4.3. REHACOP: Integrative Cognitive Remediation Program

The cognitive remediation program implemented in this thesis (used in Study V and VI) is the REHACOP (www.rehacop.deusto.es). REHACOP is a group-based integrative cognitive remediation program that combines training in neurocognition, social cognition, social skills and functional skills (Ojeda & Peña, 2012). This program was specifically designed for patients with psychosis (Ojeda, Peña, Bengoetxea, et al., 2012). It is based on the principles of restoration, compensation and optimization and it includes top-down and bottom-up strategies. REHACOP is highly structured, which allows replication and reduces the effect of differences between therapists. This intervention program includes up to 300 different tasks that are divided in different units and subtypes of abilities. Tasks within each unit are hierarchically ordered by subtype of abilities and levels of complexity to ensure an increasing level of cognitive demand. The efficacy of the REHACOP in patients with schizophrenia has already been documented in previous studies (Ojeda, Peña, Sánchez, et al., 2012; Peña et al., 2016; Sánchez et al., 2014).

In this thesis, sessions were held with nine groups, of between 4 and 8 patients each, at various centers which were part of the Mental Health Network in Álava (the Psychiatric Hospital of Álava, the Association of Relative and Patients with Mental Illness from Ayala, and the Community Rehabilitation Service Center). The clinical team who conducted the intervention was trained on administering REHACOP, and used the same materials and instructions in all the groups. Patients attended 60-min sessions, 3 days per week, during 20 weeks. The REHACOP intervention group trained the following units (Figure 3): Attention unit (4 weeks), with training on sustained, selective, alternant, and divided attention; Learning and Memory unit (4 weeks), including visual and verbal learning, recall, recognizing memory, working memory as well as compensatory strategies; Language unit (3 weeks), focused on syntax, vocabulary, grammar, verbal comprehension, verbal fluency, and abstract language; Executive Functions unit (3 weeks), including cognitive and objective planning, novel problem solving, cognitive flexibly, reasoning, categorization, conceptualization; Social Cognition unit (3 weeks), with training on emotion processing, social reasoning, moral dilemmas, and theory of mind; Social Skills unit (2 week); and Functional Skills unit (1 week), including activities of daily living. Additionally, several tasks were timed to train processing speed throughout the first four units. The intervention included paper-and-pencil tasks, role-playing, and active group discussions. Although the REHACOP program includes a Psychoeducation unit, this was not included in the remediation schedule since patients from both experimental and active control groups received psychoeducation sessions as part of the treatment as usual.

Figure 3

Units that were trained in REHACOP



When a patient missed one or more sessions for various reasons (i.e., vacations or leave), they received individual training based on the contents that had been trained in the group session or alternatively, receiving feedback through homework afterwards. This allowed the patient to meet the objectives of missed training sessions. The patient would then join the experimental group again. Due to the COVID-19 pandemic, several experimental (n = 13) and active control (n = 2) groups were temporarily discontinued at the beginning of the interventions. Therefore, individual booster sessions were conducted for two weeks before intervention groups were resumed.

The active control group carried out occupational group activities with the same frequency and duration as the experimental group. The activities included gardening, sewing, handicrafts, painting, and music.

4.4. Neuropsychological and Clinical assessment

All studies included an extensive neuropsychological and a clinical assessment to stablish the sociodemographic, cognitive, creative, functional, and clinical characteristics of the sample. The neuropsychological assessment (including the cognitive, creative, and functional domains) was administered by a trained neuropsychologist and the clinical assessment was administered by trained psychiatrics. This assessment will be explained in more detail below. In addition, a summary of this assessment in provided in Table 1. HC for Study I were assessed in working memory, cognitive flexibility, theory of mind, and creativity.

Table 1

Neuropsychological and clinical assessment

Area/domain	Assessment tool
Nonsocial cognition	
Premorbid IQ	Word Accentuation Test (WAT)
Processing speed	Symbol-Coding subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III)
	Stroop Color and Word Test (SCWT)
Working memory	Backward Digit Span subtest from the WAIS-III
Verbal memory	Hopkins Verbal Learning Test-Revised (HVLT-R)

Executive functions (cognitive flexibility and inhibition)	Modified Wisconsin Card Sorting Test (M-WCST)
	SCWT
Social cognition	
Theory of mind	Happé Test (Strange Stories Task)
Social perception	Social Attribution Task Multiple Choice (SAT-MC)
Emotion processing	Bell Lysaker Emotion Recognition Test (BLERT)
Creativity	
Figural creativity	Picture Completion subtest from the Torrance Test of Creative Thinking (TTCT)
Verbal creativity	Unusual Uses subtest from the TTCT
Functional outcome	
Functional competence	University of California San Diego (UCSD) Performance-Based Skills Assessment (UPSA)
Social functioning	Social Functioning Scale (SFS)
Hedonic capacity	Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)
Self-efficacy	General Self-Efficacy Scale (GSES)
Clinical assessment	
Clinical symptoms	Positive and Negative Syndrome Scale (PANSS)
	Brief Negative Symptom Scale (BNSS)
Awareness of mental disorder	Scale of Unawareness of Mental Disorder (SUMD)
Medication	Chlorpromazine equivalence based on Defined Daily Dose method
Other domains	
Handedness	Edinburgh Handedness Inventory (EHI)
Satisfaction with the treatment	Consumer Reports Effectiveness Scale (CRES)

Note. IQ = intelligence quotient; WAT = Word Accentuation Test; WAIS-III = Wechsler Adult Intelligence Scale-III; SCWT = Stroop Color and Word Test; HVLT-R = Hopkins Verbal Learning Test-Revised; M-WCST = Modified Wisconsin Card Sorting Test; SAT-

MC = Social Attribution Task Multiple Choice; BLERT = Bell Lysaker Emotion Recognition Test; TTCT = Torrance Test of Creative Thinking; UCSD = University of California San Diego; UPSA = UCSD Performance-Based Skills Assessment; SFS = Social Functioning Scale; ACIPS = Anticipatory and Consummatory Interpersonal Pleasure Scale; GSES = General Self-Efficacy Scale; PANSS = Positive and Negative Syndrome Scale; BNSS = Brief Negative Symptom Scale; SUMD = Scale of Unawareness of Mental Disorder; EHI = Edinburgh Handedness Inventory; CRES = Consumer Reports Effectiveness Scale.

4.4.1. Nonsocial cognition

Regarding nonsocial cognition, premorbid IQ, processing speed, working memory, verbal memory, and executive functions were measured:

Premorbid IQ. Premorbid IQ was measured with the Word Accentuation Test (WAT) (Del Ser et al., 1997), a Spanish version of the National Adult Reading Test (Nelson & Willison, 1991). In this WAT test, the participant is asked to read aloud a total of 30 words taking into account their accentuation. Premorbid IQ was estimated using raw scores converted with the full scale IQ of Gomar et al. (2011).

Processing speed. Processing speed was measured by the Symbol-Coding subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 2002) and the Word and Color values from the Stroop Color and Word Test (SCWT) (Golden, 2010). The Symbol-Coding subtest consists of copying the highest number of symbols corresponding to the numbers 1 to 9 (based on a template) in a time of two minutes. The SCWT is composed of three trials of 45 seconds (Word, Color, and Word-Color). In the Word trial, the participant is asked to read aloud a list of words (red, blue, and green) as quickly as possible. In the Color trial, the participant is asked to name the colors of a sheet with series of four X “XXXX” printed in red, blue or green as quickly as possible.

Working memory. Working memory was assessed using the Backward Digit Span subtest from the WAIS-III (Wechsler, 2002). This test consists of repeating sequences of numbers or digits backwards.

Verbal memory. Verbal memory was measured by the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001). In HVLT-R, the participant is asked to repeat in three trials as many words as she/he can recall from a list of 12 words and after 20 minutes is asked again to freely recall the words from the list. Equivalent forms of the HVLT-R were administered at baseline (version 2) and at post-treatment (version 4) to avoid learning effect.

Executive functions. For the assessment of executive functions, specifically cognitive flexibility and inhibition, the Modified Wisconsin Card Sorting Test (M-WCST; Schretlen, 2010) and the SCWT (Golden, 2010) were used. In the M-WCST, the participant is asked to make categories (color, form, and number of figures) with a total of 48 cards. The examiner informs the participant whether the answer is correct or incorrect and the category is changed every six correct answer. The number of categories completed and the number of perseverative errors were used from M-WCST. From the SCWT, the Word-Color and Interference values were used. In the Word-Color trial, the participant is asked to name as quickly as possible the color ink in which each word is presented (red, blue and green color words printed in incongruent colors). Interference was calculated by means of the following formula:

$$\text{WordColor} - \left[\frac{\text{Word x Color}}{\text{Word} + \text{Color}}\right] = \text{Interference}$$

4.4.2. Social cognition

Social cognition was measured by means of three domains: theory of mind, social perception, and emotion processing:

Theory of mind. Theory of mind was assessed using the Happé Test "Strange Stories Task" (Happé, 1994). Four different stories concerning double bluff, white lies, persuasion, and mistakes were administered at baseline and post-treatment. The participant is asked to read and then answer a question about each story. The questions require making an inference about the character's thoughts and intentions. Each response was scored within a range of 0-2. Explicit answers had a 2-point score, implicit answers a 1-point score, and no response or non-related responses scored 0 points.

Social perception. Social perception was measured by means of the Social Attribution Task-Multiple Choice (SAT-MC; Johannesen et al., 2013). SAT-MC consists of watching and answering 19 questions about an animated video of a social drama enacted by geometric figures. Version 2 of the SAT-MC was administered at baseline and version 1 at post-treatment.

Emotion processing. Emotion processing was evaluated through the Spanish adaptation of the Bell Lysaker Emotion Recognition Test (BLERT; Bell et al., 1997). BLERT consists of a video showing 21 vignettes in which the same actor portrays an emotional state (happiness, sadness, fear, disgust, surprise, anger, or no emotion) through facial, vocal-tonal, and upper-body movement cues. The participant must indicate which emotion is being portrayed in each vignette. Version 2 of the BLERT was used at baseline and version 1 of the BLERT at post-treatment.

4.4.3. Creativity

Both figural and verbal creativity were measured through two divergent thinking subtests:

Figural creativity. Figural creativity was measured through the *Picture Completion* subtest from the Torrance Test of Creative Thinking (TTCT; Torrance, 1966, 2016). This task consists of completing ten unfinished pictures by producing as many ideas as possible. The following dimensions were obtained: originality, fluency, flexibility, elaboration, resistance to premature closure, abstractness of titles, and figural creative strengths. Flexibility was scored using the criteria from the Spanish adaptation of the TTCT (Jiménez et al., 2007). Figural creative strengths score was calculated based on the manual (Torrance, 2016). Figural creative strengths consisted of 11 criterion-referenced measures: emotional expressiveness, storytelling articulateness, movement or action, expressiveness of titles, synthesis of incomplete figures, unusual visualization, internal visualization, humor, richness of imagery, colorfulness of imagery, and fantasy. Version A was administered at baseline and version B at post-treatment.

Verbal creativity. Verbal creativity was assessed with the *Unusual Uses* subtest from the TTCT (Torrance, 1966, 2016). In this activity, participants are asked to write as many unusual uses as possible for cardboard boxes (version A) or tin cans (version B) in four minutes. Originality, fluency, and flexibility dimensions were measured (Torrance, 1966, 2016). Version A was administered at baseline and version B at post-treatment.

4.4.4. Functional outcome

Functional competence. Functional competence was measured with the Spanish Version of the University of California, San Diego (UCSD), Performance-Based Skills Assessment (UPSA; Garcia-Portilla et al., 2013). With this measure, patients are asked to perform everyday activities in four areas: finances, communication, planning recreational activities, and transportation.

Social functioning. Social functioning was evaluated by means of the short Spanish version of the Social Functioning Scale (SFS) (Alonso et al., 2008). The SFS is a 15-item scale that evaluates different functioning domains including social engagement and withdrawal, interpersonal communication, pro-social activities, independence (competence and performance), recreation, and employment.

Hedonic capacity. hedonic capacity for social interactions was assessed using the Spanish adaptation of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)-Adult version (Gooding et al., 2016). The ACIPS is a scale comprised of 17 items in which higher scores indicate greater hedonic capacity.

Self-efficacy. General self-efficacy was measured with the Spanish adaptation of the General Self-Efficacy Scale (GSES; Sanjuán Suárez et al., 2000). GSES is a 10-item scale in which higher scores indicate the belief of higher self-efficacy.

4.4.5. Clinical assessment

Clinical symptoms. Clinical symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011). For Studies I, II, and III, the Positive Scale, Negative Scale, and General Psychopathology Scales were sourced from the PANSS. For Studies VI, V and VI, scores for the dimensions Positive Symptoms, Disorganization, Excitement, and Depression were obtained following the consensus 5-factor solution proposed by Wallwork et al. (2012), which included four, three, four and three items from the PANSS respectively. Additionally, as recommended by the NIMH-MATRICS Consensus Statement on Negative Symptoms (Carpenter et al., 2016; Kirkpatrick et al., 2006), in Studies II, IV, V, and VI negative symptoms were measured through the BNSS (Kirkpatrick et al., 2011), composed of 13 items.

Awareness of mental disorder. Awareness of mental disorder was assessed by the Scale of Unawareness of Mental Disorder (SUMD; Amador et al., 1993). Three items from the SUMD about awareness of mental disorder, awareness of the effects of medication, and awareness of the social consequences of the disorder were used. Higher scores in the SUMD indicate poorer awareness.

Medication. Antipsychotic medication dosage was converted to chlorpromazine (mg/day) by using the defined daily dose method (Leucht et al., 2016; Rothe et al., 2018).

4.4.6. Other domains

Additionally, other aspects such as handedness and satisfaction with the treatment received were evaluated. This assessment was also administered by a trained neuropsychologist.

Handedness. Handedness was measured through the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). The following formula was used to calculate handedness consistency. The scores obtained in EHI ranged from 100 (wholly right-handed) to -100 (wholly left-handed). Participants who obtained scores ranging from -79 to 79 were considered to be mixed-handed, and those with scores ranging from -100 to -80 or from 80 to 100 to be consistent-handed.

$$\frac{\text{right} - \text{left}}{\text{right} + \text{left}}$$

Satisfaction with the treatment. Satisfaction with the received treatment was assesses by means of the Spanish adaptation of the Consumer Reports Effectiveness Scale (CRES; Feixas et al., 2012). The CRES consists of four items evaluating satisfaction with the therapist, satisfaction with the treatment received, and the emotional state before and after the treatment. Global score of the CRES was obtained by means of the following formula:

$$(20 \times \text{item 1}) + (20 \times \text{item 2}) + [12.5 \times (4 + \text{item 4} - \text{item3})]$$

4.5. Neuroimaging Acquisition

Functional and structural imaging data were acquired on a 3T MRI (Philips Achieva Dstream) at OSATEK, Hospital of Galdakao (Spain). All sequences were acquired during a single session and the same protocol was used for pre- and post-treatment acquisitions.

T1-weighted images acquisition were obtained in a sagittal orientation (TR = 7.4 ms, TE = 3.4 ms, matrix size = 228 x 218 mm; flip angle = 9°, FOV = 250 x 250 x 180 mm, slice thickness = 1.1 mm, 300 slices, voxel size = 0.98 x 0.98 x 0.60 mm, acquisition time = 4′55″).

Diffusion-weighted images were obtained, in an axial orientation in an anterior-posterior phase direction using a single-shot EPI sequence (TR = 7540 ms and TE = 76 ms, matrix size = 120 mm x 117 mm; flip angle = 90°, FOV = 240 x 240 x 130, slice thickness = 2 mm, no gap, 65 slices, acquisition time = 9’31”, voxel size = 1.67 x 1.67 x 2.0) with diffusion weighting in 32 uniformly distributed directions (b = 1000 s/mm^2) and 1 b = 0 s/mm^2.

The resting-state fMRI was obtained in an axial orientation in an anterior-posterior phase direction. A multiband multi-slice gradient echo EPI sequence (TR = 1121 ms, TE = 30 ms, matrix size = 80 x 78 mm, flip angle = 80°, FOV = 240 x 240 x 142.75 mm, slice thickness = 3 mm, 214 slices, voxel size = 3.00 x 3.00 x 3.00 mm, acquisition time = 4′05″) sensitive to blood oxygen level dependent (BOLD) contrast was used.

Finally, fMRI was obtained using a memory paradigm (learning and recognition tasks). The fMRI images were acquired using a multi-slice gradient echo EPI sequence (TR = 2000 ms, TE = 29 ms, matrix size = 100 x 100 mm, flip angle = 90°, FOV = 240 x 240 x 136 mm, slice thickness = 3 mm; 140 slices, voxel size = 1.67 x 1.67 x 3.00 mm, acquisition time = 4′48″. The same parameters were used for the learning and recognition task.

The memory fMRI paradigm included a learning task and a recognition task. This fMRI paradigm consisted of words presented with Visual Digital MRI Compatible High Resolution Stereo 3D glasses and Presentation® Version 18.1 (Neurobehavioral Systems) running on Windows Vista 10. Participants were given two response boxes (one in each hand) to record their behavioral responses. Each of the two entire experiments, learning task and recognition task, consisted of a 10-block paradigm that alternated activation and control conditions (5 blocks each) and lasted a total of 280 s (28 s per block; see Figure 4).

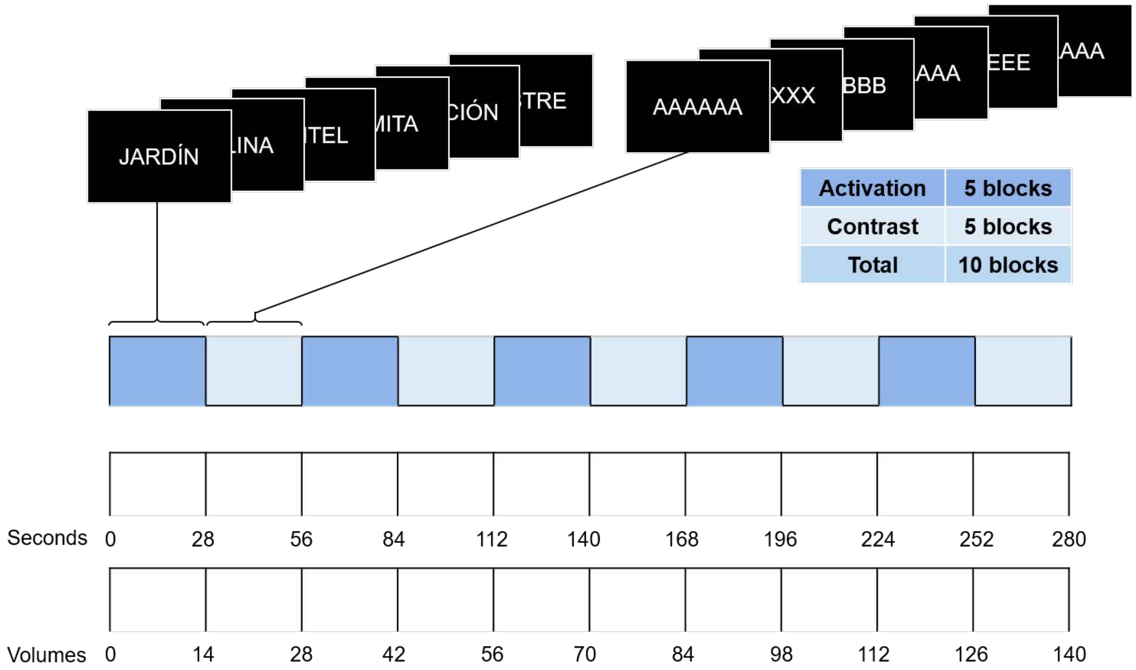
During the activation condition of the learning memory fMRI task, participants viewed 30 words, six words per block (duration of 2 s per word and an inter-word interval of 2 s), and were asked to press the right button (with their right hand) if they liked the word or the left button (with their left hand) if they did not like the word. As suggested by Marsolek et al. (1992), this task was used to ensure that participants fixed their attention on reading the words.

After 20 minutes, the activation condition of the recognition memory fMRI task was presented inside the scanner. During this recognition memory fMRI task, participants were asked to recognize words from a list of 30 words, of which 14 words had been presented during the learning memory fMRI task and 16 words were new. Participants were asked to press the button using their right hand to indicate if they remembered having read the word in the list during the learning fMRI task or the left button if they had not seen it before.

In the control condition, six concatenations of letters were projected simulating the length of a word. Three of these concatenations were the letters "AAAAAA" and the other three were random letters (e.g., "BBBBBB"). Again, participants were asked to press the right button on the response box to indicate that the item was "AAAAAA" and press the left button when other combinations of letters appeared. The control condition was the same for the learning and recognition tasks.

Figure 4

Representation of activation and contrast blocks in the memory fMRI paradigm



Responses given in the recognition task were coded as behavioral data. This was coded as "Hits" when participants answered yes and the answer was yes, as "Correct rejections" when participants answered no and the answer was no, as "False positives" when participants answered yes and the answer was no, and as "False negatives" when participants answered no and the answer was yes. Two equivalent versions of this memory fMRI paradigm were used at both time points (pre- and post-treatment) in order to avoid learning effects. In the pre-treatment version, the words were four to six letters in length and of moderate frequency of use. The post-treatment version was created including different words but with phonetic similarities and with the same number of syllables. This paradigm has previously shown cerebral activation related to recognition memory in Parkinson Disease (Díez-Cirarda et al., 2017; Lucas-Jiménez et al., 2015). Behavioral data from the recognition memory fMRI task were extracted to analyze in IBM SPSS.

4.6. Neuroimaging Preprocessing and Analyses

T1-weighted MRI, diffusion-weighted MRI, resting-state fMRI and memory fMRI paradigm data preprocessing was carried out with different techniques explained below. Neuroimaging analyses were conducted in Study IV and VI. In Study IV, only tract-based spatial statistic (TBSS) for white matter were carried out.

4.6.1. Tract-based spatial statistics

The FMRIB Software Library (FSL; Smith et al., 2004) version 5.0.11 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) was used for the preprocessing and analysis of diffusion data. First, data was corrected for head motion and eddy currents, brain-extraction was performed using the Brain Extraction Tool (BET; Smith, 2002), and the diffusion gradients (bvecs) were rotated to be corrected accordingly. Then, FA, MD, RD, axial diffusivity (AD), and mode of anisotropy (MO) images were obtained by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). Afterwards, voxelwise statistical analysis of the data was carried out using tract-based spatial statistic (TBSS; Smith et al., 2006). FNIRT tool (Andersson et al., 2007a, 2007b) was used to align all subjects' FA data into a common space by combining the nonlinear transform to the target FA image with the affine transform from that target to the Montreal Neurological Institute (MNI) 152 space. Later, the mean FA image was created using a threshold of 0.2 and thinned to create a mean FA skeleton, which represented the centers of all tracts common to the group. Each participant's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. The “tbss non FA” script from TBSS was used to analyze MD, RD, MO, and, AD data. This applies the original non lineal registration to the MD, RD, MO or AD data, merges all subjects warped MD, RD, MO or AD data into a 4D file, then projects this onto the original mean FA skeleton, and creates the 4D projected data.

Specifically in Study IV

To examine the relationship between white matter indexes and creativity, whole brain analyses by means of permutation-based inferences (5000 permutations) with the threshold-free cluster enhancement (TFCE) correction method for multiple comparisons, including the --T2 option, were carried out using FSL’s Randomise Tool (Winkler et al., 2014). Based on findings from previous literature (Bartzokis et al., 2003; Jensen et al., 2019; Kubota et al., 2015; Ryman et al., 2014; Samartzis et al., 2014; Schmithorst et al., 2005; Szeszko et al., 2008; Takeuchi et al., 2016; White et al., 2011), sex, age, premorbid IQ, and medication were entered as covariates in the regression analysis. The statistical threshold was set at $p < .05$ corrected for family-wise error (FWE), as suggested by Smith and Nichols (2009), with an extent threshold of 100 voxels. Effect sizes for each cluster of the correlations were calculated according to Cohen´s d formula. Cohen´s d of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively (Cohen, 1988). The maximum coordinates encompassed in the clusters and additional significant regions were visually inspected and located, and later labelled anatomically with the MRI Atlas of Human White Matter (Oishi et al., 2010) as well as the JHU-ICBM-DTI-81 White Matter Labels and JHU White-Matter Tractography Atlas implemented in FSL.

Specifically in Study VI

Whole brain analyses by means of permutation-based inferences (5000 permutations) with the TFCE correction method for multiple comparisons, including the --T2 option, were carried out using FSL's Randomise Tool (Winkler et al., 2014). The statistical threshold was set at $p < .05$ corrected for FWE, with an extent threshold of 30 voxels. The specific statistical analyses carried out in the four neuroimaging techniques are detailed in the *Statistical Analyses* section.

4.6.2. Voxel-based morphometry

Voxel-based morphometry (VBM; Douaud et al., 2007) analysis were carried out using the FSL version 5.0.11 (Smith et al., 2004). First, structural images were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007b). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3.5 mm (8 mm FWMH).

For whole brain analyses, permutation-based inferences (5000 permutations) with the TFCE correction method for multiple comparisons including the -T option, as recommend by the FSL, were carried out using FSL's Randomise Tool (Winkler et al., 2014). The statistical threshold was set at $p < .05$ corrected for FWE, with an extent threshold of 30 voxels. The maximum coordinates encompassed in the clusters and additional significant regions were visually inspected, located and labelled using the Harvard-Oxford Cortical Atlas.

4.6.3. Cortical thickness

Cortical Thickness changes were analyzed using FreeSurfer (version 6.0.0; http://surfer.nmr.mgh.harvard.edu). Processing of T1 high-resolution images for the cortical surface reconstruction followed the FreeSurfer analysis pipeline (Dale et al., 1999; Fischl et al., 1999; Reuter et al., 2012; Ségonne et al., 2004) and included several procedures: motion correction, intensity non-uniformity correction, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location. Cortical thickness was calculated as the closest distance from the grey matter/white matter boundary to the grey matter/cerebrospinal fluid boundary at each vertex on the tessellated surface. All surface models were visually inspected for accuracy.

Subsequently, for longitudinal processing, the longitudinal stream of FreeSurfer was used (Reuter et al., 2012), creating an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). Whole brain longitudinal differences between and within groups in cortical measures were assessed for each hemisphere using a vertex-by-vertex general linear model using FreeSurfer's command line "mri_glmfit". Data were smoothed with a Gaussian kernel of 15-mm FWHM to perform statistical analyses.

Cluster-wise correction for multiple comparisons was applied using Monte Carlo Z simulation, with a threshold of $p < .01$ as recently suggested by Greve and Fischl (2018). Additionally, a less conservative multiple comparisons correction with a threshold of $p < .05$ was also used for exploratory analyses. The simulation is a way to get a measure of the distribution of the maximum cluster size under the null hypothesis. This is done by iterating over the following steps: synthesize a Z map, smooth Z map, threshold Z map, find clusters in thresholded map, record area of maximum cluster, and repeat over 10,000 iterations (Hagler et al., 2006).

4.6.4. Data-driven approach for resting-state fMRI

Resting-state fMRI data were acquired during a so-called resting-state block. Subjects were instructed not to engage in any particular cognitive or motor activity, to keep their eyes closed, not to fall asleep and not to think about anything in particular during the resting-state fMRI. Foam padding and headphones were used to limit head movement and reduce scanner noise for the subjects. Once the resting-state fMRI acquisition finished, the radiologist talked with the patients and asked them whether they fell asleep or not. No patient reported falling asleep.

Resting-state fMRI data was preprocessed using Conn Functional Connectivity (CONN) Toolbox version 20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012). All preprocessing steps were conducted using the default preprocessing pipeline for volume-based analysis to a MNI space, which included: realignment and unwarp of functional images; functional centering; detection of functional outliers (Artifact Detection and Removal Tool-based scrubbing); functional segmentation (grey matter, white matter, and cerebrospinal fluid) and normalization into the standard MNI space; structural centering; structural segmentation and normalization into the standard MNI space; and functional smoothing using a Gaussian kernel of 8 mm FWHM. In addition, the default denoising pipeline (Nieto-Castanon, 2020) was used, which included a linear regression of potential confounding effects in the BOLD signal and temporal band-pass filtering (a frequency window of 0.008 to 0.09 Hz; Weissenbacher et al., 2009). The linear regression was done via an anatomical component-based noise correction procedure and included: noise components from cerebral white matter and cerebrospinal areas, estimated subject-motion parameters, identified outlier scans or scrubbing, constant and first-order linear session effects, and constant task effects (Nieto-Castanon, 2020).

Based on previous studies (Orliac et al., 2013; Seeley, 2019; Seeley et al., 2007; Shao et al., 2018; Spreng et al., 2016; Woodward et al., 2011), region of interest (ROI-to-ROI) analysis was conducted to analyze functional connectivity within the following networks: the DMN including middle prefrontal cortex, lateral parietal cortex, posterior cingulate cortex, precuneus, and medial temporal lobe structures; the ECN including lateral prefrontal cortex and posterior parietal cortex; the DAN including frontal aye fields, intraparietal sulcus, and superior parietal lobe; and the SN including anterior cingulate cortex, anterior insula, amygdala, hypothalamus, and thalamus. ROIs were selected from the FSL Harvard-Oxford Structures Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Following the standard criterion suggested by the CONN toolbox (Nieto-Castanon, 2020) for multiple comparisons correction, a false discovery rate (FDR)-corrected $p < .05$ cluster-level threshold in combination of an uncorrected $p < .001$ height threshold was used.

4.6.5. *Model-driven approach for memory fMRI paradigm*

Memory fMRI paradigm data were analyzed using Statistical Parametric Mapping (SPM) version 12 (Ashburner et al., 2020). The functional data of each participant were reoriented, motion-corrected, coregistered, and spatially normalized into the standard MNI space. Then, images were smoothed using a Gaussian kernel of 8 mm FWMH.

Statistical parametric maps were calculated at first-level analysis for each participant with a general linear model. After model estimation, a matrix was obtained for each participant showing higher brain activation in the activation condition than in the control condition. Whole brain statistical analyses were performed using the SPM12. The statistical threshold was set at $p < .05$ corrected for FWE, with an extent threshold of 30 voxels.

4.7. Statistical Analyses

4.7.1. Study I

Statistical analyses were carried out by means of Statistical Software Package for Social Sciences (SPSS) version 24.0 (IBM Corp, 2016). Data were tested for normality using the Shapiro-Wilk test. The $\chi 2$ test was used to analyze differences between the two groups according to sex. Spearman’s Rho correlations were performed between neuropsychological variables and illness duration. Differences between groups on sociodemographic variables were assessed by a two-tailed independent t-test. In this study, working memory and cognitive flexibility were included under the term *executive functions*. The differences between the groups in executive functions, theory of mind, and creativity variables were performed by an analysis of covariance in order to control for possible interaction of several covariates. Significance level was set at $p < .05$. Effect sizes were obtained through partial eta squared (η_p^2). This was interpreted as small (0.01), medium (0.06), and large (0.14) (Cohen, 1988). The mediation hypothesis was tested by using path analysis with the Linear Structural Relations (LISREL) software, version 9.2 (Jöreskog & Sörbom, 2015). The robust maximum likelihood (RML) method was employed, which requires an estimate of the asymptotic covariance matrix of the variances and covariates of the sample and includes the scaled $\chi 2$ Satorra-Bentler index. Missing values were imputed using the expectation maximization (EM) algorithm. The goodness of fit of the model was evaluated by the root-mean-square error of approximation (RMSEA), comparative fit index (CFI), non-normed fit index (NNFI), and standard residual mean square root (SRMR). According to Hu and Bentler, CFI and NNFI values higher than 0.90, RMSEA values smaller than 0.06, and SRMR values smaller than 0.08 reflect a good fit (Hu & Bentler, 1999).

4.7.2. Study II

SPSS version 26.0 (IBM Corp, 2019) was used for all statistical analyses. The Kolmogorov-Smirnov test was used to test data for normality. Spearman´s Rho and Pearson’s *r* correlations were performed between sociodemographic, clinical, neurocognitive, social cognitive, and creativity variables. Multiple testing correction was performed in the correlation analyses using the Benjamini-Hochberg FDR method (Benjamini & Hochberg, 1995). The resulting adjusted significance level was $p < .010$. Stepwise Multiple Regression analyses were performed to determine which variables predict creativity. In the regression analyses, those sociodemographic, clinical, neurocognitive, and social cognitive variables which correlated significantly with each creativity score were included. With regard to negative symptoms, the BNSS was included instead of the PANSS-Negative, as recommended by the NIMH-MATRICS Consensus Statement on Negative Symptoms (Carpenter et al., 2016; Kirkpatrick et al., 2006). As creativity variables did not follow a normal distribution, these were transformed (through LN or square-root transformation) to carry out regression analysis, except for total creativity variable which followed a normal distribution. Figural strengths variable was not entered in the regression analysis since this variable did not follow a normal distribution after its transformation. Multicollinearity in the regression analyses was evaluated through the variance inflation factor (VIF) and tolerance statistics. According to Kleinbaum et al. (1988), VIF $\geq$ 10 and tolerance $\leq$ 0.10 would indicate collinearity problems. No multicollinearity (tolerance and VIF statistics) among measures was found. Significance level was set at $p < .05$. All tests were two-tailed.

4.7.3. *Study III*

Statistical analyses were carried out by means of SPSS version 26.0 (IBM Corp, 2019). Data were tested for normality using the Kolmogorov-Smirnov test. Missing values were imputed using EM algorithm. Spearman´s Rho, Pearson's *r* and point-biserial correlations were performed between sociodemographic, clinical, neurocognitive, social cognitive, creative, and functional outcome variables. Significance level was set at $p <$ .05.

To test the mediation hypothesis, path analysis was used with LISREL 9.2 (Jöreskog & Sörbom, 2015). The RML method was employed, which requires an estimate of the asymptotic covariance matrix of the variances and covariates of the sample and includes the scaled $\chi 2$ Satorra-Bentler index. The goodness of fit of the model was evaluated by CFI, NNFI, and SRMR. The Satorra-Bentler's scaled chi-square difference test (Satorra & Bentler, 2001), was performed to compare two alternative models, using the specific program designed by Crawford and Henry (Crawford & Henry, 2003).

4.7.4. *Study IV*

All variables were tested for normality. Means and standard deviations were obtained using SPSS version 26.0 (IBM Corp, 2019). As creativity variables did not follow a normal distribution, these were log-transformed (LN) and all variables were then transformed into Z scores.

4.7.5. *Study V*

Statistical analyses were carried out by means of SPSS version 26.0 (IBM Corp, 2019). Data were tested for normality using the Shapiro-Wilk test. Missing values were imputed using EM algorithm. Differences between groups on sociodemographic, cognitive, creative, functional outcome, and clinical variables at baseline were assessed by a two-tailed independent *t*-test or Mann-Whitney *U*-test for non-parametric variables. Chi-squared (X^2) test was used to analyze differences between groups in categorical data.

Change scores (post-treatment - baseline) were compared between the REHACOP group and the active control group on each of the cognitive, creative, functional outcome, and clinical variables, controlling for baseline scores, by the application of an analysis of covariance. A bootstrapping procedure (Efron & Tibshirani, 1993) was performed (1,000 samples) to obtain adjusted mean differences in change scores, using the Bonferroni adjustment. Effect sizes were calculated using partial eta squared (η_p^2) and this was interpreted as small (0.01), medium (0.06), and large (0.14) according to Cohen (1988). Significance level was set at $p < .05$. All tests were two-tailed.

In order to analyze predictors of functional outcome, Spearman´s Rho and Pearson’s *r* correlation analyses were first done between those neurocognitive, social cognitive, creative, and clinical change variables and functional outcome variables that had showed improvement after the intervention. Then, LISREL 9.2 (Jöreskog & Sörbom, 2015) was used to perform a path analysis which was conducted to assess the mediating role of these change scores in the relationship between receiving integrative cognitive remediation (vs active control group) and improvement in functional outcome. The RML method was used, which requires an estimate of the asymptotic covariance matrix of the variances and covariates of the sample and includes the scaled $\chi 2$ Satorra-Bentler index. The goodness of fit of the model was evaluated by CFI, NNFI, and SRMR.

4.7.6. Study VI

Statistical analyses were carried out by means of SPSS version 26.0 (IBM Corp, 2019). Data were tested for normality using the Shapiro-Wilk test. Missing values were imputed using the expectation maximization algorithm. Differences between groups on sociodemographic, clinical, and behavioral data at baseline were assessed by a two-tailed independent *t*-test or Mann-Whitney *U*-test. Chi-squared (X^2) test was used to analyze differences between groups in categorical data.

Regarding neuroimaging analysis, first, two-sample *t*-test analysis was used for baseline differences between groups. Then, repeated-measures analysis of variance 2 × 2 for group x time interaction analysis was used to test differences between pre-treatment and post-treatment for the REHACOP group and the active control group. The between-subjects factor was group (REHACOP group or active control group) and the within-subjects factor was time (pre-treatment and post-treatment). Finally, intragroup changes were explored through paired *t*-test analysis. Total intracranial volume was included as a covariate in VBM and cortical thickness analyses, although there were no differences between groups in this variable. For fMRI analyses, antipsychotic medication was used as a covariate, because of the influence of dopaminergic treatment on brain activation (Hadley et al., 2016; Kraguljac et al., 2016). Moreover, as baseline differences were found between the REHACOP and the active control group in negative symptoms, this variable was also included as covariate in all longitudinal analyses. Effect sizes were calculated according to Cohen´s *d* formula, considering 0.20, 0.50 and 0.80 as small, medium and large, respectively (Cohen, 1988).

4.8. Ethics Statement

All participants took part voluntarily, providing written informed consent to participate, and they did not receive any monetary reward for taking part in the study. The study protocol was approved by the Clinical Research Ethics Committees of the Autonomous Region of the Basque Country in Spain (PI2017044). This study forms part of a larger ongoing project, which is registered in clinicaltrials.gov (NCT03509597).

V. Results

5. Results

5.1. Study I

"Mediating role of cognition and social cognition on creativity among patients with schizophrenia and healthy control: revisiting the Shared Vulnerability Model"

5.2. Study II

"Neurocognitive, social cognitive, and clinical predictors of creativity in schizophrenia"

5.3. Study III

"The impact of creativity on functional outcome in schizophrenia: a mediational model"

5.4. Study IV

"Brain white matter correlates of creativity in schizophrenia: a diffusion tensor imaging study"

5.5. Study V

"Cognitive, creative, functional, and clinical symptom improvements in schizophrenia after an integrative cognitive remediation program: a randomized controlled trial"

5.6. Study VI

"Analyzing structural and functional brain changes related to an integrative cognitive remediation program in schizophrenia: a randomized controlled trial"

Study I

Study II

Study III

Study IV

Study V

Study VI

VI. Discussion

6. Discussion

The present thesis aimed to analyze on the one hand, the association between creativity and different cognitive, clinical, functional outcome, and brain characteristics in schizophrenia, and on the other hand, the effect of an integrative cognitive remediation program in neurocognition, social cognition, creativity, functional outcome, clinical symptoms, and brain structure and function.

The objective of Study I was to analyze differences in various dimensions of creativity in patients with schizophrenia and HC as well as to assess the possible mediating role of cognitive flexibility, working memory, and theory of mind in the relationship between schizophrenia and creativity. Results showed that patients with schizophrenia obtained significantly lower scores in all creativity domains, except for some of the figural creative variables. These results are in line with a recent meta-analysis (Acar et al., 2017) and other studies carried out with patients with schizophrenia (Abraham et al., 2007; Wang et al., 2017). The worse performance found in verbal creativity in comparison with figural creativity may be partly due that the language dysfunction that is present in this disease (Docherty et al., 2011; Mitchell & Crow, 2005). Additionally, consistent with previous studies (Orellana & Slachevsky, 2013; Savla et al., 2013), patients with schizophrenia obtained lower scores in cognitive flexibility, working memory, and theory of mind in comparison with HC.

With respect to the second aim of Study I, as expected, differences in creative performance between patients with schizophrenia and HC were partially mediated by their performance in cognitive flexibility, working memory, and theory of mind. The role of cognitive flexibility and working memory in creativity is in line with the few studies carried out with patients with schizophrenia (Abraham et al., 2007; Jaracz et al., 2012) and with the studies carried out among healthy people (Benedek et al., 2012; Benedek, Jauk, Sommer, et al., 2014; de Dreu et al., 2012; Edl et al., 2014; Zabelina & Robinson, 2010). Regarding theory of mind, as far as the authors are aware, to date, no study has analyzed this association in schizophrenia. Nevertheless, three studies explored this relationship among healthy children (Sigirtmac, 2016; Suddendorf & Fletcher-Flinn, 1997, 1999) and found a positive association between creativity and theory of mind. These results suggest that the meta-representational skills that are involved in theory of mind may permit individuals to see information from multiple perspectives and consider different alternative solutions to a problem and consequently, improve creative thinking. The involvement of theory of mind in the association between schizophrenia and creativity opens up a new field of research in which theory of mind, or even other domains of social cognition, may be considered as possible protective factors in the Shared Vulnerability Model developed by Carson (2011). Altogether, results from Study I support and extend the Shared Vulnerability Model.

Findings from Study I and previous studies (Abraham et al., 2007; Jaracz et al., 2012) suggest that the creative performance of people with schizophrenia could be altered due to an impairment in multiple neurocognitive and social cognitive domains as well as some clinical symptoms. Nonetheless, the extent to which each domain influences creative capacity in this disorder is still unknown. Therefore, Study II aimed to simultaneously investigate the specific contribution of multiple neurocognitive, social cognitive, and clinical variables to creativity in schizophrenia. With respect to clinical symptoms, negative symptomatology was negatively related to creativity. This association is in line with results from Jaracz et al. (2012), but not with results from Abraham et al. (2007). Nevertheless, these studies did not assess negative symptoms in accordance with the recommendations of the NIMH-MATRICS Consensus Statement on Negative Symptoms (Carpenter et al., 2016; Kirkpatrick et al., 2006).

Regarding neurocognition, processing speed and working memory predicted higher creativity. The association between working memory and creativity is in line with previous research carried out with people with schizophrenia (Abraham et al., 2007) and with Study I. However, the role of processing speed on creative performance has not been studied in patients with schizophrenia. With respect to studies carried out with healthy people (Benedek, Jauk, Sommer, et al., 2014; de Dreu et al., 2012; Forthmann et al., 2018; Oberauer et al., 2008; Rindermann & Neubauer, 2004; Vartanian et al., 2009), these have also found evidence for the role of working memory and processing speed on creativity. The fact that executive functions (cognitive flexibility and inhibition) did not correlate with creativity differs from results from Study I as well as with other studies carried out with patients with schizophrenia (Abraham et al., 2007; Jaracz et al., 2012). These conflicting results across studies could be partly due to the different assessment instruments used as well as to the multiple comparison correction applied in this study, in contrast to other studies. Indeed, in Study II, cognitive flexibility and inhibition were significantly correlated with creativity, but after correcting for multiple comparisons and thus including the effect of the other variables, the correlations were no longer significant.

In relation to social cognition, the three domains analyzed, i.e., theory of mind, social perception, and emotion processing, were positively related to creativity. Moreover, it should be noted that social cognition showed a greater predictive value than neurocognition in total creativity. To date, as far as the authors are aware, the association between creativity and social cognition has only been studied with theory of mind. Specifically, the predictive role of theory of mind on creativity found in Study II is in line with Study I as well as with the few studies available with healthy children (Sigirtmac, 2016; Suddendorf & Fletcher-Flinn, 1997, 1999). Results from Study II indicate that in addition to theory of mind, other social cognition domains are involved in creative thinking. This suggests that the association between creativity and social cognition may not only be limited to the capacity for meta-representation, but may also underlie other common processes, such as intention to communicate and intention to understand (Abraham, 2019). Taken together, findings from Study II point to the important role of some neurocognitive, social cognitive, and clinical variables in creativity. Moreover, these results suggest that social cognition could be more relevant for creative thinking than some neurocognitive domains.

Literature suggests that functional outcome in schizophrenia may be explained not only by clinical and cognitive factors (Fu et al., 2017; Green, 2016; Ojeda et al., 2019), but also by other kinds of personal resources such as creativity (Nemoto et al., 2007). Therefore, the aim of Study III was to analyze the predictive role of creativity on functional outcome in patients with schizophrenia through a mediational model including sociodemographic, clinical, neurocognitive, and social cognitive variables. Results showed that figural creativity mediated the relationship between neurocognition and functional outcome as well as between negative symptoms and functional outcome. The association found between creativity and functional outcome suggests that patients with schizophrenia who have better creative skills may benefit from this resource to better adapt and cope with their multiple adversities in daily life functioning. This is consistent with the idea that creativity may help daily life functioning through the application of creative problem solving skills to daily life problems (Plucker et al., 2015; Richards, 1993). In line with results from Study III, several authors have suggested that creativity could influence functional outcome of individuals with schizophrenia (Nemoto et al., 2007), bipolar disorder (Richards, 2010) and elderly people (Grebennikova et al., 2019). In addition, the association found between creativity, neurocognition and social cognition is congruent with results from Study I and II as well as with previous studies (Abraham et al., 2007; Jaracz et al., 2012). Results from Study III also showed that neurocognition was both directly and indirectly related to functional outcome. The strong relationship between neurocognition and functional outcome is in line with previous studies (Fu et al., 2017; Green et al., 2000; Ojeda et al., 2019; Peña et al., 2018; Strassnig et al., 2015). Contrary to other studies (Galderisi et al., 2014; Schmidt et al., 2011; Sergi et al., 2006), social cognition was not related to functional outcome, which could be partly due to the reduced version of the original scale that was used to measure functional outcome. With respect to clinical symptoms, the negative association found between negative symptoms and creativity is consistent with Study II and with the study of Jaracz et al. (2012). Contrary to what was expected based on previous literature (Fervaha et al., 2014; Galderisi et al., 2014; Ojeda et al., 2019), negative symptoms were not directly associated with functional outcome, and only disorganization was related to cognitive functioning. The lack of significant results overall with clinical symptoms in Study III could be partly due to the different scales and scoring methods used for the assessment of clinical symptoms and functional outcome across studies.

To our knowledge, this is the first study analyzing the mediatory role of creativity on functional outcome of patients with schizophrenia. As a whole, findings from Study III suggest that creativity may be a key capacity in this disorder for daily life functioning and for dealing with real-life challenging situations. Moreover, these findings support the idea that training creativity directly (Nemoto et al., 2009) or indirectly through other kind of interventions, such as cognitive remediation (Kiritsis, 2018), could be beneficial for the improvement of functional outcome in schizophrenia.

Little is known about the brain mechanisms underlying the impairment of creativity in schizophrenia. Therefore, the objective of Study IV was to analyze whole brain white matter correlates of different creativity dimensions among people with schizophrenia. Results showed that creativity and specifically, figural originality, was positively associated with white matter mean FA adjacent to multiple brain regions, including frontal, temporal, subcortical, and brainstem areas as well as to interhemispheric white matter fibers. In contrast, no significant results were found in any dimension of verbal creativity, which may be due to the language impairment present in this disease (Docherty et al., 2011; Mitchell & Crow, 2005) that may have led to low overall performance in the verbal dimensions. Altogether, results from Study IV are in line with findings from the study of Takeuchi et al. (2010) carried out in healthy people, suggesting that similar brain regions are involved in creative thinking of people with schizophrenia and healthy people.

The association found between creativity and FA in the corpus callosum is consistent with previous studies carried out with healthy people (Takeuchi et al., 2010; Zeng et al., 2017). The corpus callosum promotes interhemispheric information processing and communication (Schulte et al., 2005), which is relevant for creative thinking (Hoppe & Kyle, 1990; Lindell, 2011). The relationship between creativity and white matter tracts traversing the frontal lobe is also congruent with both structural white matter studies (Takeuchi et al., 2010) and fMRI studies (Beaty et al., 2014, 2018; Japardi et al., 2018; Marron et al., 2018; Sun et al., 2019). The frontal lobe is involved in higher-order cognitive abilities, such as executive functions and working memory (Charlton et al., 2010; Jacobs et al., 2013), which are known to be related to creative thinking (Benedek, Jauk, Sommer, et al., 2014; de Dreu et al., 2012). The involvement of the temporal lobe in creativity is in line with other structural (Takeuchi et al., 2010) and functional studies (Beaty et al., 2015; Benedek, Jauk, Fink, et al., 2014), and may be due to its relationship with memory retrieval, which, as mentioned above, has been shown to be a necessary cognitive process for creative thinking (Benedek, Jauk, Fink, et al., 2014).

Regarding subcortical regions, it has been suggested that an increased white matter integrity in these area could increase functional connectivity, and therefore, improve some higher-order frontal lobe cognitive processes that underlie creative thinking, through the regulation of the dopaminergic system (Takeuchi et al., 2010). Finally, the association between the cerebral peduncle and the corticospinal tract with creativity may be due to their involvement in coordination and information processing (Picard et al., 2008) and in implicit manipulation of mental representation (Saggar et al., 2015, 2017), which may promote creative thinking.

Together, Study IV provides relevant preliminary data for brain white matter correlates of creativity in schizophrenia that could contribute to the understanding of the impairment found in this ability. Results suggest that both intra- and interhemispheric communication could be involved in creativity, enabling the integration of remote associations of ideas. Considering that many of the brain regions that correlated with creativity in this study are regions that are particularly impaired in schizophrenia (Stämpfli et al., 2019), it may be possible that the creativity impairment found in this disorder is partly due to an alteration in white matter integrity, although this idea must be considered with caution.

Although cognitive remediation has been shown to be effective in improving multiple domains in schizophrenia, results among studies applying integrative cognitive remediation are still heterogeneous and its effectiveness in improving primary negative symptoms and creativity remains unknown. Therefore, the first aim of Study V was to analyze the effectiveness of an integrative group-based cognitive remediation program (REHACOP) that combined training in neurocognition, social cognition, as well as social and functional skills among patients with schizophrenia. In line with previous studies carried out with integrative cognitive remediation programs (Bechi et al., 2015; Bowie et al., 2012; Eack et al., 2009; Fisher et al., 2017; Mueller et al., 2015; Peña et al., 2016; Sánchez et al., 2014), the REHACOP group showed significantly greater improvement in comparison to the active control group in neurocognition, social cognition, functional outcome, and clinical symptoms. The significant results obtained in social cognition are worth mentioning, since they reinforce the results from previous studies that used other types of assessment tools, such as paper and pencil tasks and static pictures instead of videos (Eack et al., 2009; Mueller et al., 2015; Peña et al., 2016). It is also interesting to note the improvement in primary negative symptoms, as previous studies have evaluated primary and secondary negative symptoms together (Eack et al., 2009; Mueller et al., 2015; Peña et al., 2016; Sánchez et al., 2014), so Study V provides initial evidence regarding the effectiveness in improving primary negative symptoms.

Based on results from Studies I and II, it was hypothesized that cognitive remediation could indirectly improve creativity through the training of other neurocognitive and social cognitive domains. To our knowledge, this is the first study analyzing the effectiveness of an integrative cognitive remediation in creativity in patients with schizophrenia compared to an active control group. Results showed significant differences between groups in the change score of figural creative strengths. Specifically, the active control group showed a greater decline in this creativity score, though neither the REHACOP nor the active control group showed higher scores in the post-treatment evaluation. The lack of significant results in other creativity domains may be due to the fact that creativity was not directly treated in the REHACOP, as well as to the kind of occupational activities that the active control group performed, since these are closely associated with creativity.

The second aim of Study V was to explore the possible mediators predicting improvement in functional outcome after the integrative cognitive remediation. Results showed that changes in verbal memory, inhibition, and emotion processing partially mediated the association between receiving the REHACOP intervention and improvement in functional competence. This is in line with some previous studies (Eack et al., 2011; Fiszdon et al., 2008; Peña et al., 2018; Wykes et al., 2012). In addition, lower baseline functional competence was also associated with a greater change in this domain. The few studies that have analyzed the relationship between baseline functioning and functional improvement after cognitive remediation in schizophrenia (Bell et al., 2008, 2014; Farreny et al., 2016; Kurtz et al., 2008; Twamley et al., 2011) have multiple methodological differences, which makes it difficult to compare these results with those of previous studies.

To summarize, Study V reinforces the idea that integrative cognitive remediation is effective in improving multiple domains including primary negative symptoms, while overcoming several methodological issues raised in previous studies (Bechi et al., 2015; Galderisi et al., 2010; Lindenmayer et al., 2018; Mueller et al., 2015; Peña et al., 2016). In addition, Study V provides initial evidence of the beneficial effect, although slight, of integrative cognitive remediation in creativity. Moreover, Study V suggests that cognitive remediation should emphasize training in verbal memory, executive functions, and emotion processing.

Little is known about the neural mechanisms underlying integrative cognitive remediation in schizophrenia. Therefore, Study VI aimed to explore the structural and functional brain changes after the REHACOP. In contrast to previous sMRI and fMRI studies (Donohoe et al., 2018; Eack et al., 2010; Eack et al., 2016; Fan et al., 2017; Keshavan et al., 2017; Morimoto et al., 2018; Penadés et al., 2013), results showed that the REHACOP was not effective in improving brain structure and function. Nevertheless, intragroup analyses showed an increase in right temporal grey matter volume and cortical thickness at post-treatment in the REHACOP group. The lack of significant results associated with the cognitive remediation could be partly due to the small sample size or to some differences with other studies, such as the type of cognitive task performed during fMRI (Donohoe et al., 2018; Ramsay, Nienow, et al., 2017; Subramaniam et al., 2014) or the type of activities performed by the active control group (Eack et al., 2016; Fan et al., 2017; Keshavan et al., 2017; Vianin et al., 2014).

The temporal lobe changes found in the REHACOP group at post-treatment, although due to the lack of a significant interaction effect cannot be attributed to cognitive remediation, are in line with the temporal lobe changes found in two previous studies (Eack et al., 2010; Morimoto et al., 2018). Specifically, from the few studies analyzing this issue (Eack et al., 2010; Morimoto et al., 2018; Ramsay, Fryer, et al., 2017), two studies have found both greater preservation and an increase in grey matter volume in the right and left temporal lobe after the cognitive remediation (Eack et al., 2010; Morimoto et al., 2018). Results from these studies (Eack et al., 2010; Morimoto et al., 2018) suggest that the temporal lobe could be a key region involved in the restoration and improvement of cognitive functioning. Interestingly, the temporal lobe is one of the brain areas most affected by the progressive loss of grey matter that occurs in this disease (Vita et al., 2012). Moreover, it has been suggested that these increases in the temporal lobe volume could be related to an increase in the serum levels of brain-derived neurotrophic factor (Morimoto et al., 2018); a biomarker that has shown to be increased after cognitive remediation in schizophrenia (M. Fisher et al., 2016; Vinogradov et al., 2015) and that is associated with the maintenance of the volume of temporal lobe regions (Miranda et al., 2019).

In summary, Study VI did not find longitudinal brain structural and functional changes related to cognitive remediation. The increase in grey matter volume and cortical thickness of right temporal regions that was found in the REHACOP group at post-treatment cannot be attributed to the cognitive remediation. Nevertheless, the few studies available (Eack et al., 2010; Morimoto et al., 2018; Ramsay, Fryer, et al., 2017) suggest that cognitive remediation could have a neuroprotective effect on the brain of patients with schizophrenia. More research is still needed to understand the neural basis of the cognitive remediation in schizophrenia.

In conclusion, all the described studies attempt to provide a greater understanding of the role of creativity in schizophrenia, as well as the effectiveness of integrative cognitive remediation in this disorder. Through these studies, this thesis has contributed to shed light on the long-standing controversial association between schizophrenia and creativity. Results of the present thesis suggests on the one hand, that creativity could play an important role in schizophrenia and specifically, in daily functioning, through the interaction of multiple neurocognitive, social cognitive, clinical, and brain characteristics. On the other hand, this thesis provides further evidence of the effectiveness of integrative cognitive remediation in numerous cognitive, clinical, and functional outcome domains and provides initial data of the effect of cognitive remediation in creativity among patients with schizophrenia, suggesting that cognitive remediation could produce an indirect slight but beneficial effect on creativity. Finally, this thesis attempts to better understand the effects of integrative cognitive remediation in brain structure and function, failing to find significant results, but suggesting that more research is needed to clarify the possible role of the temporal lobe in the neuroprotective processes involved in cognitive remediation.

This thesis highlights the importance of enhancing, among others, the capacity for creative resilience, the ability to generate creative solutions in order to adapt and cope with the adversities of everyday life. This capacity of adaptation is especially necessary in mental illness, where people must face not only the daily life adversities of any other person but also those derived from the illness itself. Therefore, results of the present thesis suggest that there should be a shift towards positive psychology when studying and treating mental illness.

Together, this thesis contributes to open up new fields of research in people with schizophrenia; fields of research in which studies should also consider positive personal resources when studying predictors of functional outcome. In addition, this thesis suggests that interventions should not only focus on addressing the negative aspects of this disorder such as cognitive impairment. Instead, training on creativity and other positive personal resources such as humor and acceptance could also be included in the integrative and multidisciplinary treatment plans. The inclusion of such positive resources may not only play an important role in improving daily functioning and quality of life of people with schizophrenia, but could also increase treatment adherence and motivation. Thus, integrated and holistic treatments that address multiple domains might produce greater improvement in real-life functioning in mental disorders. More research is needed to better understand the underpinnings of creativity in this disease, as this could have relevant implications for the development of interventions aimed at enhancing this capacity that is essential for the survival and enrichment of humankind (Carson, 2014).

VII. Conclusions

7. Conclusions

7.1. Conclusions

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

- Patients with schizophrenia showed an impairment in creativity compared to HC. Impairment in cognitive flexibility, working memory, and theory of mind partly mediated the relationship between having schizophrenia and creativity performance. Obtained results reinforce and extent the Shared Vulnerability Model and contribute to the understanding of the long-standing association between schizophrenia and creativity.

- Creative performance of patients with schizophrenia was explained by multiple variables, including neurocognitive, social cognitive and clinical variables. Social cognition showed a higher influence than some neurocognitive domains, suggesting that social cognition may play a particularly relevant role in creativity of patients with schizophrenia. These results contribute to the understanding of the underpinnings of creativity in this disorder, which could have implications for the development of interventions.

- Creativity mediated the relationship between neurocognition and functional outcome as well as between negative symptoms and functional outcome in patients with schizophrenia. Obtained results suggest that creativity may be a key capacity for the daily life functioning of patients with schizophrenia. These findings could have relevant implications for the development of new interventions in which creativity could be considered as a capacity to be addressed in this disease.

- Figural creativity correlated positively with white matter mean FA adjacent to multiple brain regions, including frontal, temporal, subcortical, brain stem, and interhemispheric regions in patients with schizophrenia. These results suggest that, similar to healthy people, widespread white matter integrity is involved in creative performance of patients with schizophrenia. Some of these regions are regions particularly impaired in this disorder, which suggests that the creativity impairment found in schizophrenia could be partly due to white matter alterations.

- Integrative cognitive remediation was effective in improving neurocognition, social cognition, functional outcome, and clinical symptoms in patients with schizophrenia. In addition, patients performing cognitive remediation showed a smaller decline in creativity, suggesting that integrative cognitive remediation could have a beneficial effect, although small, on creativity. Moreover, change in verbal memory, inhibition, and emotion processing partially explained the effect of cognitive remediation on functional competence, which indicates that cognitive remediation should reinforce the training in these domains.

- Integrative cognitive remediation failed to produce longitudinal brain structural and functional changes. However, patients undergoing cognitive remediation showed greater grey matter volume and cortical thickness in the right temporal lobe at post-treatment. Previous studies have found changes in temporal grey matter volume after cognitive remediation, which suggests that the temporal lobe may be a key area involved in the neuroprotective processes induced by cognitive remediation.

7.2. Conclusiones

Las principales conclusiones de esta tesis, derivadas de los estudios presentados, pueden resumirse de la siguiente manera:

- Los pacientes con esquizofrenia mostraron un deterioro en la creatividad en comparación con los controles sanos. El deterioro en la flexibilidad cognitiva, la memoria de trabajo y la teoría de la mente mediaron parcialmente la relación entre tener esquizofrenia y el rendimiento en la creatividad. Los resultados obtenidos refuerzan y amplían el Modelo de Vulnerabilidad Compartida y contribuyen a la comprensión de la asociación entre la esquizofrenia y la creatividad.

- El rendimiento creativo de los pacientes con esquizofrenia fue explicado por múltiples variables, incluyendo la neurocognición, cognición social y variables clínicas. La cognición social mostró un mayor valor predictivo que algunos dominios neurocognitivos, lo que sugiere que la cognición social podría desempeñar un papel especialmente relevante en la creatividad de los pacientes con esquizofrenia. Estos resultados contribuyen a la comprensión de los procesos subyacentes en la creatividad, lo cual podría tener implicaciones en el desarrollo de intervenciones para la esquizofrenia.

- La creatividad medió la relación existente entre la neurocognición y la funcionalidad, así como entre los síntomas negativos y la funcionalidad de las personas con esquizofrenia. Los resultados obtenidos sugieren que la creatividad puede ser una capacidad clave para el funcionamiento de la vida diaria de los pacientes con esquizofrenia. Estos hallazgos podrían tener implicaciones relevantes para el desarrollo de nuevas intervenciones en las que la creatividad se considere una capacidad a ser abordada en esta enfermedad.

- La creatividad figurativa correlacionó de forma positiva con la anisotropía fraccional media de la materia blanca adyacente a múltiples regiones cerebrales, incluyendo regiones frontales, temporales, subcorticales, del tronco cerebral e interhemisféricas en los pacientes con esquizofrenia. Estos resultados sugieren que, de forma similar a las personas sanas, la integridad de la materia blanca de múltiples regiones está implicada en el rendimiento creativo de las personas con esquizofrenia. Algunas de estas regiones están particularmente deterioradas en esta enfermedad, lo cual sugiere que el deterioro de la creatividad que se da en la esquizofrenia podría deberse en parte a las alteraciones de la materia blanca.

- La rehabilitación cognitiva integral fue eficaz en la mejora de la neurocognición, la cognición social, la funcionalidad y los síntomas clínicos en pacientes con esquizofrenia. Además, los pacientes que realizaron la rehabilitación cognitiva mostraron una menor disminución de la creatividad, lo cual sugiere que la rehabilitación cognitiva integral podría tener un efecto beneficioso, aunque pequeño, sobre la creatividad. Asimismo, los cambios en la memoria verbal, la inhibición y el procesamiento emocional explicaron parcialmente el efecto de la rehabilitación cognitiva en la competencia funcional, lo cual indica que la rehabilitación cognitiva debería reforzar el entrenamiento en estos dominios.

- La rehabilitación cognitiva integral no produjo cambios en la estructura y función cerebral. Sin embargo, los pacientes que realizaron la rehabilitación cognitiva mostraron un mayor volumen de materia gris y grosor cortical en el lóbulo temporal derecho en el post-tratamiento. Estudios previos han encontrado cambios en el volumen de la materia gris temporal tras la rehabilitación cognitiva, lo que sugiere que el lóbulo temporal puede ser un área clave implicada en los procesos neuroprotectores inducidos por la rehabilitación cognitiva.

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