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DOCTORAL THESIS

FUNCTIONAL ASSESSMENT BY MEANS OF TRANSCRANIAL MAGNETIC STIMULATION OF INHIBITORY TRANSMISSION IN SCHIZOPHRENIA

This dissertation is submitted by **Inés Fernández Linsenbarth**
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TESIS DOCTORAL

VALORACIÓN FUNCIONAL MEDIANTE ESTIMULACIÓN MAGNÉTICA TRANSCRANEAL DE LA TRANSMISIÓN INHIBITORIA EN ESQUIZOFRENIA

Presentada por **Inés Fernández Linsenbarth** para optar al grado de Doctora por la Universidad de Valladolid

Dirigida por: **Dr. Vicente Molina Rodríguez**

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Esta tesis fue leída en la Facultad de Medicina en la Universidad de Valladolid el día , estando compuesto el tribunal calificador por:

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A mis padres

Es preciso sacudir enérgicamente el bosque de las neuronas cerebrales adormecidas;
es menester hacerlas vibrar con la emoción de lo nuevo
e infundirles nobles y elevadas inquietudes.
-Santiago Ramón y Cajal-

Let everything happen to you.
Beauty and terror.
Just keep going.
No feeling is final.
- Rainer Maria Rilke-

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Abstract

After years of huge research efforts, there is still not a basic understanding of the pathophysiological mechanisms of schizophrenia. The research findings to date have been often inconsistent, difficult to replicate, and not sensitive or specific enough to help with diagnosis. Different lines of evidence suggest that schizophrenia is likely a heterogeneous condition that encompasses different presentations and subtypes. The view of schizophrenia as a singular disease entity could have led to an inadequate study approach and thus, to the lack of replicability and inconsistency of the research findings in the field.

The present doctoral thesis sought to address this heterogeneity considering two important facts. First, a change in the schizophrenia construct as a syndrome should be followed by a change in its research approach. Second, this change should also be accompanied by a change in the study focus, which has traditionally been far distant from the altered functions in this syndrome. Therefore, the general aims of this thesis were threefold: i) to explore de existence of patients subgroups within schizophrenia using a data-driven approach; ii) to follow-up the clinical and real-life outcomes of the identified subgroups in the medium term; and iii) to assess a neurobiological substrate closer to the psychological functions known to be altered in schizophrenia.

This doctoral thesis includes four studies. The two first studies explored the existence of subgroups within the schizophrenia syndrome using a data-driven approach based on cognition and functional network properties of the electroencephalogram (EEG), respectively. The third study assessed the clinical and functional outcomes of the previously identified cognitive subgroups. Finally, the last study focused on exploring

the association between the decreased task-related activity modulation observed in the first two subgroups studies and the inhibitory system function. The studies' sample sizes ranged from 22 to 169 schizophrenia patients and 27 to 158 healthy controls. Moreover, the two first studies included also bipolar disorder patients due to the large evidence of shared genetics, cognitive alterations, and clinical features between both diagnoses. All patients were diagnosed according to the Statistical Manual of Mental Disorders 5th edition (DSM-V) criteria and their symptoms were assessed through the Positive and Negative Syndrome Scale (PANSS).

Results from the first study showed a severely impaired and a moderately impaired subgroup of patients based on cognitive impairments. Moreover, the severely impaired group was associated with higher symptom scores and larger neurobiological alterations.

In the second study, we were able to identify two subgroups of patients within the schizophrenia syndrome using EEG-based network parameters derived from graph theory and obtained during an auditory oddball task. One subgroup showed altered global properties of functional and structural connectivity. The other subgroup showed an EEG network pattern similar to healthy controls. Remarkably, both subgroups studies showed that all identified patients subgroups were associated to task-related modulation deficits compared to healthy controls.

The third study gave additional external validity to the described subgroups based on cognition. Results showed that the subgroup with larger cognitive impairments and more severe biological alterations was associated with greater clinical severity and more difficulties in real-life functioning in the medium term.

Finally, the last study replicated the task-related cortical activity modulation deficit previously reported in schizophrenia patients. Moreover, results showed that patients with schizophrenia were associated with higher cortical reactivity following transcranial magnetic stimulation (TMS) single pulses over the dorsolateral prefrontal cortex compared to healthy controls. This finding is consistent with the decreased inhibitory function previously described in schizophrenia. Furthermore, we found a significant association between task-related activity modulation and the amplitude of the evoked response to TMS single pulses.

In summary, the studies included in this doctoral thesis support the identification of different subgroups within the schizophrenia syndrome with different neurobiological underpinnings. Our findings highlight the fact that schizophrenia is likely not a single disorder entity but a collection of several distinct conditions with different substrates. In this line, data-driven methodologies seem to be a more suitable approach to encompass the large heterogeneity observed in schizophrenia. Moreover, three out of four of the articles included in this doctoral thesis replicated an EEG modulation deficit during cognitive activity in both schizophrenia and bipolar disorder patients. This deficit likely reflects an alteration in the synchronization of the neural assemblies that underlie cognitive activity and states this variable as a possible biomarker of the altered function in these disorders. Finally, our findings support the idea that a hypofunction of the inhibitory system could hamper the task-related modulation of EEG activity, since we were able to identify a dimensional association between the task-related EEG activity modulation and the amplitude of the evoked response to TMS single pulses in both healthy controls and patients.

Contents

Acronyms

APB	Abductor Pollicis Brevis
AUC	Area Under the Curve
BACS	Brief Assessment of Cognition in Schizophrenia
BD	Bipolar Disorder
BNSS	Brief Assessment of Negative Symptoms Scale
ClC	Clustering Coefficient
CLARA	Clustering Large Application
CS	Connectivity Strength
CWT	Continuous Wavelet Transform
DLPFC	Dorsolateral Prefrontal Cortex
DSM-V	Statistical Manual of Mental Disorders 5^{th} Edition
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighted Images
EEG	Electroencephalography
ERP	Event-Related Potentials
FA	Fractional Anisotropy
FE	First Episodes
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GEOPTE	Spanish Group for Schizophrenia Treatment Optimization Test
GM	Grey Matter
HC	Healthy Controls
ICA	Independent Component Analysis
IC_S	Independent Components
IQ	Intelligent Quotient

JCR	Journal Citation Report
LDA	Linear Discriminant Analysis
LICI	Long Interval Cortical Inhibition
LMFP	Local Mean Field Power
LORETA	Low-Resolution Tomography
MDD	Major Depressive Disorder
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MSCEIT	Mayer-Salovey-Caruso Emotional Intelligence Test
NMDA	N-Methyl-D-Aspartate
PANSS	Positive and Negative Syndrome Scale
PCA	Principal Component Analysis
PL	Path Length
PLV	Phase-Locking Value
PSD	Power Spectral Density
RMT	Resting Motor Threshold
ROI	Region Of Interest
SE	Shannon Entropy
SICI	Short Interval Cortical Inhibition
SW	Small-World
TMS	Transcranial Magnetic Stimulation
TR	Treatment Resistant
WCST	Wisconsin Card Sorting Test

Chapter 1

Introduction

The present doctoral thesis focuses on exploring the large heterogeneity observed in schizophrenia and assessing the neurobiological underpinnings of the potential subgroups existing within this syndrome. This research work has led to the publication of three scientific articles in Journal Citation Report (JCR) indexed journals between November 2020 and November 2022. Additionally, a fourth article has recently been submitted for publication (May 2023). This scientific production has enabled the writing of this thesis as a compendium of publications.

In this introduction chapter, the thematic consistency of the doctoral thesis is firstly justified. Subsequently, the main characteristics and biological mechanisms described for schizophrenia are briefly summarized. The following subsections of this chapter focus on justifying the need to explore the heterogeneity and to shed light on the pathophysiology of the schizophrenia syndrome.

1.1. Compendium of publications: Thematic consistency

Decades of research have revealed a great heterogeneity in the etiopathology, symptomatology, course, and treatment response of patients with schizophrenia. The traditional view of schizophrenia as a singular disease entity may have been erroneous and could explain the lack of replicability and inconsistency of the research findings in the field. The deconstruction of the schizophrenia concept from a biotyping approach would allow a shift in its study focus, considering that it would encompass not just one but several disorders within that entity. In recent years, the need for a paradigm shift

in the study of schizophrenia has become evident (Faden & Citrome, 2023; Molina & Blanco, 2013; Tandon, Nasrallah, & Keshavan, 2009) with a growing body of studies using data-driven methodologies instead of comparing between healthy subjects and schizophrenia as a unity. Furthermore, this landscape has also questioned the predominant object of study up to this point, which has been traditionally focused on biological processes far distant from the psychological functions known to be altered in schizophrenia.

Given this scenario, this doctoral thesis focuses on two main aspects. First, exploring the possibility of identifying meaningful subgroups within the schizophrenia syndrome. Second, assessing the neurophysiological substrates closer to the psychological function altered in schizophrenia, *i.e.*, the mental function. Thus, the thematic consistency of this doctoral thesis is understood by the following structure. First, the existence of subgroups within the schizophrenia syndrome using a data-driven approach was explored in two studies, based on cognition and functional network properties of the electroencephalogram, respectively. These subgroups' studies led to two research paths. One focused on assessing the clinical and functional outcomes of the identified cognitive subgroups. The other path focused on exploring the association between the inhibitory system function and the decreased task-related activity modulation observed in the subgroups identified in the first two studies. This latter study gives the title to this thesis.

The present doctoral thesis is organized into 8 chapters. This introduction is followed by the aims and hypothesis, the four articles, a general discussion, and conclusions.

1.2. Schizophrenia

Schizophrenia is considered one of the most severe psychiatric disorders in terms of human suffering and socio-economic burden. It encompasses a diverse set of signs and symptoms, including distortions of thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communication, and restricted affective expression (Tandon et al., 2009). Schizophrenia usually emerges between ages 18-25 and affects about one per cent of the world's population (Insel, 2010). However, this incidence varies greatly among places and migrant groups, as do symptoms, treatment response, and illness course across individuals (van Os & Kapur, 2009). Although not universally present neither specific to schizophrenia, individuals who develop this disorder often tend to exhibit an array of cognitive, emotional, and social function impairments (Jauhar, Johnstone, & McKenna, 2022; Tandon et al., 2009) before the psychosis onset, *i.e.*, the so-called prodromal symptoms. Moreover, the lifespan of individuals diagnosed with schizophrenia is reduced by 13-15 years compared with general population, often related to comorbid medical disorders, poor dietary habits, overweight, suicide, or comorbid substance use (Hjorthøj, Stürup, McGrath, & Nordentoft, 2017).

1.2.1. Signs and symptoms

The diverse set of signs and symptoms that characterize schizophrenic disorders are usually classified into three main domains (Jauhar et al., 2022; Tandon et al., 2009; van Os & Kapur, 2009): i) *positive symptoms*, including delusions, hallucinations, and formal thought disorder; ii) *negative symptoms*, consisting of lack of volition, reduced speech output, anhedonia, apathy, and flattening of affect; and iii) *cognitive deficits*,

with patients commonly showing a broad-based cognitive impairment, specially affecting attention, processing speed, working and long-term memory, executive function, and social cognition (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; van Os & Kapur, 2009).

A dopaminergic mesolimbic hyperactivation seems to underlie positive symptoms, which could explain this kind of symptoms being the most attenuated ones in response to antipsychotic medication (Keshavan, Tandon, Boutros, & Nasrallah, 2008). On the other hand, the pathophysiology of negative symptoms is still poorly understood (Keshavan et al., 2008). Although positive symptoms are the most striking symptoms of schizophrenic disorders, negative symptoms appear to contribute importantly to the poor occupational and social functioning observed in these disorders (Foussias, Agid, Fervaha, & Remington, 2014). Furthermore, cognitive symptoms seem to have a profound impact on the difficulty to regain social function and vocation (Bowie et al., 2008; Michael Foster Green, Kern, Braff, & Mintz, 2000).

1.2.2. Etiology

The etiology of schizophrenia remains unknown. Different hypotheses have been proposed to explain the causes of this psychiatric disorder. From a neurochemical view, alterations in dopaminergic, glutamatergic, and GABAergic neurotransmission systems have been related to schizophrenia.

The dopamine hypothesis proposes that certain clinical manifestations of schizophrenia may reflect an underlying neurochemical imbalance of this neurotransmitter (Maia & Frank, 2017; Meltzer & Stahl, 1976). Specifically, a mesolimbic hyperdopaminergia would be causing positive schizophrenia symptoms. This hypothesis is based on three complementary findings: i) the effect of

antipsychotic drugs depends on their ability to block the dopamine D_2 family of postsynaptic receptors, reducing dopamine function (Creese, Burt, & Snyder, 1976; Johnstone, Crow, Frith, Carney, & Price, 1978); ii) higher dopamine receptor concentration has been found in post-mortem schizophrenia studies (Maia & Frank, 2017); and iii) the abuse of some drugs that stimulate dopamine release, such as amphetamine, usually leads to similar clinical states as schizophrenia (Connell, 1958). However, some studies question the basic postulate of the dopaminergic hypothesis. On the one hand, the hyperdopaminergia described in this hypothesis appears to be not present in all patients with schizophrenia. In this line, some studies differentiate between "hyperdopaminergic" and "normadopaminergic" patients (Howes & Kapur, 2014) describing patients with elevated dopamine synthesis and release in the striatum or without dopamine alterations, respectively. On the other hand, there are other disorders such as bipolar disorder or autism in which an increased dopamine level has also been described (Pavăl, 2017).

The glutamatergic hypothesis proposes a hypofunction of the N-methyl-D-aspartate (NMDA) glutamate receptor in patients with schizophrenia (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012; Kantrowitz & Javitt, 2010). Support for this hypothesis comes mainly from studies administrating a NMDA receptor antagonist such as ketamine, which results in increased positive and negative symptoms that resemble those described for schizophrenia (Beck et al., 2020; Pomarol-Clotet et al., 2006), as well as a similar profile of transient cognitive impairments (Gilmour et al., 2012). Furthermore, genetic, post-mortem, and animal studies lend further support to the NMDA hypothesis (Beck, Javitt, & Howes, 2016). However, this hypothesis is not free from questioning either. There is no clear evidence for alterations in NMDA receptor

numbers in schizophrenia post-mortem studies, with an exception in the dorsolateral prefrontal cortex (Catts, Lai, Weickert, Weickert, & Catts, 2016). Moreover, the therapeutic effects of drugs targeting the NMDA receptor are inconclusive (Beck et al., 2016).

Finally, within the neurochemical theories, the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has also been proposed to play a role in schizophrenia. As will be seen in successive sections, this theory becomes particularly relevant in the context of this doctoral thesis. It is considered that an optimal balance between excitatory and inhibitory forces in the brain must take place for a correct brain electrical synchrony to occur. GABA inhibitory interneurons play a key role in this excitatory/inhibitory balance, by selectively attenuating the activity of excitatory neurons in the cortex, in a neurophysiological process known as cortical inhibition (Farzan et al., 2010). Thus, GABA inhibitory interneurons seem to prevent global indiscriminate brain hyperactivation and allow the adequate selection of synapsis assemblies (Buzsáki, 2006). The GABA inhibitory system has been consistently reported to be functionally altered in schizophrenia (Gonzalez-Burgos, Fish, & Lewis, 2011; Lewis, Fish, Arion, & Gonzalez-Burgos, 2011; Lewis, Hashimoto, & Volk, 2005). Again, these alterations do not seem to be specific to schizophrenia, as they are also present in other psychiatric disorders such as bipolar disorder (Benes & Berretta, 2001; Levinson, Young, Fitzgerald, & Daskalakis, 2007) and depression (Fee, Banasr, & Sibille, 2017).

Contemporary schizophrenia research consider that the causes of this mental disorder involve events in early life, including even prenatal or perinatal events (Insel, 2010; Jauhar et al., 2022), contemplating it as a neurodevelopmental disorder. This

neurodevelopmental model of schizophrenia is based on longitudinal studies showing the trajectory in children who develop the illness, including reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways during their development, which could lead to an altered excitatory/inhibitory balance (Insel, 2010). However, none of these possible neurodevelopmental mechanisms has been proved to cause the syndrome.

Genetics also play an important role in the vulnerability for schizophrenia. Although twin and family research studies demonstrate high heritability (Kety, 1987; McGuffin & Gottesman, 1999), the identification of specific genetic variations still appears to be a challenge. Schizophrenia can be considered a polygenic disorder, representing the cumulative effects of hundreds of genes, each with small effect sizes and dispersed widely across the genome (Jauhar et al., 2022). In addition, a small proportion of schizophrenia incidence could be explained by rare genetic variants (Bassett, Scherer, & Brzustowicz, 2010; International Schizophrenia Consortium, 2008; Pocklington et al., 2015). However, these rare genomic variants often affect only one individual or family and thus cannot account for the whole genetic heritability of schizophrenia. It is also remarkable that genetics of schizophrenia overlap with the genetics of autism and other disorders (Guilmatre et al., 2009; Sebat et al., 2007).

How can the same genetic variation lead to different neurodevelopmental syndromes? The key to answering this question appears to be the environmental factors and the gene-environmental interaction effects. Increased risk for schizophrenia has been associated with several environmental factors of small effect, including obstetric and perinatal complications, older paternal age, and prenatal infection and famine, among others (Brown, 2011; Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Cannon,

Jones, & Murray, 2002; Van Os, Kenis, & Rutten, 2010; Wohl & Gorwood, 2007). Moreover, a link between traumatic events in childhood, such as sexual, physical, and emotional abuse and later development of schizophrenia has been reported (Varese et al., 2012). Finally, cannabis consumption is strongly associated with increased risk of schizophrenia (Casadio, Fernandes, Murray, & Di Forti, 2011; Di Forti et al., 2019).

1.2.3. Diagnosis, treatment, and outcome

To date, the most widely used system for diagnosing schizophrenia is based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013). According to DSM-V criteria, a person receives a diagnosis of schizophrenia if he/she experiences two or more of the following symptoms for a significant portion of time during a 1-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, or negative symptoms. At least one of them must be one of the first three. Moreover, the level of the person's functioning in one or more major areas (*i.e.*, work, interpersonal relations, or self-care) must be markedly below the level achieved prior to the onset. These disturbances must have persisted for six months or longer and may include periods of prodromal or residual symptoms. Finally, some differential diagnoses such as schizoaffective disorder, depressive disorder, bipolar disorder with psychotic features, substance abuse effects, or other recognizable organic etiological explanation for psychotic symptomatology, must be discarded.

It is important that the diagnosis is made based on a combination of individual self-reported experiences and clinical observations by psychiatrists. Despite years of significant efforts to find objective and reliable biological measures for the diagnosis of schizophrenia, the findings to date have been inconsistent and not sensitive and

specific enough to help with diagnosis. As stated before, the diagnosis relies on confirmation of the key symptoms and ruling out the most likely differential diagnoses. It is easy to imagine the wide variety of people with different profiles of symptomatology that can fall under this same diagnostic label, giving rise to the great heterogeneity observed in these patients (Palaniyappan, 2023). Moreover, the core symptoms described above are largely shared with other mental disorders.

Once the diagnosis is made, antipsychotic drugs, which work by blocking the D2 family of postsynaptic dopamine receptors, are the main treatment of psychosis. First-generation antipsychotics (*e.g.*, chlorpromazine and haloperidol) were followed by second-generation antipsychotics (*e.g.*, risperidone and olanzapine). These latter antipsychotic drugs, which are based on blocking not only dopaminergic but also serotonergic receptors (Stępnicki, Kondej, & Kaczor, 2018; Yang & Tsai, 2017), emerged with the aim of reducing the extrapyramidal side effects caused by the earlier ones. However, except for clozapine, second-generation antipsychotics do not seem to provide additional efficacy compared to first-generation antipsychotics (Tandon, Nasrallah, & Keshavan, 2010).

Antipsychotic drugs suffer severe limitations which include (Stępnicki et al., 2018): i) They are effective in relieving positive symptoms but most of them lack effectiveness in controlling negative and cognitive symptoms, which contribute to the difficulty to enhance functional recovery; ii) they might result in a wide range of side effects such as extrapyramidal, sedative, and metabolic effects; and iii) between 20% and 30% of patients do not show symptom improvements, *i.e.*, the so-called treatment resistant patients. It is still unknown what makes the difference between responsive and unresponsive patients (Stępnicki et al., 2018). Clozapine is the antipsychotic drug of

choice for treatment resistant patients, and it has shown to reduce symptoms in approximately 30% of them (Kane, Honigfeld, Singer, & Meltzer, 1988).

The response to antipsychotics varies largely among patients and even along the course of a single patient (Molina & Blanco, 2013), and the choice of the specific drug to use is based on a trial-and-error strategy, which often leads to long periods of time until reaching the optimal treatment. The heterogeneity in treatment response to antipsychotic drugs seems to argue for a diversity in the biological mechanisms underlying the diagnostic of schizophrenia, likely encompassing different disease entities within it. It is thus unlikely that all symptoms can be treated with a single drug. A deeper understanding of the pathomechanisms and causes of this syndrome is needed to define more specific treatment targets.

A multimodal intervention including psychosocial therapies in combination with antipsychotic medication seems to be necessary to help alleviate symptoms and to improve social functioning, treatment adherence, and quality of life (Kern, Glynn, Horan, & Marder, 2009; Patterson & Leeuwenkamp, 2008). These psychotherapeutic interventions include techniques such as psychoeducation, Cognitive Behavior Therapy (CBT), cognitive remediation, and community-case management, among others (Tandon et al., 2010; van Os & Kapur, 2009). The therapeutic effects of these multimodal interventions have often yielded inconsistent results, perhaps due to methodological variations (Tandon et al., 2010).

The outcome of schizophrenia is highly variable, with a large variation in the illness progression across patients. In general, over the long-term course of the illness, positive symptoms tend to become less severe while negative ones tend to become more prominent (Tandon et al., 2009). A significant proportion of patients show no

complete remission of symptoms and spend large periods in psychiatric wards (Harrison et al., 2001; Jobe & Harrow, 2005). However, several studies suggest that most people diagnosed as having schizophrenia do not experience progressive deterioration but instead improve or recover (Murray, Bora, Modinos, & Vernon, 2022). In this line, some meta-analyses have reported favorable outcomes in approximately 40% of patients diagnosed with schizophrenia (Menezes, Arenovich, & Zipursky, 2006). Predictors of good prognosis include acute onset of illness, presence of affective symptoms, rapid response to treatment, less negative symptom severity, better premorbid function, superior cognition function, and female gender, among others (Flyckt, Mattsson, Edman, Carlsson, & Cullberg, 2006; Valencia et al., 2015).

1.2.4. Brain pathophysiology

Schizophrenia has been associated with altered brain structure and function. Neuroimaging studies have shown brain volume reduction, particularly affecting frontal lobe and hippocampus grey matter, lateral ventricular enlargement, and focal alteration of white matter tracts (Ellison-Wright & Bullmore, 2009; Glahn et al., 2008; Haijma et al., 2013). Follow-up studies show that some of these brain alterations, such as decreased grey matter volume (Cahn, Pol, Lems, van Haren, Schnack, van der Linden, Schothorst, van Engeland, & Kahn, 2002; Vita, De Peri, Deste, & Sacchetti, 2012) or thalamic connectivity abnormalities (Chan et al., 2022), may be progressive, being already present in an early stage of the illness and related to the disease process and antipsychotic medication. On the other hand, most neurochemical studies have shown increased dopamine synthesis and release, and increased resting-state dopamine concentrations (Guillin, Abi-Dargham, & Laruelle, 2007; McCutcheon, Beck,

Jauhar, & Howes, 2018). These findings, coupled with the fact that the main treatment of schizophrenia is based on the use of antipsychotic drugs which block dopamine D2 receptors (Kapur, Agid, Mizrahi, & Li, 2006), support the well-known dopamine hypothesis of schizophrenia. Finally, functional magnetic resonance imaging (fMRI) studies have shown alterations in brain during rest and in response to cognitive tasks. In this way, schizophrenia has been associated with mixed results of both hypofrontality and hyperfrontality (Callicott et al., 2003; Hill et al., 2004; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009) (*i.e.*, reduced and increased frontal activity, respectively). Moreover, other studies have shown a failure of deactivation in the medial frontal cortex during cognitive tasks (Pomarol-Clotet et al., 2008; Salgado-Pineda et al., 2011), considered a key region of the default mode network.

While some of these brain alterations have been widely replicated, they are not sensitive nor specific enough to be of diagnostic usefulness (Allen, Griss, Folley, Hawkins, & Pearlson, 2009; Palaniyappan, 2017). Moreover, there seems to be a great gap between these biological alterations and the symptoms reported by patients. Finally, it is also worth noting that some evidence exits about the fact that antipsychotic treatment, among other factors, potentially contributes to the wide range of brain structural alterations in psychosis (Navari & Dazzan, 2009). This should be considered in the interpretation of neuroimaging findings.

1.3. The need for a paradigm shift

As addressed in previous sections, there is a great heterogeneity within what is now known as schizophrenia. This heterogeneity encompasses a wide range of clinical aspects, including symptomatology, etiology factors, illness course, and treatment

response, among others. Moreover, after years of research, there is still not a basic understanding of the pathophysiological underpinnings of schizophrenia. One reason behind this landscape could be that the study of schizophrenia has traditionally been inadequately approached. In the last decades, there have been solid proposals for a change in how psychotic disorders are approached, from both a clinical and research perspective. Among these proposals, it is worth highlighting those which defend the view that psychosis should no longer be regarded as an all-or-none entity but rather as a continuum or quantitative trait distributed across the population (Johns & Van Os, 2001; Kendell, 1991). According to this view, the distribution of psychotic traits in the general population would follow a half-normal distribution, with the majority proportion of population having very low values and a small proportion having non-zero values (Johns & Van Os, 2001). A more recent proposal is the Research Domain Criteria Project (RDoC) proposed by the US National Institute of Mental Health (Cuthbert & Insel, 2010). This proposal argues that research should cut across traditional disorder boundaries, in order to focus on the marked heterogeneity between and within psychotic disorders (Cuthbert & Insel, 2010). Moreover, it stands out that one of the greatest challenges in the research of psychotic disorders is to understand how the structural and functional brain alterations reported in schizophrenia translate into the symptoms of the disorder. Also in this line, some authors propose that behind the heterogeneity observed in schizophrenia could be the fact that this disorder is probably neither a single disease entity and nor is it a circumscribed syndrome (Tandon et al., 2009). It seems reasonable to think that schizophrenia is an “umbrella” concept with several different neurobiological causes, and what we consider to be schizophrenia might be several distinct conditions (Faden

& Citrome, 2023). Despite these proposals, the fundamental systems in which psychotic disorders have been addressed in recent years have been slightly or not updated. Thus, the following question arises: How can these proposals be translated into new research approaches?

This doctoral thesis addresses this question by considering two important facts. First, the current formulation of the schizophrenia construct might be hampering the research process concerning the biological substrates of this syndrome (Molina & Blanco, 2013). Thus, a new research approach in line with this alternative understanding of the schizophrenia construct as a syndrome seems to be necessary. Second, probably due to the great heterogeneity and the poor understanding of the pathophysiological mechanisms of schizophrenia, the research has traditionally focused on biological processes far distant form the psychological functions altered in the syndrome. In this line, a shift in the focus of study seems to be required to bridge the gap between biological alterations and the symptoms reported by patients.

1.3.1. An alternative study approach: biotyping

The traditional view of schizophrenia as a unitary entity has led to a great body of research based on the comparison between healthy controls and patients diagnosed with schizophrenia. This research framework has assumed that the patients samples included in the studies are sufficiently homogeneous to allow the description, replication, and generalization of abnormalities to the ensemble of schizophrenia patients (Molina & Blanco, 2013). As reviewed before, there are numerous reasons to consider that schizophrenia encompasses a conglomeration of disease entities due its heterogeneity (Faden & Citrome, 2023; Molina & Blanco, 2013; Tandon et al., 2009). From such a deconstruction of the schizophrenia concept, this traditional research

approach may have hampered the identification of the biological underpinnings of this syndrome.

Some alternative research approaches appear to be more suitable for addressing the great heterogeneity observed in schizophrenia syndrome. Data-driven methodologies are based on the clustering of patients based on their common alterations, regardless of clinical diagnosis. Among the advantages of these methodologies, the following can be highlighted: i) they enable the reconceptualization of schizophrenia as a syndrome that may have different subgroups with different substrates within it; ii) they allow the validation of the identified subgroups assessing their relationship with other clinical and biological measures than the ones used for the clustering; iii) they enable a more refined and specific clinical and functional outcome monitoring over time of the potentially identified subgroups; and iv) they could facilitate the development of new therapeutic targets based on the specific neurobiological alterations and clinical manifestations of the identified subgroups.

Recent studies support the identification of different patients subgroups within schizophrenia applying this research approach on brain structural data (Holton, Chan, Brockmeier, Öngür, & Hall, 2023; Lubeiro et al., 2016; Planchuelo-Gómez, Lubeiro, Núñez, et al., 2020), functional outcomes related to network connectivity (Chan et al., 2021), eeg-based neurophysiologic profiles (Hall et al., 2012; Qu et al., 2020), positive and negative symptoms (Hall, Holton, Öngür, Montrose, & Keshavan, 2019), and cognitive performance (Carruthers, Van Rheenen, Gurvich, Sumner, & Rossell, 2019; Clementz et al., 2016; Green, Girshkin, Kremerskothen, Watkeys, & Quidé, 2019; Van Rheenen et al., 2017; Weinberg et al., 2016). Taken together, these findings seem to point towards a more productive framework in the study of the schizophrenia

syndrome and therefore, this doctoral thesis aims to contribute to this line of biotyping research.

1.3.2. Searching for a substrate closer to the altered function: the EEG and the inhibitory function

As stated before, it seems to be a great gap between some of the most replicated brain alterations in schizophrenia, such as brain volume reduction or lateral ventricular enlargement, and the predominant altered function in this disorder (*i.e.*, the mental function). This doctoral thesis proposes the study of some neurophysiological substrates closely related to that altered function, which are briefly revised in the following paragraphs.

Complex mental contents, such as those altered in many individuals with schizophrenia, imply the coordinated work of different brain areas (Dehaene & Changeux, 2011; Varela, Lachaux, Rodriguez, & Martinerie, 2001), involving the synthesis and evolution of synchronized synaptic assemblies. These synaptic assemblies encompass the coordinated and reentrant activity of most cortical regions (Buzsáki & Draguhn, 2004; Varela et al., 2001), characterized by the synchronous (*i.e.*, phase-locked) neuronal firing during a brief time. The synthesis and cancellation of the synaptic assemblies is only possible with an adequate inhibitory function, based on GABA interneurons (Buzsáki, 2006). As mentioned before in this introduction chapter, the GABA inhibitory system has been consistently reported to be functionally altered in schizophrenia (Gonzalez-Burgos et al., 2011; Lewis, Curley, Glausier, & Volk, 2012; Lewis et al., 2005). Moreover, it has been postulated that schizophrenia might be a disconnection disorder, with an impaired functional integration between neurons and brain areas as its central problem (Friston, 1998). Thus, it is reasonable to argue that

the synaptic assemblies' synthesis and cancellation underlying complex mental processes might be hampered in schizophrenia patients, or at least in a significant group of them, due to an excitatory/inhibitory imbalance. Translating this perspective into the research field of schizophrenia would involve the assessment of both synaptic assemblies' synthesis and the inhibitory function. The following paragraphs contain a brief description of how-to assess these parameters.

The electroencephalogram is a good starting point to evaluate the underlying processes of mental contents, since it allows the assessment *in vivo* of the electrical oscillations originating from groups of synchronously firing pyramidal neurons. Among the many measures that can be derived from the electroencephalogram, two are particularly relevant within the framework of this doctoral thesis: Shannon Entropy (SE) and functional network parameters derived from graph theory.

Shannon Entropy is a useful global index for quantifying the degree of disorder contained in an EEG signal. From its original definition as the average amount of information of a probability distribution (Shannon, 1948) it was extended to the EEG field in terms of power spectral density (PSD) (Inouye et al., 1991). It consists of an estimation of the EEG signal spectral content flatness (Scheeringa et al., 2011), with lower SE values reflecting a spectrum with a narrow frequency range (*i.e.*, a more regular signal) and higher SE values reflecting a broader spectral content (*i.e.*, a more irregular signal). These EEG frequency bands have been proposed to play a key role in the coordinated activity of different cortical regions (Kopell, Ermentrout, Whittington, & Traub, 2000; Von Stein, Chiang, & König, 2000; Womelsdorf et al., 2007). Thus, SE allows the evaluation of the underlying mechanisms of cognitive processing through the analysis of the average signal variability across different conditions and between

different groups. Using this parameter, previous studies have shown that the EEG signal becomes more regular (*i.e.*, SE levels are reduced) during task performance but only in healthy controls, with schizophrenia patients showing a decreased task-related modulation (Bachiller et al., 2014; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018; Molina et al., 2018). This decreased task-related modulation was associated with a basal hypersynchrony (Cea-Cañas et al., 2020; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018), and with an increased density of theta spectral power at baseline (Iglesias-Tejedor et al., 2022). It is worth noting that these alterations were unrelated to pharmacological treatment (Molina et al., 2020).

Graph theory is a useful tool to assess the functional properties of the brain, which is a complex interconnected system (Bullmore & Sporns, 2009; Friston, 2011; Sporns, 2009, 2018). Under this theory, the brain is regarded as a set of nodes interconnected by a set of edges (Bullmore & Bassett, 2011). Applying this to an EEG signal, nodes are represented by sensors while edges are the neural coupling (in terms of synchrony) of the signal recorded in these sensors. This neural coupling can be computed as means of phase-locking value (PLV) (Lachaux, Rodriguez, Martinerie, & Varela, 1999). Some useful parameters derived from graph theory have been proposed for the study of brain network connectivity patterns (Farahani, Karwowski, & Lighthall, 2019; Finotelli & Dulio, 2015; Sporns, 2018; Stam & Reijneveld, 2007). Among them (Gomez-Pilar, de Luis-García, Lubeiro, de la Red, et al., 2018; Rubinov & Sporns, 2010): i) network segregation by means of clustering coefficient, as it quantifies the ratio between the number of triangles in which a given node participates and the maximum possible number of triangles including that node; ii) network integration using path length, defined as the average of shortest distances for all possible pairs of nodes; and iii)

global synchrony of the network by means of connectivity strength, also known as density. Furthermore, it has been proposed that the brain networks have a small-world (SW) organization (Sporns, 2011; Yu, Huang, Singer, & Nikolić, 2008), characterized by a balanced integration (long-distance communication) and segregation (local areas communication) which could facilitate parallel information transmission (Finotelli & Dulio, 2015). In this framework, previous studies have reported a hyperactive functional connectivity of the brain network during the pre-stimulus window in a cognitive task in patients with schizophrenia compared to healthy controls (Bachiller et al., 2014; Cea-Cañas et al., 2020; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018). This finding was associated with smaller SE modulation (Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018) and higher positive symptoms (Gomez-Pilar, de Luis-García, Lubeiro, de la Red, et al., 2018). Moreover, SW organization has also been found to be altered in patients with schizophrenia (Gomez-Pilar et al., 2017; Shim, Kim, Lee, & Im, 2014).

Finally, as stated before, an adequate inhibitory function seems necessary in order to keep an excitatory/inhibitory balance that makes the coordinated activity between different regions possible. The inhibitory status of the cortex can be assessed in vivo using a combination of transcranial magnetic stimulation and EEG. Concurrent TMS-EEG has emerged in recent years as a powerful tool to study neural mechanisms which are not readily accessible with other neuroimaging techniques (Farzan & Bortoletto, 2022). TMS technique is based on the Faraday's law of induction of electric current by means of a time-varying magnetic field (Hallett, 2000). When a TMS pulse is applied to the scalp, an electrical current runs through the TMS coil inducing a time-varying magnetic field perpendicular to the coil which in turn induces an electrical field parallel

to the coil in the brain tissue stimulated. Thus, time-locked depolarization of the underlying neurons is obtained, and this activity can be recorded by means of EEG electrodes placed on the scalp (Tremblay et al., 2019). By manipulating the number, frequency, and interval between TMS pulses different brain physiological mechanisms can be proved (Mehta, Naik, Thanki, & Thirthalli, 2019). Recent systematic reviews of TMS-EEG studies reveal deficits in both excitatory and inhibitory functions, neural oscillations, connectivity, and motor cortical plasticity in schizophrenia patients compared to healthy controls (Di Hou, Santoro, Biondi, Shergill, & Premoli, 2021; Li et al., 2021; Vittala, Murphy, Maheshwari, & Krishnan, 2020). More specifically, the inhibitory function of the cortex has been assessed using both single- (Du et al., 2018; Ferrarelli, Riedner, Peterson, & Tononi, 2015; Fitzgerald et al., 2003) and paired-pulses (Farzan et al., 2010, 2009) paradigms. In this line, an altered GABAergic-mediated neurotransmission in the dorsolateral prefrontal cortex (DLPFC) has been reported in schizophrenia patients compared to healthy controls (Farzan et al., 2010, 2009; Noda et al., 2017; Radhu et al., 2015).

In the present doctoral thesis, a cross-diagnostic research approach using data-driven methodologies and combining the above-described measures with other relevant variables revised in this introduction chapter is proposed as a more constructive and hopeful framework for studying the underlying mechanisms and new therapeutic targets for potential subgroups within the schizophrenia syndrome.

Chapter 2

Aims and Hypotheses

2.1. Aims

General Aims

The general aims of this thesis were threefold:

1. To explore the existence of patients subgroups within schizophrenia, characterizing these potentially resulting subgroups with demographic, clinical, and biological data.

2. To follow-up outcomes of the identified patients subgroups in the medium term, to give them additional external validity.

3. To assess the association between task-related cortical activity modulation and the inhibitory system function *in vivo* in schizophrenia patients and healthy controls.

Specific Aims

The following specific aims were derived from the general ones:

1. To explore the existence of patients subgroups based on i) cognitive data and ii) the global functional network properties of the electroencephalogram and their modulation during cognitive activity using a statistical data-driven approach.

2. To validate the resulting subgroups of patients using demographic (*i.e.*, sex distribution, age, and education level), clinical (*i.e.*, illness duration, lifetime hospitalizations, medication dosage, and symptoms), and biological (*i.e.*, eeg functional network properties, frontal connectivity, cortical thickness, and subcortical volumes) data.

3. To assess the clinical and real-life outcomes in two different time points after patient's inclusion in the cognitive subgroups study, assessing the following data: job tenure, treatment compliance, number of readmissions in psychiatric wards, alcohol or other drug abuse, clozapine prescriptions, presence of satisfactory interpersonal relations, and clinical monitoring.

4. To replicate the task-related cortical activity modulation deficit previously reported in schizophrenia patients.

5. To assess the inhibitory system function in schizophrenia patients and healthy controls using a combination of TMS-EEG.

2.2. Hypotheses

1. Different patients subgroups will be identified using a data-driven approach based on cognitive and functional EEG network properties data.

2. The identified subgroups of patients will show differences in the clinical and biological variables described before.

3. Subgroups characterized by different cognitive profiles will differ in the medium term in their clinical and real-life outcomes.

4. Our results will replicate the task-related activity modulation deficit previously reported in schizophrenia patients.

5. The replicated decreased task-related activity modulation will be related to a hypofunction of the inhibitory system in schizophrenia.

6. The association between EEG modulation and the inhibitory system function will differ dimensionally rather than categorically between patients with schizophrenia and healthy controls.

Chapter 3

Neurobiological underpinnings of cognitive subtypes in psychoses: A cross-diagnostic cluster analysis

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Chapter 4

Search for schizophrenia and bipolar biotypes using functional network properties

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Chapter 5

Real-life outcomes in biotypes of psychotic disorders based on neurocognitive performance

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Chapter 6

Relation between task-related activity modulation and cortical inhibitory function in schizophrenia and healthy controls: A TMS-EEG study

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Chapter 7

Discussion

This doctoral thesis has focused on the large heterogeneity observed after decades of research among schizophrenia patients. Taken together, the findings of the studies included here support the utility of using data-driven approaches for addressing this large heterogeneity. It demonstrates the possibility of identifying meaningful subgroups within the schizophrenia syndrome, classifying patients based on their common alterations regardless their clinical diagnosis. Moreover, the present doctoral thesis contributes to bridge the gap between biological alterations and the symptoms reported by patients, by focusing on the study of underlying mechanisms closer to the altered function described in the schizophrenia syndrome. As a whole, these findings may contribute to shed light into the lack of consistent research findings replication in the field and emphasize the need of change in the traditional way in which the psychiatric disorders' classification has been approached.

In the first study, we were able to identify two subgroups of patients within the schizophrenia syndrome based on cognitive performance. Results revealed a group with severe cognitive impairment and another group with moderate cognitive impairment with different biological underpinnings. The severely impaired group was characterized by lower thalamus and hippocampus volume, prefrontal connectivity alterations assessed with DTI, a hypersynchronic basal EEG state, and higher illness duration and symptom scores. Going beyond these distinctive characteristics, both

patients subgroups showed lower cortical thickness and task-related modulation deficits compared to healthy controls.

In the second article, using EEG-based network parameters derived from graph theory obtained during an auditory oddball task, we could identify two subgroups of patients within the schizophrenia syndrome. One subgroup showed an EEG network pattern similar to healthy controls. The other subgroup was associated with altered global properties of functional and structural connectivity. As in the first study, both subgroups of patients showed regionally decreased cortical thickness and modulation deficits of their EEG activity during a cognitive task.

Considering together both studies, it can be highlighted that data-driven approaches seem to be a more suitable approach to encompass the large heterogeneity among patients within the schizophrenia syndrome. Thus, it is important to note that a study of the clinical, cognitive, and neurobiological underpinnings of these patients from a more classical approach (*i.e.*, pooling them as a homogeneous group and comparing them with healthy controls) would have led to incorrect and inconclusive findings. Moreover, both studies have followed some important recommendations from classical proposals for changing the way in which psychotic disorders have been traditionally approached. First, both have incorporated additional validity to subgroups' identification by characterizing them with other clinical and biological measures than the ones used for clustering. Second, using a cross-diagnostic approach, both studies have contributed to cut across traditional psychotic disorders' boundaries to better understand the great heterogeneity between and within them. In this line, both studies have included not only patients with schizophrenia but also patients with bipolar disorder. These latter patients were included due to the strong evidence of

shared genetics (Cardno & Owen, 2014; Van Den Bogaert, Del-Favero, & Van Broeckhoven, 2006), clinical features (Tamminga et al., 2013), and cognitive deficits (Hill et al., 2013) between schizophrenia and bipolar disorder patients. Thus, it seems reasonable to include both diagnoses within a global psychosis spectrum. Remarkably, results of both studies showed that patients did not group themselves based in diagnostic categories, with each diagnosis being represented in all the identified subgroups. In this line, certain anatomical and functional brain abnormalities seem to occur in patients within different diagnostic categories. Furthermore, patients within the same diagnostic category can differ in their clinical and neurobiological underlying mechanisms. Finally, from the biotyping research framework it has been suggested the need for following-up the identified subgroups in terms of clinical and functional outcomes in order to assess their external validity.

Regarding the last point, the third article included in this doctoral thesis aimed to assess the clinical and functional outcomes of the subgroups identified in the first study. Results revealed that the subgroup with larger cognitive deficits and more severe biological alterations was associated with more difficulties in real-life functioning and greater clinical severity in the medium term. Specifically, patients included in that subgroup showed a decreased capacity for job tenure, more admissions to psychiatric wards, and higher likelihood for quitting psychiatric follow up.

Finally, the fourth study explored the underpinnings of the decreased task-related activity EEG modulation observed in the subgroups identified in the first two studies. The results showed that schizophrenia patients showed higher cortical reactivity following transcranial magnetic stimulation single pulses over the left dorsolateral

prefrontal cortex compared to healthy controls. Moreover, this study highlights a potential relationship between EEG signal modulation during a cognitive task and the amplitude of the evoked response to TMS single pulses in both healthy controls and patients. In other words, the higher amplitude of the evoked response to TMS stimulation was related to a decreased task-related modulatory capacity of the EEG.

In the following sections, the findings of the studies included in this doctoral thesis are discussed and integrated in light of previous literature in the field.

7.1. Cognitive subtypes across schizophrenia syndrome

A broad-based cognitive impairment has previously described in schizophrenia, especially affecting attention, processing speed, working and long-term memory, executive function, and social cognition (Fioravanti et al., 2005; van Os & Kapur, 2009). However, this cognitive domain is not free from heterogeneity either, varying to different degrees among patients with schizophrenia (Keefe, Eesley, & Poe, 2005; Saykin et al., 2005). Some of these alterations are also shared with other psychotic disorders such as bipolar disorder (Hill et al., 2013). Considering this heterogeneity, the use of cognitive features as the target of subtyping within the psychosis spectrum is promising. Furthermore, it seems a good starting point for further revealing the neurobiological underpinnings of the potential resulting subgroups, since the average sizes for cognitive alterations are about twice as large as those obtained for brain alterations (Dickinson, Ramsey, & Gold, 2007; Keshavan et al., 2008; Reichenberg & Harvey, 2007). Thus, in the last decades, a growing number of studies have used this approach to delineate genetic (Green et al., 2013; Hall et al., 2012; Hallmayer et al., 2005) and brain alterations (Shepherd et al., 2015; Van Rheenen et al., 2018) common

to schizophrenia patients within subgroups defined by cognitive impairments. The first article included in this doctoral thesis adds to this research line.

There is no clear consensus regarding the number of cognitive subtypes existing in the schizophrenia syndrome. Attending to cognitive subtyping studies including only patients with schizophrenia, the most common finding is a 3-cluster solution, including a relatively intact, intermediate, and severely impaired group (Bechi et al., 2019; Carruthers et al., 2019; Gilbert et al., 2014; Van Rheenen et al., 2017; Wells et al., 2015). Nevertheless, there are several other studies revealing a 4-cluster (Gambini, Campana, Garghentini, & Scarone, 2003; Hill, Ragland, Gur, & Gur, 2002; Rangel et al., 2015; Weinberg et al., 2016) or even a 5-cluster solution (Dawes, Jeste, & Palmer, 2011). However, the study with the largest sample yielded a two cognitive cluster solution (Green et al., 2013), as in our study. Cross-diagnostic cluster studies do not seem to solve this inconsistency of results, with most finding a 4-cluster solution (Bora, Veznedaroğlu, & Vahip, 2016; Lewandowski, Sperry, Cohen, & Öngür, 2014; Lewandowski, Baker, McCarthy, Norris, & Öngür, 2017; Reser, Allott, Killackey, Farhall, & Cotton, 2015) but being very few to draw solid conclusions.

A recent systematic review highlighted this disagreement regarding the findings of cognitive subtyping studies in schizophrenia (Green, Girshkin, Kremerskothen, Watkeys, & Quidé, 2020). The main reason behind this inconsistency is likely due to the large range of sample sizes and different statistical approaches used for clustering procedures. Despite this, a severely impaired subtype with larger cognitive impairments is common to all cluster solutions (Green et al., 2020), as the one identified in our study.

Consistent with previous findings of cross-diagnostic studies mixing schizophrenia and bipolar disorder patients (Bora et al., 2016; Lewandowski et al., 2014; Lewandowski et al., 2017; Reser et al., 2015; Van Rheenen et al., 2017), our results revealed a greater proportion of bipolar disorder patients being allocated to the cognitively moderately impaired subgroup. Moreover, our severely impaired subgroup was associated with lower educational attainment and more severe symptoms, which is also in agreement with previous findings in the field (Bora et al., 2016; Lewandowski et al., 2014; Lewandowski et al., 2017).

In the framework of subtyping studies it is important to rule out that results are driven by chronicity or treatment. In our study, the sample included first episodes of schizophrenia to control for chronicity as a major contribution to the solution. Although patients in the severely impaired group were associated with higher illness duration due to a larger representation of chronic patients in this group, first episode patients were represented in both subgroups, suggesting that chronicity is not likely driving our results as a major factor. Furthermore, our results are in line with other studies in the field revealing similar impaired cognitive profiles in first episode patients and chronic patients (Sauvé et al., 2018). Finally, the effect of treatment could be ruled out since our analysis revealed that both cognitive subgroups did not differ in treatment dosage, nor were the correlations between antipsychotic doses and cognitive scores significant.

The neurobiological underpinnings of cognitive subtypes in schizophrenia have received little attention to date. Our study not only adds to the subtyping research field but also seeks to enrich it by providing a wider range of variables for the biological characterization of the resulting cognitive subgroups. We observed that patients

within the severely impaired group were associated with more prominent brain structural and functional abnormalities. This pattern of findings is consistent with previous studies also reporting decreased grey matter volumes, specially affecting the hippocampus, thalamus, and frontal and temporal lobes in the more deteriorated cognitive subgroups (Clementz et al., 2016; Shepherd et al., 2015; Van Rheenen et al., 2018; Weinberg et al., 2016; Woodward & Heckers, 2015). Regarding neuroanatomical-based biotyping studies, our findings are also in line with previous reports of subgroups of patients showing higher cortical curvature and lower cortical thickness (Lubeiro et al., 2016) and global cortical thinning associated to cognitive deficit (Planchuelo-Gómez, Lubeiro, Núñez-Novo, et al., 2020). Taken together, these studies give support to the idea that not all schizophrenia patients but some cases within the syndrome may be characterized by biological substrates traditionally attributed to schizophrenia as a whole, such as hippocampal or thalamic volume reductions. Thus, these kinds of studies may contribute to a better understanding of the heterogeneity within psychosis and their neurobiological underpinnings. They could also raise the possibility of defining new biomarkers and developing new and personalized treatments.

7.2. Functional network EEG subtypes across schizophrenia syndrome

As stated before, higher mental functions depend on global cerebral functional coordination (Dehaene & Changeux, 2011; Varela et al., 2001). EEG and graph-theory measurements are a useful tool for assessing functional and structural characteristics of the bioelectrical signal underlying mental functions (Bullmore & Sporns, 2009). Since mental activity is altered in patients with schizophrenia, we decided to explore the possible existence of groups of patients based on EEG-based network parameters

derived from graph-theory and obtained during a cognitive task. As far as we now, there are no previous studies exploring the existence of different subgroups within the psychosis spectrum based on the global network properties of the EEG during a cognitive task.

Applying graph-theory to EEG data recorded during the same odd-ball task used in this thesis, our research group has found several baseline alterations in schizophrenia patients as a whole. We described higher CLC values at the pre-stimulus window (*i.e.*, a hyper-segregated network) and a decreased modulation of the functional connectivity during cognition in patients with schizophrenia (Gomez-Pilar et al., 2017). Besides, we also reported higher CS values at the pre-stimulus window (*i.e.*, a hypersynchronic basal state) in schizophrenia patients compared to healthy controls (Gomez-Pilar, de Luis-García, Lubeiro, de la Red, et al., 2018; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018) and bipolar disorder patients (Cea-Cañas et al., 2020). Later on, we were able to refine these results through the first article included in this doctoral thesis, showing that the higher CS previously described in schizophrenia patients as a whole was only characteristic of the cognitively severely impaired subgroup (Fernández-Linsenbarth et al., 2021). In agreement with these results, a previous report showed that patients with schizophrenia showing impaired working memory capacity were associated with decreased functional connectivity between DLPFC and other areas compared to healthy controls and the remaining patients (Wu et al., 2017). Considering these findings and the heterogeneity previously described in schizophrenia, it was reasonable to think that functional network alterations could be more severe in a subgroup of patients, which encouraged us to study the possible existence of subgroups based on these EEG parameters.

Our results confirmed this hypothesis, showing a subgroup of patients with a pattern of functional EEG network properties similar to healthy controls and other subgroup of patients with a global impaired functional EEG network (*i.e.*, higher prestimulus CS, CLC, PL, and lower SW index compared to healthy controls). Although cortical thickness was regionally decreased in both subgroups, this decrease was more widespread in the subgroup with altered global functional connectivity properties. As in our first study, the effect of treatment and chronicity could be ruled out since no significant differences in antipsychotic dosages nor illness duration were found between subgroups.

Contrary to our hypothesis, subgroups based on functional network characteristics did not differ in their symptoms scores or cognitive performance. As stated in the article, depending on the clustering criteria the resulting subgroups' correlates may differ slightly, which leads to opening the debate about whether there are variables that may be more suitable for biotyping studies. Nonetheless, the results of our study suggest that both normal and altered EEG network characteristics may be associated with similar degrees of cognitive alteration and symptoms manifestations. In fact, this pattern of results is consistent with the biological heterogeneity of schizophrenia substrates (Arnedo et al., 2015; Molina & Blanco, 2013; Volk et al., 2012). In this line, similar clinical manifestations and cognitive impairments might have different underlying brain substrates. Our results suggest that one of such substrates may relate to an alteration of the functional network but only in a subgroup of patients within the schizophrenia syndrome. Perhaps the clinical and cognitive manifestations of other potential subgroups, such as the other identified in our study, may have different underlying substrates that cannot be reflected in the analysis of the functional

architecture of the EEG. One of such possible alternative underlying substrates could be a biochemical disbalance based in inhibitory function alterations. This idea encouraged us to design the fourth article included in this doctoral thesis, in which both the properties of the EEG and the GABAergic inhibitory function were studied as a possible substrate of the altered function in schizophrenia patients.

7.3. Clinical outcome and real-life adaptation of cognitive subtypes

Cognitive impairments in schizophrenia constitute one of the main obstacles to clinical and functional recovery (Harvey et al., 2022). Some previous reports propose neurocognition as a predictor of everyday functioning in patients with schizophrenia, independently of positive and negative symptoms (Galderisi et al., 2014; Mucci et al., 2021; Stirling et al., 2003). Previous reports support a relation between cognitive performance and functional outcome in schizophrenia patients (Gold, Goldberg, McNary, Dixon, & Anthony Lehman, 2002; Green, Horan, & Lee, 2019; Green et al., 2000). Specifically, different aspects of neurocognition have been related to subjective quality of life (Kurtz & Tolman, 2011), work skills (Mucci et al., 2021; Oomen et al., 2021), job tenure (Gold et al., 2002), real-world social functioning (Deste et al., 2020), satisfaction with family and social contacts (Fujii et al., 2004; Milev et al., 2005), and with adherence to antipsychotic treatment (García et al., 2016) in schizophrenia patients.

As stated in the introduction chapter, current pharmacological options have limited effects on cognition, with some side-effects even aggravating some of these deficits (Kaar, Natesan, McCutcheon, & Howes, 2020). It's worth noting that despite patients with greater cognitive impairments are associated with more psychiatric follow-up and treatment compliance than patients with milder cognitive impairments, their

functional outcome is worse. Perhaps it would be interesting to consider a treatment design more focused on functional rehabilitation (such as cognitive remediation) and not so much on psychiatric follow-up in those patients with more cognitive impairment. Although cognitive remediation programs show significant benefits on cognition, there is a high inter-individual variability among patients in the improvement degree and generalization to daily functioning (Deste et al., 2020; Kharawala et al., 2022). Furthermore, there are other studies that do not support the proposed association between cognitive performance and functional outcome (Reichenberg et al., 2014). This scenario is consistent with growing evidence suggesting the existence of different subgroups within the psychosis spectrum based on cognitive performance (Bora et al., 2016; Lewandowski et al., 2014; Lewandowski et al., 2017; Reser et al., 2015; Shepherd et al., 2015; Van Rheenen et al., 2018) and also with the idea that those potential cognitive subgroups may differ in their clinical outcomes and social functioning. In fact, one of the proposed future research lines in the article of cognitive subtypes was to better clarify the resulting subgroups in terms of disease outcome profiles, treatment response, and stability over the time. This led us to carry out the third article included in this doctoral thesis, exploring the real-life outcomes of the cognitive subgroups identified in that first article. Taken together, the results of the third article included in this doctoral thesis confirmed our hypothesis, revealing more difficulties in real-life functioning and greater clinical severity in the subgroup of patients with more severe cognitive deficits.

As stated in the introduction section, among the advantages of data-driven methodologies is the fact that they allow the validation of the resulting subgroups by assessing their relationship with other biological and clinical variables than the ones

used for the clustering. To the best of our knowledge, no previous studies have explored the functional and clinical outcomes of cognitive subgroups within the psychosis spectrum. Thus, a conclusion that can be derived from the third article included in this doctoral thesis is that comparing real-life adjustment variables among the identified cognitive subgroups can be considered as an additional source of validity together with biological variables within biotyping studies.

7.4. Changing the study focus: closer underlying mechanisms

In previous reports of our research group, we have replicated in three different samples a deficit in EEG activity modulation during a cognitive task in schizophrenia patients compared to healthy controls (Bachiller et al., 2014; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018; Molina et al., 2018). In other words, spectral entropy levels are reduced (*i.e.*, EEG signal becomes more regular) during task performance, but only in healthy controls. This lower modulation has been associated with higher pre-stimulus connectivity strength (Cea-Cañas et al., 2020; Gomez-Pilar, de Luis-García, Lubeiro, de Uribe, et al., 2018), and with an increased density of theta spectral power at baseline (Iglesias-Tejedor et al., 2022). The task-related modulation deficit has been shown to be unrelated to psychopharmacological treatment or structural connectivity (Molina, Lubeiro, de Luis-García, & Gómez-Pilar, 2020). Moreover, spectral entropy modulation with task performance was found to be decreased not only in patients with schizophrenia but also in patients with bipolar disorder, leading to propose it as a biomarker for the altered function in these disorders (Molina et al., 2020). This task-related EEG modulation deficit might reflect alterations in the synchronization of the neural assemblies that underlie cognitive activity. Consistent with these previous findings, three out of the four articles included

in this doctoral thesis replicate this EEG modulation deficit during cognitive activity. Thus, the two subgroup studies demonstrate that, regardless the clustering criteria, all the identified clusters were associated with a spectral entropy modulation deficit during a cognitive task, and the last article replicates this result once again in a completely new sample. Taken together, the results of these articles provide robustness to the previous findings.

A possible neurophysiological substrate of these findings may be related to a decreased inhibitory function previously described in schizophrenia. Several post-mortem studies have shown GABAergic deficits in patients with schizophrenia, in terms of decreased GABA concentrations (Perry, Kish et al., 1979), reduced $GABA_B$ receptors expression (Mizukami, Ishikawa et al., 2002; Mizukami, Sasaki et al., 2000), and decreased interneurons density (Benes, 1991). Moreover, several EEG-based studies have identified alterations in gamma frequency oscillations in patients with schizophrenia (Hunt, Kopell, Traub, & Whittington, 2017). This gamma frequency oscillations are produced by the firing patterns of parvalbumin-expressing fast-spiking inhibitory interneurons (Vittala et al., 2020), playing a key role in the excitatory/inhibitory balance of the brain.

Recent studies using TMS-EEG have made a great contribution in understanding the pathophysiological bases of schizophrenia (Di Hou et al., 2021; Li et al., 2021; Vittala et al., 2020). Specifically, previous studies have reported decreased short-interval and long-interval cortical inhibition (SICI and LICI, respectively) in the DLPFC of patients with schizophrenia, suggesting $GABA_A$ and $GABA_B$ receptor-mediated dysfunctions in this region (Farzan et al., 2010, 2009; Noda et al., 2017; Radhu et al., 2015). Furthermore, reduced connectivity between the premotor cortex and prefrontal

cortex (Ferrarelli et al., 2015) and reduced TMS-induced gamma oscillations in fronto-central regions (Ferrarelli et al., 2008) have been found in patients with schizophrenia. In line with these results, another study reported increased cortical inhibition in clozapine treated schizophrenia patients (Daskalakis, Farzan, Radhu, & Fitzgerald, 2012). Our finding of higher cortical reactivity following TMS single pulses over the DLPFC in patients with schizophrenia is consistent with the inhibitory function alterations described in previous TMS-EEG studies stated above. They are also in agreement with the inverse correlation between cortical reactivity after TMS stimulation and EEG modulation that we found both in patients and healthy controls in our last article.

Although the last article included in this doctoral thesis is a pilot study and its sample size is not large enough to allow a data-driven approach, it makes an important contribution in changing the focus of the traditional biological processes studied in the schizophrenia field, which are far distant from the psychological functions known to be altered. The EEG modulation during a cognitive task as a proxy of the synaptic assemblies' synthesis and dissolution, and the GABAergic inhibitory function as a mechanism that allows proper neural assemblies evolution, seem to constitute underlying biological mechanisms closely related to the altered function of psychiatric disorders such as schizophrenia, *i.e.*, the mental contents.

7.5. Limitations of the study

This doctoral thesis has some limitations that should be noted:

First, all patients included were under antipsychotic medication. This lack of untreated patients makes not possible to completely discard an effect of treatment on the measured variables. However, this effect was controlled by using correlation analysis

between antipsychotic dosages and relevant variables. Moreover, the inclusion of first episodes of schizophrenia and bipolar disorder patients aimed to discard possible treatment effects on the studied variables.

Second, larger sample sizes would have been desirable. Also, some biological variables were not available in all subjects. Moreover, we experienced a high dropout's rate in the third article. Nonetheless, it is important to note that the first article included in this thesis has the largest sample size and is the most relevant in terms of subgroups identification. Larger sample sizes would enhance the statistical power of the results, especially in the last article. It is important to note that sample collection from this last article started from zero, which was reflected in the small simple size.

Third, subgroups of patients identified in the two firsts articles were compared with controls, considering the latter as a homogeneous population. However, as mentioned in the introduction section, some proposals argue for a dimensional approach on psychotic traits distribution across the population, including healthy controls.

Fourth, concerning the first article included in this doctoral thesis, we did not replicate our findings in an independent sample to assure the generalization of the subgroups solution. Remarkably, we were able to do this replication analysis in our second article, including a main and a replication dataset.

Fifth, in the subgroups studies we selected one data-driven method for subgroups' identification (*i.e.*, K-means cluster analysis). Results may slightly vary depending on the chosen data-driven method and the selected grouping variables. However, we tried to solve this employing different clustering methods to compare their classification results and we obtained similar findings, which gives robustness to our results.

Sixth, regarding the article studying real-life outcomes of the cognitive subtypes, our follow-up period was relatively short, and the different illness duration of the participants included is a potentially confounding factor when interpreting the results.

Seventh, in relation to our last article included in this doctoral thesis, we did not use neuronavigation to localize the left DLPFC. However, following previous studies in the field, the coil was placed in a position that provides the most accurate estimation of this brain region. Besides, our study design cannot fully disentangle the contribution of excitatory vs. inhibitory mechanisms to the cortical reactivity following TMS pulses and thus to the EEG activity modulation during a cognitive task.

In eighth place, EEG is not completely free of volume conduction. Although these effects were minimized by using a reference average approach and by comparing two experimental contrasts (*i.e.*, pre-stimulus and response conditions), EEG results should be cautiously interpreted. However, it is important to note that these effects hamper mostly source localization analyses, and our network studies instead consider the global properties of cortical activity.

Ninth, the thesis title is primarily restricted to the last article included in this doctoral thesis, not capturing the overall aims of the work.

Finally, correlational analysis as the ones used in the included studies describe association but not causality.

Chapter 8

Conclusions

8.1. Main conclusions of the study

Different subgroups with distinct neurobiological underpinnings could be identified within the psychosis spectrum. On one hand, using a data-driven approach we could segregate two subgroups of patients based on neurocognitive performance, including a severely impaired and a moderately impaired group. The severely impaired group was associated with more severe clinical manifestations and larger neurobiological alterations than the moderately impaired group. Furthermore, a medium-term follow-up of the patients included in the cognition-based subgroup study gave additional validity to the identified subgroups. Results revealed that the subgroup with larger cognitive deficits and more severe biological alterations was associated with greater clinical severity and more difficulties in real-life functioning in the medium-term. On the other hand, also using a data-driven approach two different subgroups of patients could be identified within the psychosis spectrum based on the functional network properties of the EEG during a cognitive task. The results support the existence of a subgroup of patients with altered global properties of functional and structural connectivity. Taken together, these findings shed light on the significant heterogeneity and lack of replicability of results in the field of schizophrenia substrates. Likewise, they support the idea that schizophrenia is likely not a single disorder entity but a collection of several distinct conditions with different neurobiological underpinnings.

Additionally, in three out of four of the articles included in this doctoral thesis we replicated an EEG modulation deficit during cognitive activity in both schizophrenia and bipolar disorder patients. This deficit could reflect an alteration in the synchronization of the neural assemblies that underlie cognitive activity and states this variable as a possible biomarker of the altered function in these disorders. Our results are also in agreement with previous reports of a hypersynchronic basal state and inhibitory function alterations in patients with schizophrenia, revealing higher cortical reactivity following TMS single pulses applied over the left DLPFC. Finally, we were able to identify a dimensional association between the task-related EEG activity modulation and the amplitude of the evoked response to TMS single pulses in both healthy controls and patients, supporting the idea that a hypofunction of the inhibitory system could hamper the task-related modulation of EEG activity. These results shed light to physiological mechanisms closely related to the altered function in patients with schizophrenia.

8.2. Future research lines

- To continue exploring the utility of data-driven approaches.
- To characterize the identified subgroups more deeply by using other types of variables such as childhood trauma, genetic, and/or functional spectroscopy data.
- To include a treatment-naïve group of patients to completely discard the effect of treatment.
- To perform longitudinal data-driven studies ideally focusing on the initial stages of the illness to better clarify potential subgroups in terms of disease outcome profiles, response to treatment, and stability over the time.

- To replicate the finding of an association between SE modulation and cortical reactivity following TMS single pulses in a larger sample.
- To explore the possibility of identifying different subgroups of patients based on their cortical reactivity following TMS single pulses over the DLPFC. The identification of a potential subgroup with greater inhibitory deficits could aid in the development of more specific therapeutic targets.
- To explore possible associations between the inhibitory system function assessed through TMS-EEG and other variables such as cognitive performance or symptom severity.
- To study a possible change in cortical reactivity following TMS-EEG single pulses over the DLPFC in treatment resistant patients with schizophrenia before and after receiving clozapine.
- To explore the association between the inhibitory function assessed through TMS-EEG and other neurophysiological parameters different from the auditory oddball paradigm, such as P50 elicited by sensory gating paradigm or the auditory-steady state response, which have been closer related to inhibitory mechanisms.
- To enrich the design of our TMS-EEG study to be able to disentangle the contribution of excitatory vs. inhibitory mechanisms to the association between task-related EEG activity modulation and cortical reactivity following TMS single pulses. For example, through the use of paired-pulse paradigms such as LICI and SICI or by including measures of functional spectroscopy of GABA levels.

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