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Tesis Doctoral

Characterization of Dynamical Neural Activity by Means of EEG Data: Application to Schizophrenia

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acuerda otorgarle la calificación de

En Valladolid, a

A mis padres, Isabel y Martín, por apoyarme en todo momento.

No te rindas, aún estás a tiempo
de alcanzar y comenzar de nuevo,
aceptar tus sombras, enterrar tus miedos,
liberar el lastre, retomar el vuelo.
No te rindas que la vida es eso,
continuar el viaje,
perseguir tus sueños,
destrabar el tiempo,
correr los escombros y destapar el cielo.

No te rindas, por favor no cedas,
aunque el frío queme,
aunque el miedo muerda,
aunque el sol se esconda y se calle el viento,
aún hay fuego en tu alma
aún hay vida en tus sueños.
porque la vida es tuya y tuyo también el deseo
porque lo has querido y porque te quiero.

Porque existe el vino y el amor, es cierto.
porque no hay heridas que no cure el tiempo.
abrir las puertas, quitar los cerrojos,
abandonar las murallas que te protegieron,
vivir la vida y aceptar el reto,
recuperar la risa, ensayar un canto,
bajar la guardia y extender las manos
desplegar las alas e intentar de nuevo,
celebrar la vida y retomar los cielos.

No te rindas, por favor no cedas,
aunque el frío queme,
aunque el miedo muerda,
aunque el sol se ponga y se calle el viento,
aún hay fuego en tu alma,
aún hay vida en tus sueños
porque cada día es un comienzo nuevo,
porque esta es la hora y el mejor momento,
porque no estás solo, porque yo te quiero.

No te rindas
Mario Benedetti

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Abstract

Schizophrenia is a disabling, chronic and severe mental illness characterized by disintegration of the process of thinking, contact with reality and emotional responsiveness. Schizophrenia has been related to an aberrant assignment of salience to external objects and internal representations. In addition, schizophrenia has been identified as a dysconnection syndrome, which is associated with a reduced capacity to integrate information among different brain regions. Relevance attribution likely involves diverse cerebral regions and their interconnections. As a consequence, many efforts have been devoted to identifying abnormalities in the cortical connections and their relation to schizophrenia symptoms and cognitive performance.

Neural oscillations are one of the largest contributing mechanism for enabling coordinated activity during normal brain functioning. Alterations in neural oscillations and cognitive processing in schizophrenia have long been assessed using electroencephalographic (EEG) recordings (*i.e.* time-varying voltages on the human scalp generated by the electrical activity on the cerebral cortex). Event-related potentials (ERP) depict EEG data as a response to a cognitive task. ERP analyses are used to gain further insights into the neural mechanisms underlying cognitive dysfunctions. In this Doctoral Thesis, a 3-stimulus auditory-oddball paradigm was used for examining cognitive processing as response to both relevant and irrelevant stimuli. A total of 69 ERP recordings were analyzed in the research papers included in the Thesis, which comprises 20 chronic schizophrenia patients, 11 first episode patients and 38 healthy controls.

This Doctoral Thesis is focused on the study, design and application of biomedical signal processing methodologies in order to facilitate the understanding of cognitive processes altered by the schizophrenia. EEG data were examined using a two-level analysis: (*i*) local activation studies to quantify functional segregation of the brain network, by means of spectral analysis and by assessing neural source generators of P3a and P3b components; and (*ii*) EEG interactions studies to explore functional integration across brain regions, including pair-wise couplings and exploring hierarchical organization of neural rhythms.

Functional segregation aims to identify the brain areas dedicated to specific processing tasks. As a first step, spectral analysis of local activation was performed. Three local activation measures were computed: the relative power (RP) (*i.e.* the proportion of total power attributable to a given frequency band), the median frequency (MF) (*i.e.* the frequency which comprises the 50% of the power) and the spectral entropy (SE) (*i.e.* a measure of the irregularity of the EEG data). RP analyses showed an increase of power from the baseline window to the response window for low frequency bands and a decrease for high frequency bands. Nevertheless, the changes were statistically significantly higher ($p < 0.01$) in controls than in patients. In addition, MF and SE revealed a widespread decrease from baseline to response window for healthy controls, whereas these changes were lower in schizophrenia patients. Our findings also suggested a statistically significantly larger ($p < 0.01$) MF and SE decrease as a response to target

stimuli than as a response to distractor stimuli. Secondly, source imaging techniques were applied to detect neural generators that contribute to the scalp recorded ERP as a response to target (P3b) and distractor (P3a) tones. Our findings were consistent with previous reports, revealing a lower P3a and P3b source activation mainly in frontal and cingulate regions for schizophrenia patients than for healthy controls. Likewise, the intra-group differences between P3a and P3b were larger in patients than in controls, suggesting an inefficient hyperactivation during the processing of target stimuli.

On the other hand, functional integration evaluates the dependencies among brain areas. Functional neural coupling analyzes the statistical dependence between the neural activity at different EEG electrodes. In this study, three complementary functional connectivity measures (wavelet coherence (WC), phase-locking value (PLV) and Euclidean distance (ED)) were applied to analyze correlation, synchrony and similarity patterns. In comparison to healthy controls, schizophrenia patients are characterized by a lack of increase of coupling from baseline to response in the theta band and a lack of decrease for beta_2 band. These findings suggested that schizophrenia patients failed to response to relevance (*i.e.* they are not able to change their connectivity patterns between the auditory response and pre-stimulus baseline). In addition, EEG rhythms in different frequency bands can interact with each other, which reflects the complex and hierarchical organization of cognitive processes. This Doctoral Thesis evaluated event-related phase amplitude coupling (ERPAC), obtaining an association between alpha phase and gamma amplitude. Higher prevalence of alpha-to-gamma ERPAC after stimulus onset was found over central-parietal brain areas than over frontal and temporal brain regions. These findings could evidence the role of alpha rhythms as a core feature of cortical communication.

In summary, our proposal evaluates time-frequency EEG data when subjects were performed an auditory cognitive task, obtaining a reliable characterization of dynamical neural patterns. For this purpose, segregation and integration were characterized by means of a two-level analysis of EEG data including: spectral analysis, neural source generators, functional connectivity and hierarchical complex organization of neural rhythms. Our findings revealed that schizophrenia patients showed an attention-dependent modulation of spectral distribution, source generators and functional connectivity in specific frequency bands. In conclusion, these results support the aberrant salience and dysconnection hypotheses: schizophrenia patients show a failure to contextualize stimulus processing through a failure on neuronal firing synchronization.

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Acronyms

AUC	Area Under ROC Curve
BA	Brodmann Area
BACS	Brief Assessment of Cognition in Schizophrenia
CFC	Cross-Frequency Coupling
COI	Cone of Influence
COMT	Catechol-O-Methytransferase
CP	Chronic Patients
CWT	Continuous Wavelet Transform
DNA	Deoxyribonucleic Acid
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
ECoG	Electrocorticography
ED	Euclidean Distance
EEG	Electroencephalography
ERP	Event-Related Potentials
FDR	False Discovery Rate
FIR	Finite Impulse Response
fMRI	Functional Magnetic Resonance Imaging
FT	Fourier Transform
GABA	Gamma-Aminobutyric Acid
GWAS	Genome-Wide Association Studies
HF	High-Frequencies
ICA	Independent Component Analysis
IQ	Intelligence Quotient
JCR	Journal Citation Reports
K	Potasium
LDA	Linear Discriminant Analysis
LF	Low-Frequencies
LFP	Local Field Potentials
LOO-CV	Leave-One-Out Cross-Validation
LORETA	Low-Resolution Brain Electromagnetic Tomography
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
MTP	Minimally Treated Patients
Na	Sodium
NMDA	N-methyl-D-aspartate
NPT	Non-parametric Permutations Tests
PAC	Phase-Amplitude Coupling
PANSS	Positive and Negative Syndrome Scale

PLV	Phase-Locking Value
PSD	Power Spectral Density
ROC	Receiver Operating Characteristics
RP	Relative Power
SCH	Schizophrenia
SE	Shannon Entropy
SD	Standard Deviation
sLORETA	Standardized LORETA
STFT	Short-Time Fourier Transform
TR-LCMV	Time-reduction Region-suppression Linearly Constrained Minimum Variance
WAIS-III	Wechsler Adult Intelligence Scale third edition
WC	Wavelet Coherence
WCS	Wavelet Cross-Spectrum
WOI	Window of Interest

Chapter 1

Introduction

1.1. Introduction

Schizophrenia is still one of the most mysterious and costliest mental disorders in terms of human suffering and societal expenditure (van Os and Kapur, 2009). Active symptoms of schizophrenia typically emerge in late adolescence or early adulthood and may become a chronic condition. Thereby, it is considered a relevant socio-economic problem for health care systems.

The current Doctoral Thesis focuses on characterizing the neural dynamics underlying clinical manifestation and cognitive processing in schizophrenia by means of biomedical signal processing methodologies. This investigation has led to results published in journals indexed in the Journal Citation Reports (JCR) from Thomson Reuters Web of Science™.

The thematic consistency of the articles included in the Doctoral Thesis is justified in this introductory Chapter. A brief introduction to Biomedical Engineering and neural signal processing can be also found. Moreover, there are sections devoted to explain schizophrenia characteristics, the electroencephalography (EEG) and event-related potentials (ERP). Finally, cognitive electrophysiology issue and the two-level hierarchical analysis of neural signals have been described.

1.2. Context: Biomedical Engineering and neural signal processing

The research field of this Doctoral Thesis is 'Biomedical Engineering'. Biomedical Engineering is an interdisciplinary field that focuses on altering, controlling, or understanding biological systems by applying engineering principles (Bronzino, 2006). One of the greatest Biomedical Engineering benefits is the ability to identify issues and needs in healthcare systems. Hence, biomedical engineers apply engineering principles and methodologies to understand, model and solve problems associated with medicine and biology (Bronzino, 2006).

Among the different branches of expertise, this Doctoral Thesis is focused into the field of 'biomedical signal processing' and particularly in 'neural signal processing'. Biomedical signals are produced by biological structures and systems (Cohen, 2000). Therefore, attending to their origin they can be classified into bioelectric, biomagnetic, bioacoustic, biomechanical, biochemical, biooptical signals, among others (Sörnmo and Laguna, 2005). Usually, the information contained in biomedical signals is not directly inter-

pretable; hence, a processing stage is needed in order to obtain a meaningful measure of the data (Sörnmo and Laguna, 2005). Biomedical signal processing is essential to uncover signal components that may be very difficult, if not impossible, to observe by the naked eye (Sörnmo and Laguna, 2005). Signal processing techniques aim at reducing the noise present in the signals and the subjectivity of the manual measurements, as well as at increasing the reproducibility of the results (Sörnmo and Laguna, 2005). The biomedical signals that will be analyzed in this Doctoral Thesis are EEG recordings. These discrete signals reflect the electrical activity of the cerebral cortex by means of the recording of time-varying voltages on the human scalp.

This Doctoral Thesis aims at helping in the characterization of dynamical neural activity associated with the schizophrenia disorder. For this purpose, EEG data during the performance of an auditory cognitive task have been analyzed. Likewise, novel time-frequency signal processing techniques have been applied and assessed. Hence, all the above mentioned reflect the framework in which this Doctoral Thesis is encompassed. The next section introduces the schizophrenia and describes the aetiology and the treatment of this disorder.

1.3. Schizophrenia

Schizophrenia is a disabling, chronic and severe mental illness characterized by disintegration with the process of thinking, contact with reality and emotional responsiveness (American Psychiatric Association, 2013). The syndrome of schizophrenia was first described in 1896 by the German physician Emil Kraepelin, as a global disruption in perceptual and cognitive functioning (Boyle, 2002). He named the disorder 'dementia praecox' (early dementia) to distinguish it from other types of dementia that typically occur on elderly people (Boyle, 2002). Eugen Bleuler continued Kraepelin's work and coined the term 'schizophrenia' in 1911. The analysis of the psychopathological features of the schizophrenia suggests that the symptoms can be clustered into four main categories (van Os and Kapur, 2009):

I. Psychosis (including delusions and hallucinations – commonly known as positive symptoms).

II. Alterations in drive and willingness (lack of motivation, reduction in spontaneous speech, social withdrawal – also known as negative symptoms).

III. Alterations in neurocognition (difficulties in memory, attention and executive functioning).

IV. Affective dysregulation (giving rise to depressive symptoms or to manic symptoms).

These symptoms are associated with a decrease in social and/or occupational functioning (American Psychiatric Association, 2013).

The onset of schizophrenia commonly occurs within late adolescence and early adulthood and may become a chronic condition. Epidemiological data indicate that schizophrenia prevalence rates depend upon a wide range of factors, such as the availability of a response to treatment (Bhugra, 2005). Individually, schizophrenia has a global lifetime prevalence of 0.3-0.7% of the population, whereas incidence are 10.2-22.0 per 100,000 persons/year (van Os and Kapur, 2009). In addition, schizophrenia accounts for an approximately 20% decrease in life expectancy compared with the average life of the healthy population (Laursen et al., 2014). There are no significant differences between males and females, nor between those of urban, rural and mixed sites (Bhugra, 2005).

Nevertheless, several studies have found a higher prevalence of schizophrenia in people with a low socioeconomic status, compared with a high socioeconomic status (Lewis and Lieberman, 2000).

The following subsections address the relationship among the aetiology, the diagnosis and the treatment of the schizophrenia (Figure. 1.1). Firstly, the aetiology looks for a better understanding of the causes of schizophrenia; it appears that schizophrenia usually results from a complex interaction between biological and environmental factors. Secondly, the identification of schizophrenia causes and symptoms is necessary to achieve a diagnosis. Finally, treatment subsection introduces pharmacologic treatments for schizophrenia.

1.3.1. Aetiology

The aetiologyical mechanisms of schizophrenia remain unclear. Schizophrenia appears to be a polygenic disorder, which is associated with biological and environmental factors (Lewis and Lieberman, 2000). Biological models include among their causes a genetic hypothesis and a neurotransmitter dysfunction. In addition, several authors pointed out that environmental factors may also play a role in the pathogenesis of schizophrenia via subtle alterations of neurodevelopment (Howes et al., 2004; Lewis and Lieberman, 2000). Efforts to identify the pathophysiology of schizophrenia currently focus on several lines of research: (*i*) neuroanatomical and neurofunctional abnormalities; (*ii*) genes that confer susceptibility to schizophrenia and epigenomics studies; (*iii*) celular and immunological alterations; (*iv*) environmental risk factors; (*v*) neuropsychological disorders; and (*vi*) the mechanism of action of drugs that relieve symptoms (Orellana and Slachevsky, 2013).

In the next subsections, these different schizophrenia factors are further developed. Figure. 1.2 shows the relationship among these schizophrenia causes, life course and their diagnosis.

1.3.1.1. Genetic hypothesis

Genetic studies have consistently demonstrated that hereditary factors play a very important role in major psychosis (Petronis, 2004). Specifically, family, twin and adoption studies have demonstrated that the morbid risk of schizophrenia correlates with the degree of shared genes (*i.e.* the closer family degree, the higher incidence of schizophrenia) (Jablensky, 2006; Lewis and Lieberman, 2000). In this regard, the heritability (*i.e.* genetic contribution to the phenotypic variance observed) is generally accepted to be in the range of 64-81% (Lichtenstein et al., 2009; Sullivan et al., 2003). In the last years, genome-wide association studies (GWAS) of schizophrenia further have examined the genetic profile associated to psychotic disorders. GWAS are an important tool for understanding the biological underpinnings of schizophrenia, they allow to associate several genes or loci with the schizophrenia. A recent and relevant GWAS study identified 108 loci that met genome-wide significance (Ripke et al., 2014). This study suggested that between half to a third of the genetic risk of schizophrenia is indexed by common alleles genotyped by the GWAS (Ripke et al., 2014).

In addition to genetic heritability, epigenetic misregulation provides a critical etiopathogenic factor (Petronis, 2004). Epigenetic alterations could partially explain the effects of environmental factors in schizophrenia. The DNA (deoxyribonucleic acid) sequence itself can be also modified through cytosine methylation or histones modifications. Functional states of histones and DNA have a direct effect on gene expression, as well as on other functions of a chromosome (*i.e.* recombination, segregation, mutagenesis) that determine functional and morphologic peculiarities of a cell (Petronis, 2004). Although the

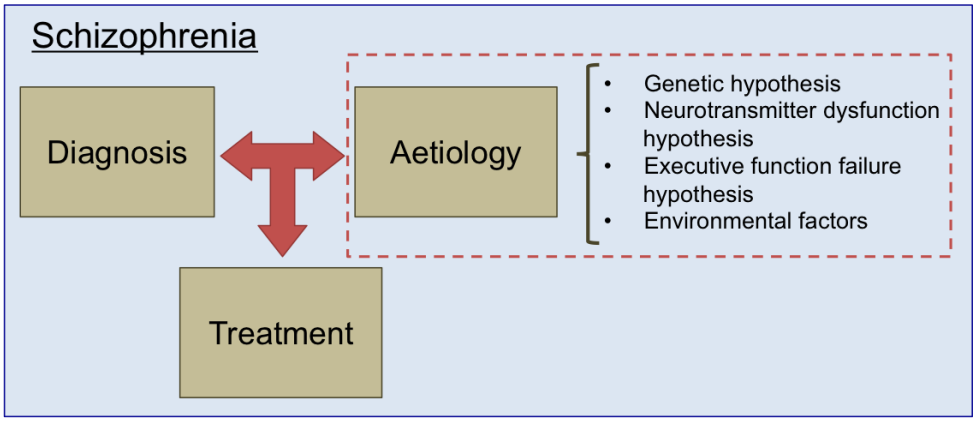

Figure 1.1: Relationship among diagnosis, aetiology and treatment of the schizophrenia.

real effect of epigenetic factors in schizophrenia is unknown, several studies have focused on the possibility of an epigenetic contribution to schizophrenia (Roth et al., 2009).

1.3.1.2. Neurotransmitter dysfunction hypotheses

This model focuses on chemical transmission, mainly in the prefrontal cortex, hippocampus and temporal lobes of the brain. Currently, there are three major neurochemical models for the schizophrenia: the dopaminergic, glutamatergic and GABAergic (Javitt and Sweet, 2015).

I. Dopamine has been widely regarded as an important neurotransmitter in schizophrenia (Stone et al., 2007). Salience attribution theory suggested that a dysregulation of dopaminergic neurons could underlie hallucinations and delusions in schizophrenia, through the aberrant attribution of abnormal salience to normal internal and external events (Heinz and Schlagenhauf, 2010; Kapur, 2003). The dopamine hypothesis of schizophrenia is the principal explanatory model of antipsychotic drug action. In order to reduce psychotic symptoms, antipsychotic drugs block dopamine receptors, specifically D2 receptors (Carlsson et al., 2004).

II. Glutamate receptors are also considered to play a role in cortico-cortical interactions and communication. Glutamatergic models relate schizophrenia symptoms to neurocognitive deficits by blocking neurotransmission at NMDA (N-methyl-D-aspartate) receptors (Javitt and Sweet, 2015; Stone et al., 2007). Increased prefrontal glutamate concentrations have been also associated with poorer global functioning and may show a disconnection in cortical communication in schizophrenia (Friston, 1998).

III. The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been proposed to play a role in schizophrenia. GABAergic dysfunction is specifically linked to impaired generation of high-frequency oscillatory activity (Javitt and Sweet, 2015). It has been proposed that GABA reductions may be linked to deficits in cognitive memory tasks found in schizophrenia (Lewis et al., 2005).

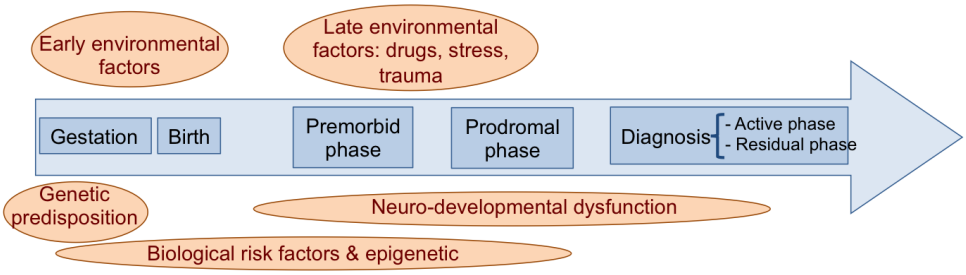

Figure 1.2: Schizophrenia is a complex syndrome with no clear etiology. This figure shows the relationship among schizophrenia causes, life course and diagnosis. It includes before birth causes, such as the genetic load and *in utero* biological and environmental risk factors. Four different phases has been identified in schizophrenia: (*i*) Premorbid phase is a period with a normal functioning; (*ii*) prodromal phase is characterized by signs and symptoms that precede full manifestation of schizophrenia; (*iii*) in the active phase, two or more symptoms must be present for at least one month period; and (*iv*) residual phase is a period of remission where symptoms are absent or no longer prominent.

1.3.1.3. Executive function failure hypothesis

The executive function is a set of abilities, which allows us to invoke voluntary control of our behavioural responses (Orellana and Slachevsky, 2013). These functions enable human beings to develop and carry out several functions, such as plans, make up analogies, obey social rules, solve problems, adapt to unexpected circumstances, do many tasks simultaneously or locate episodes in time and place (Orellana and Slachevsky, 2013).

Neuropsychological and neurocognitive paradigms implement experimental and clinical tests to better characterize cognitive abnormalities. They are increasingly being used to identify dysfunctional structures and brain systems that underlie cognitive and behavioral disorders of schizophrenia (Orellana and Slachevsky, 2013). It is possible to identify central cognitive deficits by studying how schizophrenia patients perform on neurocognitive tests. It may explain a significant proportion of the social and vocational morbidity of this disorder (Orellana and Slachevsky, 2013).

Impairment of executive function is one of the most commonly observed deficits in schizophrenia. Besides, the disorders detected by executive tests are consistent with evidences obtained from functional neuroimaging. They have shown a dorsolateral prefrontal cortex dysfunction in schizophrenia patients while performing several cognitive tasks (Orellana and Slachevsky, 2013). In particular, it has been suggested that executive function impairments are associated with negative schizophrenic symptoms (Freedman and Brown, 2011).

1.3.1.4. Environmental factors

The concordance rate among identical monozygotic twins for schizophrenia is high (∼50%), suggesting that this disorder has a strong genetic component (Javitt and Sweet, 2015). Nevertheless, it also suggests that environmental factors may also play a key role in the pathogenesis of schizophrenia (Lewis and Lieberman, 2000). Individuals with schizophrenia tend to inhabit lower socioeconomic strata and to be more numerous in urban and selected immigrant populations, suggesting an environmental effect on schizophrenia (Lewis and Lieberman, 2000). Several studies have shown that early environmental factors, such as prenatal infections and nutrition, traumatic stress during

gestation or childhood, obstetric complications or cannabis consumption are more common in people with schizophrenia than in the general population (Howes et al., 2004). Moreover, maturational processes occurring in the postnatal period through adolescence (*i.e.* apoptosis, synaptic pruning and myelination) may unmask the genetic vulnerability to schizophrenia (Lewis and Lieberman, 2000).

As a conclusion, diverse studies suggest that the aetiology of schizophrenia involves the interaction of many factors. It is probably caused by the interaction of predisposing genes and hazardous environmental factors (Petronis, 2004). Stress in adolescence or early adulthood, such as drug use or social isolation, may interact to cause neurodevelopmental impairments leading to schizophrenia (Broome et al., 2005). A basic knowledge of schizophrenia causes helps into the identification of its signs and symptoms in order to achieve a diagnosis.

1.3.2. Diagnosis

Schizophrenia essentially represents a broad clinical entity defined by subjective symptoms, behavioural signs and patterns of course (Jablensky, 2006). Currently, the diagnosis of schizophrenia is based on criteria from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013). These criteria take into account the self-reported experiences of the individual, and a clinical assessment by a mental health professional. For diagnosis, psychotic symptoms (*i.e.* delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior or negative symptoms) must have been significantly present for at least one month, with some indication of the disorder having been present for a six month period. A diagnosis of schizophrenia should not be made if the symptoms are not better accounted for a schizoaffective disorder, a mood disorder with psychotic features, or by the physiological effects of a substance or medical disorder (American Psychiatric Association, 2013).

The symptoms of schizophrenia span a wide range of psychopathology and can display an interindividual variability and temporal inconsistency (Jablensky, 2006). Therefore, different subtypes of schizophrenia could be delineated based on clinical features, statistically derived subtypes, putative genetic indicators and endophenotypes (Jablensky, 2006).

It is well established that there is a 'prodromal phase' (*i.e.* a period during which specific symptoms are present before a diagnosis has been made). During this phase, schizophrenia patients exhibit specific behavioral and cognitive characteristics that are considered precursors of an psychosis episode (Klosterkötter et al., 2001; Yung and McGorry, 1996). Early symptoms include reduced concentration and attention, depressed mood, brief psychotic symptoms and sleep disturbance (Yung and McGorry, 1996). Once diagnosed with schizophrenia, the long-term prognosis of the disorder is diverse. Schizophrenia patients could have a remission that is followed by relapse periods, remission with no further relapse, or have no remission at all (American Psychiatric Association, 2013).

1.3.3. Treatment

Schizophrenia is most commonly treated with antipsychotic medication and complementary psychotherapeutic approaches (Buckley, 2008). Most antipsychotic medication interacts with neurotransmitter receptors, some binds to dopamine receptors and some interacts with serotonin receptors (Buckley, 2008). These drugs reduce many of the positive symptoms, but they are less effective in the treatment of negative and cognitive

symptoms. Pharmacologic treatments for schizophrenia and bipolar disorder have been available since the 1950s. Early medications, also known as 'typical' antipsychotics (e.g. chlorpromazine and haloperidol), were based on dopamine antagonism (Edwards and Smith, 2009). Nevertheless, they introduced problems related to tolerability, including tardive dyskinesia and extrapyramidal motor side-effects (Patterson and Leeuwenkamp, 2008). 'Atypical' antipsychotics represented a significant improvement over first generation antipsychotics. These include drugs such as risperidone, olanzapine, clozapine and quetiapine (Patterson and Leeuwenkamp, 2008). They are at least as effective as typical antipsychotics, controlling acute psychotic symptoms and having lower propensity for inducing some types of adverse events, such as extrapyramidal symptoms or elevation of prolactin levels (Kapur and Remington, 2001; Patterson and Leeuwenkamp, 2008). Nevertheless, they tend to have metabolic side-effects, such as weigh gain and increasing triglycerides and choresterol (Kapur and Remington, 2001). Finally, it is well known that schizophrenia patients respond in different ways to antipsychotic medications. Hence, medical and patients usually work together to find the most adequate medication, as well as the right dose. With medication and psychosocial therapy, many schizophrenia patients are able to control their symptoms, gain greater independence and lead fulfilling lives (Buckley, 2008).

1.3.4. Neurobiology and phenomenology in schizophrenia

Kapur (2003) proposed a heuristic framework for linking the neurobiology (brain), the phenomenological experience (mind) and the pharmacological aspects of schizophrenia. Aberrant salience hypothesis relates schizophrenia to an aberrant assignment of salience to external objects and internal representations (Kapur, 2003). During the performance of a cognitive task, schizophrenia patients tend to pay more attention to non-salient events and less to salient events. It shows the central role of dopamine to mediate the salience of environmental events and internal representations, suggesting a dopamine hypothesis of antipsychotic action (Kapur, 2003).

In addittion, schizophrenia has been identified as a dysconnection syndrome, which is associated with a reduced capacity to integrate information among different brain regions (Friston, 1998; Stephan et al., 2009). Friston et al. (2016) have revisited the definition of dysconnection hyphothesis, trying to establish a link between the symptoms and signs of schizophrenia and the underlying neuronal pathophysiology. Both theories are related, an aberrant neuromodulation of synaptic activity mediates the influence of intrinsic and extrinsic connectivity (Friston et al., 2016). Relevance attribution likely involves diverse cerebral regions and their interconnections. As a consequence, many efforts have been devoted to identifying abnormalities in the cortical connections and their relation to schizophenia symptoms and cognitive performance (Uhlhaas and Singer, 2010).

In summary, we hypothesized that schizophrenia patients would show a failure to contextualize stimulus processing through a failure to optimize the synchronous gain of neuronal populations, leading to a functional disintegration or disconnection (Bachiller et al., 2015b). The physiological correlates of this disconnection would be expressed in terms of a failure to modulate synchronous activity; particularly when asked to attend to target stimuli (Friston et al., 2016).

Most studies used structural magnetic resonance imaging (MRI), functional MRI or diffusion tensor imaging (DTI) to study schizophrenia brain organization (Gur and Gur, 2010; Kubicki et al., 2007; Molina et al., 2010; Shenton et al., 2001). However, EEG provides high temporal resolution and allows for the assessment of the spatio-temporal patterns of neural activity and their interactions in the time range of milliseconds (Meehan and Bressler, 2012; Uhlhaas, 2013).

1.4. Electroencephalogram

The human brain is a very complex structure formed by millions of interconnected neurons that communicate via electric impulses. Many neurons firing in sequence are able to generate an electric field strong enough to be measurable by scalp electrodes, producing the EEG signal (Nunez and Srinivasan, 1981). Therefore, EEG is the measurement of time-varying voltages on the human scalp generated by the electrical activity of the brain, especially in the cerebral cortex (Nunez and Srinivasan, 1981). Brain electrical activity was firstly measured by the German neurologist Hans Berger in the 1920's. He observed rhythmic fluctuations of around 10 cycles per second (*i.e.* 10 Hz). Since then, EEG has been enhanced as a clinical tool; allowing its use in the study of brain pathologies (such as Alzheimer disease, epilepsy or schizophrenia), sleep disorders and disorders of the nervous system (Jeong, 2004; Merica et al., 1998; Roach and Mathalon, 2008; Salinsky et al., 1987).

The recorded EEG is the summation of the electrical activity primarily from groups of pyramidal neurons, which provides a sample of temporal brain activity (Olejniczak, 2006). EEG measures electric potential differences between pairs of scalp electrodes placed generally in an elastic cap with uniform coverage of the entire scalp. Recording protocols usually follow the International 10-20 system (Figure. 1.3). It is the accepted instrumentation standard for scalp electrode placement (Jasper, 1958).

EEG is a good tool for studying neurocognitive processes, since it provides a high temporal resolution, within the millisecond range. It allows to capture cognitive dynamics in the time frame in which cognition occurs (Cohen, 2014). However, the electrical activity generated by the cortex is partially distorted as it passes through the cortex, meninges and skull; hence, EEG data have small amplitudes and are spatially poorly localized (Wang, 2010). Better measurements could be obtained invasively using subdural electrocorticogram (ECoG), with the electrodes directly placed on the cortical surface, or mesoscopic local field potential (LFP), where electrodes are inserted deep into the brain (Wang, 2010). EEG signal provides multidimensional information useful to characterize neural processes (*i.e.* it comprises information in at least five dimensions: time, space, frequency, magnitude and phase) (Cohen, 2014). In comparison to brain-imaging tools, such as MRI, EEG allows to assess directly neurocognitive processes (Cohen, 2014). The oscillations that can be observed in the EEG signal reflect neural oscillations in the cortex. On the other hand, brain-imaging techniques do not directly measure neural events, but they are well suited for studies in which precise spatial localization are important (Cohen, 2014).

The next subsections further characterize the EEG signal. Firstly, section 1.4.1 addresses the neurophysiology (*i.e.* the study of the functioning of the nervous system). Secondly, the main mechanism for enabling coordinated activity during normal brain functioning was assessed: the neural oscillations. Then, cognitive electrophysiology section examines how neural oscillations are related to cognition and behavior. Finally, section 1.4.4 depicts event-related potentials (ERP), distinguishing between two main approaches: (*i*) evoked potentials and (*ii*) single-trial analysis.

1.4.1. Neurophysiology

Neurons are electrically excitable cells that process and transmit information through electrical and chemical signals, by means of a synapse. A typical neuron consists of a cell body (known as the soma) that contains the nucleus, dendrites (short extensions of the cell body involved in the reception of stimuli) and a single elongated extension of the cell, called axon. Across the neuron membrane there exists a resting potential of

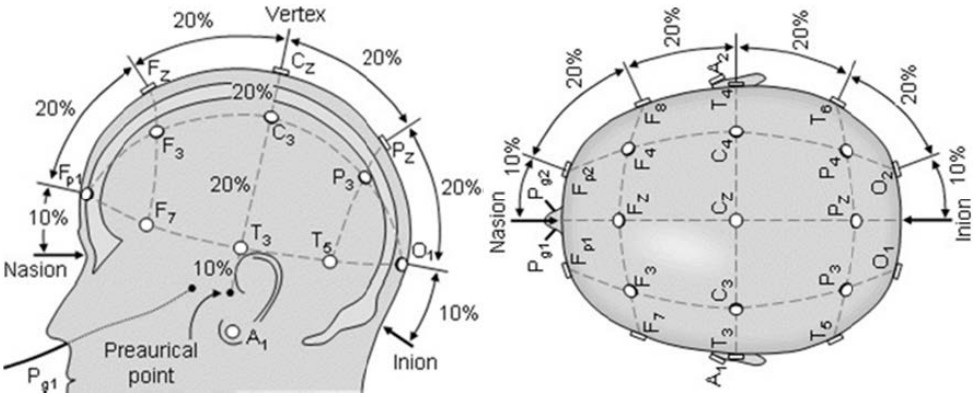

Figure 1.3: International 10-20 EEG electrode location system for EEG recording. Picture adapted from Jasper (1958).

approximately -70 mV (Kandel et al., 1991).

Communication among neurons is elicited by electrochemical processes underlying the generation of 'action potentials', which consist on a rapid swing of the polarity across the neuron membrane. A synapse is a region where nerve impulses are transmitted and recieved. It can be observed in the junction between the axon terminals of a pre-synaptic neuron and a dendrite of a post-synaptic neuron. When an action potential reaches a synapse, it triggers the release of neurotransmitters that bind to the receptors of a post-synaptic neuron (Figure 1.4). Neurotransmitters can change the permeability of the membrane by means of a flow of sodium (Na+) and potassium (K+) ions. Post-synaptic potentials can be excitatory or inhibitory (Kandel et al., 1991):

- If the neurotransmitter is excitatory (e.g. amino acid glutamate), positive ions flow from the post-synaptic neuron to the environment. It causes a reduction of the membrane potential (depolarization).
- If the neurotransmitter is inhibitory (e.g. GABA), positive ions flow from the environment to the post-synaptic neuron. It causes an increase of the membrane potential (hyperpolarization).

These action potentials are the primary origins for the EEG recorded on the scalp. EEG reflects the degree of simultaneous activation of millions of local neurons in the cortex. In detail, it is the summation of synchronized synaptic activation from pyramidal neurons that have long straight dendrites perpendicular to the surface of the cortex (Olejniczak, 2006; Wang, 2010). Therefore, larger amplitudes in the EEG indicate a synchronous rhythmic activity in a local brain area (Lopes da Silva, 2013).

1.4.2. Neural oscillations

EEG signal can be divided into rhythmic and transient activity. Transient activity includes random oscillations and high frequency noise. On the other hand, rhythmic one represents synchronized neural activity over a brain region. These oscillations have characteristic frequency ranges, spatial distributions and have been associated with different states of brain functioning (Cohen, 2014). EEG oscillations can be further subdivided into five different rhythms according to the frequency band of the signal (Cohen, 2014).

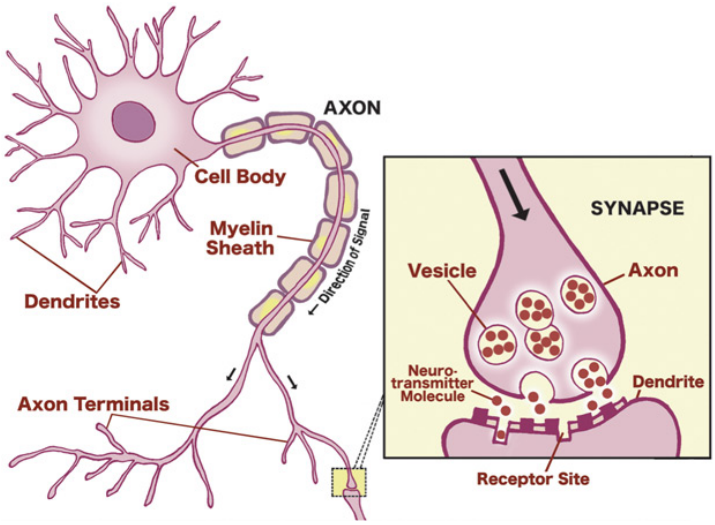

Figure 1.4: Neurotransmission from pre-synaptic and post-synaptic neurons and neuron synapsis. Figure obtained from (Carter et al., 2009).

- Delta band (δ, 1-4 Hz): High-amplitude waves typically found in deep slow wave sleep. Delta activity is mainly observed in the frontal regions in adults.
- Theta band (θ, 4-8 Hz): It is associated with drowsiness and is enhanced during sleep. Theta rhythms are found in the frontal midline region and they have been associated with inhibition of elicited responses.
- Alpha band (α, 8-13 Hz): It is the predominant rhythm in awaked subjects in a relaxed or reflected state, especially under eyes closed conditions. They are most pronounced in the posterior and occipital regions. Alpha rhythms have been related to inhibition control. They reflect the timing inhibitory activity in different locations across the brain.
- Beta band (β, 13-30 Hz): It shows reduced amplitudes as compared to alpha waves. Beta rhythms are associated with states of active concentration, anxiety or tension. They are exhibited symmetrically at both sides of the brain, they are most pronounced in the frontal regions. Beta band is commonly divided into β_1 and β_2 sub-bands, that include the frequency ranges 13-19 Hz and 19-30 Hz, respectively.
- Gamma band (γ, $>$ 30 Hz): It is associated with an active processing of information in the cortex. Gamma rhythms are most pronounced near the somatosensory cortex during multi-modal sensory processing, involving the linking of multiple sensations or memories.

The study of brain oscillations has brought special attention to brain research community for a long time. Nevertheless, it has recently gained popularity the study of how these oscillations relate to cognition and behavior (Lopes da Silva, 2013). The field in neuroscience that investigates the relationship between brain rhythms and cognition is called cognitive electrophysiology (Cohen, 2014).

1.4.3. Cognitive electrophysiology

Scientists have expressed skepticism about the usefulness of brain oscillations and EEG rhythmic activities in advancing the understanding of brain processes underlying cognitive functions (Lopes da Silva, 2013; Sejnowski and Paulsen, 2006). However, experimental evidences support the statement that scalp electrical signals reflect well-defined neurophysiological mechanisms that are relevant to understand how cognitive processes emerge (Lopes da Silva, 2013). Cognitive electrophysiology is a field that investigates the relationship between the brain rhythms and cognition (*i.e.* it links neuroscience and psychology). It focuses on understanding how cognitive functions (perception, memory, language, emotions, behavior control or social cognition) are supported or implemented by the electrical activity produced by populations of neurons (Cohen and Gulbinaite, 2014). Cognitive electrophysiology is a broad field of research that includes a wide range of objectives. From the point of view of cognitive processes, the electrophysiology is a useful tool for transient dissociating cognitive processes and their subcomponents. In this regard, the main objective is to understand the cognitive components of behavior rather than the physiological properties of the brain (Cohen, 2014). On the contrary, cognitive paradigms can be used as a useful tool to elicit specific patterns of neural activity. In this case, the ultimate goal of the research is to understand how the brain works rather than to dissect components of behaviour (Cohen, 2014). Both issues should be jointly addressed in order to avoid misunderstandings.

The mathematical development of time-frequency based data analyses has contributed to advance beyond the understanding of the neurophysiological events. Nevertheless, a better understanding of the neurophysiological processes that underlie the time-frequency features observed in scalp neural data would require complementary methodological approaches, such as simultaneous invasive and non-invasive recordings or MRI analysis (Cohen and Gulbinaite, 2014). Future complementary studies will allow linking the activity at the level of individual neurons and populations of neurons recorded at scalp EEG.

In this Doctoral Thesis, event-related potentials (ERP) analyses are used to gain further insights into the neural mechanisms underlying cognitive dysfunctions (Uhlhaas et al., 2008). ERP coupling patterns based on time-frequency representations could provide a more sensitive measure to describe schizophrenia alterations than resting-state EEG analysis (Uhlhaas, 2013; Uhlhaas and Singer, 2006).

1.4.4. Event-related potentials

Event-related potentials (ERPs) provide a safe and non-invasive method for exploring the psychophysiological correlates of mental processes. ERPs are very small voltages recorded from the scalp, which are originated in the brain structures as a response to specific sensory, cognitive or motor events. They appear as a series of peaks and troughs interspersed in EEG waves (Huang et al., 2015). Experimentally, their basic function is to observe the transient changes in neural activity of the cortex, as a function of sensory stimulation or internal event processing. Thus, ERPs are considered to be indicative of the role of different cortical areas to various sensory or behavioural functions (Niedermeyer and Lopes da Silva, 2005).

An ERP signal is composed of background, phase-locked and non-phase-locked activity. Background activity is unrelated to task events. It provides little useful information in cognitive electrophysiology studies and can be discarded by applying inter-trial time-averaging and baseline normalization procedures (Cohen, 2014). Nevertheless, phase-locked and non-phase-locked are task-related activities (*i.e.* their time-frequency char-

acteristics change as a function of engagement in task events). In detail, phase-locked activity (also called 'evoked') is phase aligned with the event onset. It can be observed both in time-domain averaging and in time-frequency-domain averaging representations. On the other hand, non-phase-locked activity (also known as 'induced') is time-locked but not phase-locked to the event onset. Therefore, it is observed in time-frequency-domain averaging but not in time-domain averaging (Cohen, 2014; Roach and Mathalon, 2008).

A large debate has been developed to investigate the neurophysiological mechanisms that produce ERPs. David et al. (2006) suggested that ERPs are formed through complex additive and nonlinear effects. Other models proposed that ERPs are the result from an alignment of the phases of ongoing oscillations (Makeig et al., 2002), or that ERPs are an amplitude asymmetry in the EEG oscillations (Mazaheri and Jensen, 2008). One issue that complicates matters is that different ERP components may have different neural origins; hence, it is not possible to achieve a unique explanation that includes the underlying mechanisms involved in the generation of all ERP components (Cohen, 2014). Figure 1.5 shows how traditional analyses of ERP data are divided into two different approaches: (*i*) time-domain analysis where evoked ERP is obtained, and (*ii*) time-frequency-domain analysis, which is performed over single-trial ERP data.

1.4.4.1. Time-averaging auditory evoked potentials

The time-domain approach obtains an evoked ERP wave as the average of a set of data epochs or trials time-locked to repetitive external events. As a result of averaging across a large number of trials, the background and non-phase-locked activity in the EEG cancels out and, thus, evoked ERPs are positive or negative voltage deflections that survive this averaging process (Roach and Mathalon, 2008). The traditional view of ERP assumes that averaged ERPs reflect transient bursts of neuronal activity time-locked to an external event (Makeig et al., 2004). Nevertheless, it could arise from one or more neural generators. The neural generators of ERP components remain imprecisely delineated, although appreciable progress has been carried out in the last years (Huang et al., 2015).

There are several cognitive tasks for evaluating brain responses, including auditory paradigms. In this regard, auditory oddball paradigm is a common experimental design used in ERP analyses to obtain a meaningful measure of cognitive function. Different components have been established on time-averaging auditory evoked ERPs, such as P50, N100, N200 and P300 components (Figure 1.6). The most extensively explored evoked ERP component in investigations of cognitive functions is the P300 wave (Huang et al., 2015). It is described as a positive deflection, which reaches its peak amplitude around 300 ms after stimulus onset. The P300 component mainly appears over superior temporal and parietal cortex and it has been associated with several processes, such as attention, relevance and memory (Polich, 2007). P300 wave includes two components: the P3a, elicited by distractor stimuli for which no subject-response is expected; and the P3b, evoked by target stimuli for which the subject is instructed to respond. Both P300 waves were traditionally assessed by means of their amplitude (the maximum evoked ERP voltage) and latency (the delay between stimulus onset and the time course of P300) (Polich, 2007).

Several studies have identified schizophrenia alterations in ERP waves. Reductions in the auditory P300 amplitude, as well as increases in the auditory P300 latency have been found in people with schizophrenia compared to healthy controls (Jeon and Polich, 2003; Mathalon et al., 2000; O'Donnell et al., 2004). Likewise, source localization of P300 wave has recently achieved a relevant importance (Jung et al., 2012; Kim et al., 2014;

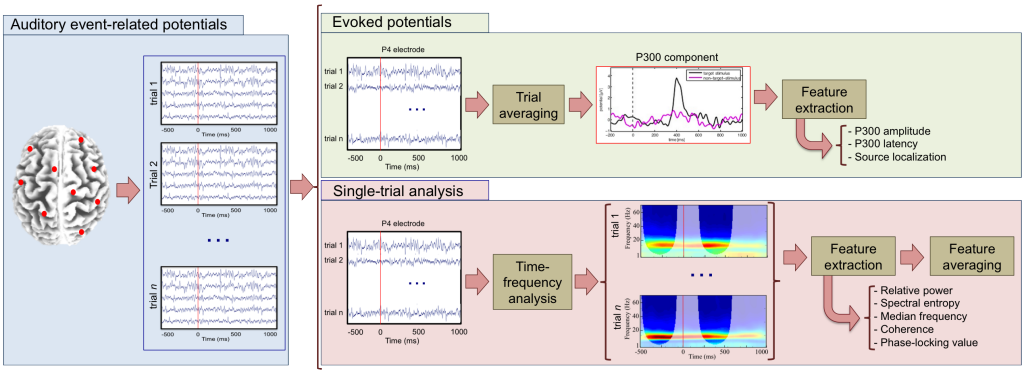

Figure 1.5: Auditory ERP data analyses are divided into two different approaches: (*i*) evoked ERPs perform the time-domain averaging of ERP trials time-locked to a repetitive external event; and (*ii*) single-trial analyses assess time-frequency properties of each ERP trial.

Strobel et al., 2008; Sumiyoshi et al., 2009; Volpe et al., 2007). In detail, the neural generators of two P300 components: the P3a, evoked by distractor stimuli for which no subject-response is expected; and the P3b, elicited by target stimuli for which the subject is instructed to respond were evaluated in this Doctoral Thesis (Bachiller et al., 2015c).

1.4.4.2. Single-trial analysis

The examination of time-averaging evoked ERPs has provided useful insights into the nature and timing of neuronal events that subserve sensory, perceptual and cognitive processes. Nevertheless, the whole ERP data have received relatively less attention (Roach and Mathalon, 2008). Time-frequency domain approach assesses the changes in the frequency power spectrum of the whole ERP data time-locked to the same external events (Makeig et al., 2004). Time-frequency analyses provide additional information about neural synchrony not apparent in the evoked ERPs (Makeig et al., 2004). In detail, they allow to view the brain as a parallel processor of information, with oscillations at multiple frequencies reflecting various neural processes co-occurring and interacting (Lisman and Buzsaki, 2008). Therefore, they may provide a greater sensitivity to the true nature of the neuropathophysiological processes underlying schizophrenia (Roach and Mathalon, 2008).

Studying single trial ERP oscillations allows decomposing time-varying neural oscillations into magnitude and phase information for each frequency component (Makeig et al., 2004). Neural oscillations are one of the largest contributing mechanism for enabling coordinated activity during normal brain functioning. Several studies have associated oscillations at low frequency ranges (delta, theta and alpha) with long-range synchronization (Sauseng et al., 2004; Uhlhaas and Singer, 2010; von Stein and Sarnthein, 2000), whereas high frequency ranges (beta and gamma) reflect synchronization in both local cortical networks (Womelsdorf et al., 2007) and large-scale networks (Roux et al., 2013). Impairments in these oscillations may contribute to pervasive network dysfunction in schizophrenia (Uhlhaas and Singer, 2010), which may lead to functional disconnections between and within cortical regions (Friston, 1998).

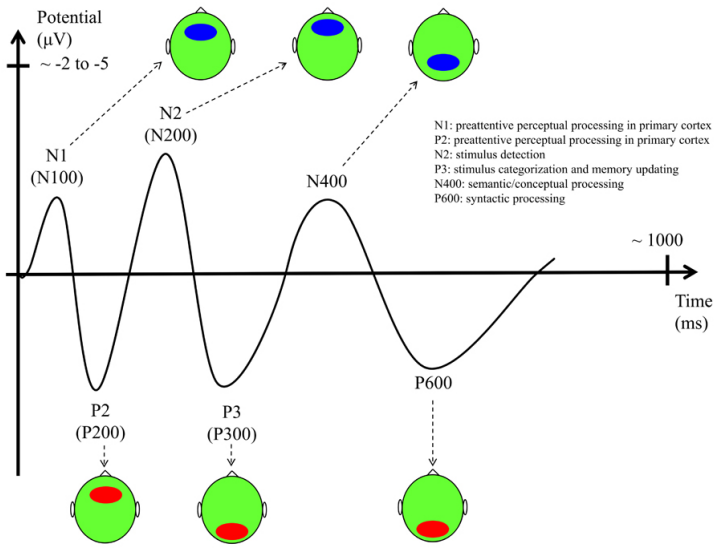

Figure 1.6: Main ERP components with their functional interpretation, latencies, and scalp topography (ellipses indicate the scalp location where the component has the largest amplitude. Red: positive potential. Blue: negative potential). Figure obtained from (Daltrozzo and Conway, 2014).

1.5. Hierarchical analysis of neural signals

In the last decades, brain functions have been brought into focus in neuroscience. They can be studied from different viewpoints depending on the way in which interactions are taken into account (Stam and van Straaten, 2012). A long-standing controversy in neuroscience was set on the 20th century. On the one hand, localizationist views of brain functions held that complex cognitive functions are linked to specific brain regions, emphasizing the specificity and modularity of brain organization. On the other hand, holist views proposed global neural functions in the whole brain (Tononi et al., 1994). The modern understanding of neurocognitive networks gradually emerged over these opposing views in neuropsychology (Bressler and Menon, 2010). Based on this principle, functional segregation and integration were defined:

- Functional segregation aims to identify the brain areas that are dedicated to specific information processing tasks. In particular, functional segregation suggests that a cortical area is specialized for some aspects of perceptual or motor processing and that this specialization is anatomically segregated within the cortex (Friston, 2011).

- Functional integration evaluates the dependencies among different brain areas. It provides an important tool for understanding brain networks as a highly interconnected organization (He et al., 2011). Neural integration could be characterized by functional connectivity, which is usually defined in terms of statistical dependencies among measurements of neuronal activity, such as EEG recordings.

On the basis of these principles, functional segregation could be formed by local network communities that are intrinsically densely connected and strongly coupled. Whereas, functional integration measures global communication between distant brain areas (Sporns, 2013). It is noteworthy that a balance between segregation and integration

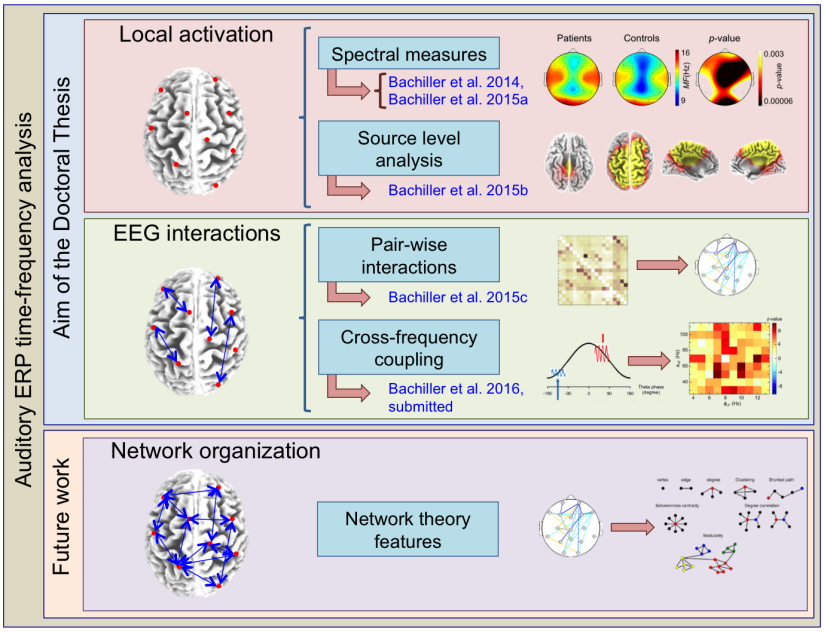

Figure 1.7: Hierarchical analysis of EEG data. A two-level of analysis has been applied in this Doctoral Thesis, which characterizes: (*i*) functional segregation by means of local activation; and (*ii*) functional integration analyzing EEG interactions. A third level, which assesses the relationship between segregation and integration brain functions by means of complex network analysis, will be addressed in future studies.

is essential for the operation of distributed brain networks underlying cognitive function (Sporns, 2013). The clustered local network communities support functional segregation and specialization, likewise it ensure efficient communication and information integration among brain areas (Sporns, 2013).

In this Doctoral Thesis, the dynamic brain activity has been explored from the perspective of a complex organized network. EEG data were examined using a two-level analysis (Figure 1.7): (*i*) local activation, that comprises the characterization of ERP data by means of their spectral properties and the performance of neural generators at source level; and (*ii*) EEG interactions, that include functional interactions between pairs of electrodes and the analysis of high-level relationship between brain rhythms by means of cross-frequency coupling. A third level, that uses of complex network theory for characterizing EEG brain networks, will be addressed in future studies.

Before addressing local activation and EEG interaction description, it is noteworthy to introduce the time-frequency tools used in this Doctoral Thesis.

1.5.1. Time-frequency analysis of EEG oscillations in humans

A typical approach for characterizing electromagnetic brain recordings is based on the analysis of their spectral content. These analyses are all based on the core assumption made by Fourier: any signal can be represented by a sum of sine waves of different frequencies (Blanco et al., 1995). In order to describe the power of the signal for each different frequency, the power spectral density (PSD) function can be estimated. PSD represents how the power is distributed in the frequency domain.

There are two main points that motivate the use of time-frequency techniques. Firstly,

Fourier transform is based in comparing the signal with complex sinusoids that extend through the whole time domain, providing a lack of information about the time evolution of the spectral content (Blanco et al., 1995). Secondly, EEG recordings are non-stationary signals, whose characteristics may change over time (Blanco et al., 1995). Therefore, non-stationary signal analysis techniques, such as time-frequency distributions, are appropriate to accurately describe their dynamic properties (Aviyente et al., 2004; Poza et al., 2008).

Time-frequency analysis comprises many methods and measures that capture different aspects of EEG magnitude and phase relationships (Roach and Mathalon, 2008). In particular, from time-frequency analysis, two types of information can be extracted for each particular frequency band and time position: the power (*i.e.* the strength with which an oscillation was presented); and the phase (*i.e.* the position along the sine wave). These two properties of the time-frequency representation allow implementing various dynamical measures at the three aforementioned levels of analysis: local activation, pairwise interactions and network organization.

In this Doctoral Thesis, three different time-frequency approaches have been used depending on the application: short-time Fourier transform (STFT), wavelet transform and Hilbert transform. The mathematical details of the different analyses will not be presented here, as they are outlined in every 'Materials and Methods' section in the different Chapters.

1.5.2. Local activation

As a first step, the function of elementary units of EEG data was independently examined (*i.e.* the signal at each electrode was independently analyzed). The majority of neuroscience studies in the past few decades was related to a better understanding of the conditions underlying local activation of functional brain units (Stam and van Straaten, 2012).

As previously established, EEG is the sum of the electrical activity over a broad brain area. Therefore, the analysis of local activation from EEG recordings contributes to functional localization. In addition, the use of complementary techniques, such as fMRI, DTI or LFP will help characterization of the cognitive functions associated with a brain area (Cohen, 2014).

1.5.2.1. Spectral analysis of local activation

According to the aberrant salience hypothesis, schizophrenia patients show a heightened response to novel but irrelevant stimuli and a decreased response to relevant stimuli (Cortinas et al., 2008; Gur et al., 2007). Therefore, the analysis of spectral changes from baseline to the processing stages of a cognitive task may help to better understand the dynamic information processing abnormalities observed in schizophrenia (Uhlhaas et al., 2010).

In this Doctoral Thesis, several local activation measures based on the information theory were assessed to analyze the cognitive response to a three-tone auditory oddball task. Firstly, the whole frequency spectrum was divided into the conventional frequency bands (δ, θ, α, β_1, β_2 and γ) and the relative power (RP) was computed (*i.e.* the proportion of total spectral power attributable to a given frequency band). Likewise, two additional parameters were obtained from PSD function: the spectral entropy (SE) and the median frequency (MF). SE allows quantifying the degree of disorder contained in a signal, whereas MF is defined as the frequency value that comprises 50% of the power,

offering a simple way of summarizing the whole spectral content of PSD (Poza et al., 2012). Chapters 3 and 4 include a better description of RP, SE and MF computation.

1.5.2.2. Neural source generators

The electrical brain activity is generated in 3-D, but EEG captures a 2-D image from the surface of the skull. Therefore, it cannot be assumed that the electrical activity recorded by each electrode has been generated directly below that electrode. The computation of intracerebral images of electric neuronal activity based on scalp-recorded EEG is known as the 'inverse problem'. It provides useful information on the time course and localization of brain functions (Pascual-Marqui et al., 2002). Selection of a particular solution of the inverse problem often requires a priori knowledge acquired from the overall physiology of the brain. Source imaging techniques have been commonly used to detect neural generators that contribute to ERPs as a response to a cognitive task. Since P300 is associated with attention and memory operations in the brain, investigation of the neural generators of this ERP component can improve our understanding of these mechanisms (Sabeti et al., 2016).

The low-resolution brain electromagnetic tomography (LORETA) is one of the most reliable methods for localizing ERP electrical activity (Pascual-Marqui et al., 2002). In particular, LORETA asseses source current density from scalp-recorded EEG using a realistic head model from Montreal Neurological Institute (MNI) (Mazziotta et al., 2001), in which the 3-D solution space was restricted to only the cortical grey matter (Lancaster et al., 2000). Chapter 5 assesses bioelectrical ERP neural sources distribution by using standardized LORETA (sLORETA) approach. Compared to previous versions of LORETA, sLORETA is superior in temporal resolution and has fewer localization errors (Kim et al., 2014). Thus, sLORETA approach has been used in several studies to investigate brain sources when subjects are performing a cognitive task (Kim et al., 2013; Sumiyoshi et al., 2009).

EEG local activation yield information of interest in neurocognitive studies, but an essential aspect is to investigate how these signals interact (Lopes da Silva, 2013).

1.5.3. EEG interactions

In the last decade, neuroscience has experimented a paradigm shift, giving more importance to interactions and networks in contrast to other approaches focused primarily on the localization of cognitive functions to specific brain areas through the study of local brain activity (Stam and Reijneveld, 2007). EEG rhytms yield information of interest in neurocognitive studies, but an essential aspect is to investigate how these signals interact (Lopes da Silva, 2013). Brain oscillations have typically been divided into specific frequency ranges that are associated with different cognitive processes (Buzsáki and Draguhn, 2004). However, brain rhythms in different frequency bands can interact with each other in several ways involving either the phase, amplitude or the frequency of the signals (Canolty and Knight, 2010; Jirsa and Müller, 2013; Szczepanski et al., 2014).

This section addresses two out of the main EEG interactions. Firstly, neural connectivity patterns play a crucial role in determining the functional properties of neurons and neuronal systems (Sporns, 2007). Pair-wise interactions assess the interdependences between the neurophysiological signals measured at different electrodes. Secondly, several studies have demonstrated that cognitive processes involve the coordination of oscillations at different frequencies (Engel et al., 2001; Szczepanski et al., 2014; Wang et al., 2014). Cross-frequency coupling (CFC) is an emerging area of neural research, which is based on the idea that neural oscillations have a complex and hierarchical organization.

1.5.3.1. Pair-wise interactions

Coordinated neuronal activity and interactions among neurons and neuronal populations are basic features of brain function (Jiruska et al., 2013). Cognitive processes require precise integration of neural activity at specific spatio-temporal scales (Uhlhaas and Singer, 2006; Varela et al., 2001). Currently, cortical interactions could be classified into: anatomic, functional and effective connectivity (He et al., 2011). In detail:

- Anatomic connectivity refers to the physical neural connections among various regions of interest. These connections can either be on the microscopic or macroscopic level.
- Functional connectivity is defined as the temporal correlation between spatially remote neurophysiological events.
- Effective connectivity is defined as the directed or causal inference of one system over another. It describes the direction of the functional interactions between brain regions.

This Doctoral Thesis is focused on the study of functional connectivity among neural oscillations at the different frequency bands. Our focus on functional connectivity is motivated by the notion that disconnectivity in schizophrenia is accompanied by a failure to modulate synchronous activity (Bachiller et al., 2015b). From EEG recordings, functional neural connectivity has been commonly assessed by looking at the relationship between EEG data at two different electrodes (Varela et al., 2001). Functional connectivity approach allows to obtain a time-frequency feature characterization. Firstly, it is highly time-dependent; statistical patterns among EEG data fluctuate on multiple time scales. Secondly, functional connectivity can be assessed in the frequency domain, obtaining different connectivity patterns for each frequency band.

As we will see in Chapter 6, three complementary functional connectivity measures have been used: coherence, phase-locking value (PLV) and Euclidean distance (ED). They are based on three different conceptual frameworks: connectivity, synchrony and similarity. It provides original insights to describe dynamical neural interactions induced by attended stimuli in control subjects and schizophrenia patients.

1.5.3.2. Cross-frequency coupling

CFC is an emerging area of neural research based on the idea that neural oscillations have a complex and hierarchical organization. CFC reflects how neurophysiological processes in the brain can be temporally organized across different frequency bands (van Driel et al., 2015). Several studies demonstrated that the rhythms in different frequency bands can interact with each other in behaviorally meaningful ways (Canolty and Knight, 2010; Szczepanski et al., 2014). In particular, phase-amplitude CFC (PAC) describes the statistical dependence between the phase of a low-frequency (LF) brain rhythm and the amplitude of a high-frequency (HF) component of brain activity (Canolty and Knight, 2010). Thereby, it reflects the dynamical relationship between two oscillations that are generated by distinct neurophysiological mechanisms (Dvorak and Fenton, 2014). PAC is based on the idea that the distribution of HF power values is modulated by the LF phase (Dvorak and Fenton, 2014). It has been suggest that PAC provides a bridge between local microscale and systems-level macroscale neuronal ensembles, allowing for dynamic network communication (Voytek and Knight, 2015a).

Conventional PAC (cPAC) algorithms yield an averaged PAC value across a defined time window that is bounded by the frequency of the coupling phase (Canolty et al., 2006;

Cohen, 2008; Voytek et al., 2010). Several researches pointed out an important limitation of cPAC algorithms: it is a metric sensitive to noise and to the time window selected (Tort et al., 2010). The previous limitation does not allow analyzing time-varying CFC changes when subjects are performing a cognitive task (Voytek et al., 2013). In order to solve this problem, a recent research proposed a novel approach for measuring transient PAC directly in an event-related way: event-related PAC (ERPAC) (Voytek et al., 2013). It provides a method for assessing sub-second coupling dynamics supporting cortical processing (Voytek et al., 2013). Nonetheless, the use of ERPAC could introduce a spurious PAC due to unspecific non-stationarities not related to neural processes (Aru et al., 2015). Therefore, the design of a suitable surrogate procedure is required to prevent non-stationarity and non-linearity misunderstandings, as well as to assess statistical significance (Aru et al., 2015).

On the basis of these ideas, Chapter 7 of this Doctoral Thesis is focused on two main objectives: (*i*) obtaining a time-varying measure of PAC; and (*ii*) studying the role of PAC abnormalities in schizophrenia.

1.5.4. Network organization

Brain networks have been recently explored in neuroscience. It allows to use a wide array of quantitative tools and methods from complex network theory (Sporns, 2013). Networks are simple mathematical objects that efficiently encode the structure of relations among a large number of interdependent elements. In particular, brain network theory introduces the application of complex network theory in the study of neural dynamics. The brain can be assimilated to a complex anatomical and functional network (Varela et al., 2001). Hence, it can be represented by means of a graph, where the electrodes correspond to the nodes of a graph and the vertices are formed by the functional coupling between them (Stam and Reijneveld, 2007).

Complex network theory has been used to characterize the healthy brain, which has been identified as a highly interconnected structural network that functionally connects adjacent and distant brain areas (Rubinov and Sporns, 2010). In addition, network neuroscience has recently provided novel insights into the mechanisms of neurological diseases, such as epilepsy, Alzheimer's disease, autism or schizophrenia (Stam and van Straaten, 2012). Therefore, the analysis of EEG complex network patterns will be addressed in future studies.

1.6. Doctoral Thesis overview

The characterization of neural dynamics underlying cognitive processing in schizophrenia is the common thread shared by all the articles included in the compendium of publications. Two out of the five papers aimed at studying the local activation of EEG data during an auditory oddball task by means of relative power, spectral entropy and median frequency (Bachiller et al., 2014, 2015a), whereas another paper focused on analyzing the neural source generators underlying cognitive processing in schizophrenia (Bachiller et al., 2015c). A fourth paper involved the characterization of the time-varying functional coupling differences between healthy controls and schizophrenia patients (Bachiller et al., 2015b). Finally, a fifth paper focused on the analysis of the hierarchical organization of neural oscillations (Bachiller et al., 2017).

This Doctoral Thesis is organized by chapters as follows:

- **Chapter 2: Hypothesis and objectives** establishes the hypothesis and objective statement of this Doctoral Thesis.

- **Chapter 3: Decreased spectral entropy modulation in patients with schizophrenia during a P300 task.**

  This Chapter summarizes the first paper included in the compendium of publications. It describes the application of RP, MF and SE for quantifying the EEG signal as a response to an 3-stimulus auditory oddball task. Hence, the global changes from resting baseline [-250 0] ms to active task [150 550] ms windows were calculated for 31 patients with schizophrenia and 38 healthy controls. An statistical analysis was carried out to assess the spectral changes from baseline to active response window within each group and the spectral differences between patients and controls groups.

- **Chapter 4: Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task.**

  The analysis of the interaction between novelty and relevance may be of interest to test the aberrant salience hypothesis of schizophrenia. The aim of this Chapter was to quantify differences between distractor (*i.e.*, novelty) and target (*i.e.*, novelty and relevance) tones in an auditory oddball paradigm. For this reason, MF and SE were computed from the EEG data of 31 patients with schizophrenia and 38 healthy controls. The findings support the notion that schizophrenia is associated with a reduced response to both novelty and relevance during an auditory P300 task.

- **Chapter 5: Auditory P3a and P3b neural generators in schizophrenia: An adaptive sLORETA P300 localization approach.**

  This Chapter investigates the neural substrates underlying cognitive processing in schizophrenia patients. The P3a and P3b brain-source generators were identified by time-averaging of LORETA current density images. In contrast with the commonly used fixed window of interest (*WOI*), we proposed to apply an adaptive *WOI*, which takes into account subjects' P300 latency variability. Our findings suggest that target and distractor processing involves distinct attentional subsystems, both being altered in schizophrenia. Therefore, the study of neuroelectric brain information can provide further insights to understand cognitive processes and underlying mechanisms in schizophrenia.

- **Chapter 6: A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia.**

  The aim of this Chapter is to explore the coupling patterns of brain dynamics during an auditory oddball task recorded from 20 schizophrenia patients and 20 healthy controls. The coupling changes between auditory response and pre-stimulus baseline were calculated in conventional EEG frequency bands (θ, α, β_1, β_2 and γ), using three coupling measures: coherence, phase-locking value and Euclidean distance. Our findings may reflect an impaired communication among neural areas, which may be related to abnormal cognitive functions.

- **Chapter 7: Investigating ERPAC patterns of brain activity: Evidence of alpha-to-gamma hierarchical organization elicited by an auditory oddball task.**

  This Chapter proposes a novel measure of PAC dynamics in an event-related way (event-related PAC). It was applied to auditory-oddball EEG response recorded from 28 schizophrenia patients and 51 healthy controls. Our findings showed that the phase of alpha rhythm is coupled with the power of low gamma oscillations. Additionally, a statistically significant association between alpha amplitude and ERPAC in healthy controls was found. Both findings support the role of inhibitory process in neural oscillatory hierarchy, suggesting that the CFC patterns can be altered in schizophrenia.

- **Chapter 8: Discussion** outlines the results of the present research and their interpretation.

- **Chapter 9: Conclusions** highlights the main contributions of this research work and presents the key results, which we believe will be of most use to future researchers working in this field. Likewise, the limitations of the research and the most important future lines are highlighted.

Chapter 2

Hypotheses and objectives

2.1. Introduction

The understanding of neural mechanisms underlying cognitive processes in schizophrenia has become an interesting issue of research. This Doctoral Thesis focuses on analyzing EEG activity to characterize the interplay of functional segregation and integration. Functional segregation could be formed by local network communities that are intrinsically densely connected and strongly coupled. Functional integration measures the global interaction between distant brain areas. Therefore, in order to obtain a comprehensive characterization of human neural networks, EEG activity is explored using a two-level analysis: (*i*) local activation studies to explore functional segregation in the brain network; and (*ii*) EEG interactions analyses to examine the functional integration across brain regions. On the one hand, local activation contributes to functional segregation characterization by analyzing the time-frequency properties of ERP data and the localization of neural generators at source level. On the other hand, functional integration was assessed by means of the study of EEG interactions; it includes the analysis of functional connectivity between pairs of electrodes and the high level relationship between brain rhythms by means of CFC.

These actions have been implemented following the next scheme:

i) EEG acquisition.

ii) Pre-processing of EEG data.

iii) Time-frequency decomposition of EEG data.

iv) Two-level analysis: local activation and EEG interactions.

v) Statistical analyses and interpretation of results.

This research proposal is substantiated by the hypotheses and objectives described below.

2.2. Hypotheses

Neurophysiological studies have associated the schizophrenia with an aberrant attribution of salience to external objects and internal representations caused by an aberrant

neuromodulation of synaptic activity. In this regard, *local activation analyses provide a meaningful measure of functional segregation that is relevant to understanding how cognitive processes emerge.* The analysis of time-varying neural activity can be useful to understand brain dynamics underlying cognitive processes. Hence, *EEG signals as a response to a cognitive task are well-suited to reflect neurophysiological mechanisms due to their high temporal resolution in the time range of milliseconds.* In particular, time-frequency local activation analysis addressed whether *schizophrenia disease causes impairments in neural oscillations at different frequency ranges* and brain source analysis assesses *schizophrenia neural generator abnormalities as a response to novelty and relevance.*

Relevance attribution likely involves diverse cerebral regions and their interconnections. It is therefore reasonable to hypothesize that *EEG interaction studies could be helpful to further understand the dynamic neural mechanisms underlying cognitive processes in schizophrenia.* According to the dysconnection hypothesis, *a disturbed dynamic coordination between neural oscillations contributes to the pathophysiology of schizophrenia.* The physiological correlates of this lack of coordination would be expressed in terms of a failure to modulate synchronous activity: schizophrenia patients would show a failure to contextualize stimulus processing through a deficit on modulating the synchronous gain or excitability of neuronal populations, leading to a functional disintegration or dysconnection.

Dysconnection hypothesis has been related to aberrant salience hypothesis (*i.e.* the physiological correlates of this dysconnection would be expressed in terms of a failure to modulate their neural rhythms). To validate these hypotheses, this Doctoral Thesis proposes the use of *a two-level hierarchical analysis of neural signals in order to obtain a meaningful framework for assessing functional segregation and integration.* In other words, it allows to identify the brain areas that are dedicated to cognitive information processing task, as well as to evaluate the dependencies among these different brain areas.

2.3. Objectives

The general goal of this Doctoral Thesis is *to study, to design and to apply biomedical signal processing methodologies in order to explore and characterize cognitive processes altered by the schizophrenia.* EEG data were examined using a two-level analysis with the aim of achieving a reliable characterization of dynamical neural dysfunctions in schizophrenia. Therefore, this research proposal assesses: (*i*) local activations and (*ii*) EEG interactions among evoked-averaged and single-trial brain activity.

In order to achieve the main objective, the following specific objectives are raised:

1. To review the bibliography and state-of-the-art related to biomedical signal processing methodologies useful to characterize EEG data. Particularly, this objective is focused on identifying appropriate techniques that can be used in an event-related approach.

2. To build a database, including EEG recordings, socio-demographic data and clinical variables from adult schizophrenia patients and healthy controls.

3. To reduce common artifacts in EEG recordings by defining a semi-automatic three-step artifact rejection procedure based on statistical data analysis.

4. To develop and perform (using Matlab®) the signal processing algorithms that are more suitable to characterize event-related brain dynamics in schizophrenia.

5. To assess the time-varying modulation of local activation brain activity during a cognitive task in schizophrenia using time-frequency functional segregation measures.

6. To explore the alterations in stimulus processing as a response to relevant (P3b) and to novel but not relevant (P3a) stimuli inputs. This specific objective is aimed at quantifying the contribution of each frequency band at different temporal scales (*i.e.* during the pre-stimulus baseline and the task-processing stages of an auditory odd-ball task).

7. To properly localize P300 brain-source generators and to analyze the differences between auditory P3a and P3b underlying cortical sources between schizophrenia patients and healthy controls.

8. To obtain a global pattern of event-related functional connectivity changes between the response of an auditory cognitive task and the pre-stimulus baseline.

9. To assess the temporal organization of brain activity by analyzing cross-frequency interactions among neural oscillations.

10. To conduct statistical analyses of the results to evaluate each methodology applied to EEG recordings, as well as to identify the pathophysiological patterns in schizophrenia.

11. To compare and discuss the results to extract appropriate conclusions. This objective includes the comparison with the state-of-the-art ERP studies and the comparison of our findings with the results obtained using other techniques, such as MEG, LFP or fMRI.

12. To publish the obtained results and conclusions in high-impact journals, as well as in international and national conferences.

Chapter 3

Decreased spectral entropy modulation in patients with schizophrenia during a P300 task

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Abstract: Spectral entropy (SE), also known as Shannon entropy, is a useful parameter for quantifying the global regularity of the electroencephalographic (EEG) signal. Hence, it is of interest in the assessment of the electrophysiological correlates of cognitive processing in schizophrenia. However, to date, SE has been barely used in studies comparing resting EEG recordings between patients and controls. In this work, we compared SE between resting baseline [-250 0] ms and active task [150 550] ms windows of a P300 task in 31 patients with schizophrenia and 38 controls. Moreover, we also calculated the median frequency (MF) and relative power in each frequency band for these windows to assess the correlates of the possible SE differences. Controls showed a significant (p 0.0029) SE decrease (*i.e.*, meaning higher signal regularity) from baseline to the active task window at parietal and central electrode sites. This SE decrease from baseline to active conditions was significantly lower in patients. In controls, this SE decrease was accompanied by a statistically significant decrease in MF (*i.e.*, a significant slowing of the EEG activity), not observed in patients. In this latter group, the difference in SE between resting baseline and active task windows was inversely correlated to positive and total symptoms scores, as measured with the positive and negative symptoms scale. Our data support the relevance of SE in the study of cerebral processing in schizophrenia.

3.1. Introduction

The analysis of the fast bioelectrical changes from baseline to the processing stages of a cognitive task may be useful to better understand the dynamic abnormalities of information processing in schizophrenia (*i.e.*, alterations that may appear at some but not all stages of this processing). Several attempts have been made to investigate neural dynamics associated with schizophrenia by the use of complexity measurements of the EEG. However, to date, this approach has yielded contradictory results (Fernández et al., 2013).

Among the potentially relevant complexity parameters for the study of schizophrenia, SE allows for quantifying the degree of disorder contained in a signal. SE is a measure derived from the original definition suggested by Shannon Shannon (1948), who defined entropy as the average amount of information of a probability distribution. The concept was extended to EEG power spectral density by Inouye et al. Inouye et al. (1991). A high SE value implies a flat, uniform spectrum with a broad spectral content (*i.e.*, a more irregular signal), whereas a low SE indicates a spectrum with a narrower frequency range (*i.e.*, a more regular signal). In this framework, SE allows for the assessment of differences in information content and signal variability average across time. Moreover, SE enables to compare the signal dispersion between groups, (Freeman and Quiroga, 2012) thus holding potential for the study of cognitive processing substrates. Likewise, SE may allow for a novel approach to improve our understanding of the altered cortical processing mechanism in mental illness, especially when considering task-related differences between baseline and active conditions.

SE values indirectly reflect spectral EEG composition (lower values imply a more regular signal). The EEG frequency bands likely have different functions for the coordination of activity across cortical regions (Kopell et al., 2000; von Stein and Sarnthein, 2000; Womelsdorf et al., 2007). Therefore, tasks involved in the activation of diverse cerebral regions are advisable to assess SE differences in patients. The odd-ball paradigm may be useful in this respect, since it is involved in the activation of several different brain areas (Linden et al., 1999; Polich, 2007), and it has the additional advantage of its relative simplicity, which reduces possible performance-related problems. Patients with schizophrenia have shown reduced delta and theta activity 200–500 ms post-stimulus during a P300 task, along with reduced ERPs amplitudes (Doege et al., 2009), suggesting smaller SE differences in relation to task performance. The altered inter-regional connectivity reported in schizophrenia (Kubicki et al., 2005) also suggests that the modulations of oscillations may be abnormal during a cognitive task in patients with this syndrome.

To date, SE has been scarcely used in schizophrenia research. In this regard, its discriminatory ability in comparison with other parameters has been assessed by Sabeti et al. [(Sabeti et al., 2009). They did not find any differences between groups in SE values during resting-state activity. However, using a SE-based method, an increased connection entropy was described in patients with schizophrenia in the gamma band (Schoen et al., 2011).

In the present study, we have further explored the ability of SE to characterize abnormal cognitive processing during a P300 task elicited in patients with schizophrenia. Two additional parameters were used to clarify the basis of possible differences in SE: median frequency (*i.e.*, the frequency value that divides the signal power in half) and relative power (*i.e.*, the proportion of total spectral power attributable to a given band). These parameters have been used to quantify the contribution of different frequency bands to spectral power in patients with schizophrenia and healthy controls during the baseline and the task-processing stages of an auditory odd-ball test. Finally, the relation between significant changes in SE and clinical scores was also explored.

3.2. Materials and methods

3.2.1. Participants

Thirty-one patients with paranoid schizophrenia, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th revised edition criteria, and 38 controls were included in the study. Patients group was formed by 20 chronic, stably treated (CP) and 11 minimally treated patients (MTP). These patients were labeled as MTP because prior to their inclusion they had not received any previous treatment (first episode patients, $n = 8$) or they had dropped their medications for longer than 1 month. Owing to an acute psychotic state of these patients, a small amount of haloperidol (2–4 mg) was administered with a wash-out period of approximately 24 h before EEG acquisition. The objective was to minimize the likely bias of only including patients able to cooperate with the EEG recording during an acute psychotic episode and without any previous treatment. In order to rule out the acute effects of haloperidol on power, five controls (included in the 38 controls of the study) gave their informed consent to be studied with EEG before and 24 h after a 2 mg dose of haloperidol, approximately reproducing the treatment conditions of MTP.

The clinical status of the patients was scored using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). We used the Spanish version of the Wechsler Adult Intelligence Scale third edition (WAIS-III) to assess IQ. Cognitive assessment was acquired by the Spanish version of the brief assessment of cognition in schizophrenia (BACS) scale (Segarra et al., 2011). Employment status was stratified as: employed (currently studying or working) or unemployed (looking for a job or retired); and educational level as completed academic courses.

Controls were recruited through newspaper advertisements and remunerated for their cooperation. They were previously assessed by a semi-structured psychiatric interview by one investigator (V. Molina) to discard major psychiatric antecedents (personal or familial) and treatments.

Demographic and clinical characteristics are shown in Table 3.1.

The exclusion criteria included: (i) total intelligence quotient (IQ) below 70; (ii) a history of any neurological illness; (iii) cranial trauma with loss of consciousness; (iv) past or present substance abuse, except nicotine or caffeine; and (v) the presence of any other psychiatric process or drug therapy and treatment with drugs known to act on the central nervous system. We

Table 3.1: Demographic; clinical, cognitive and EEG parameters. Values are shown as mean (standard deviation, SD); P300 amplitudes are shown in microvolts; *CP*, chronic stable patients, *MTP*, minimally treated patients; *NA* not applicable. Significance of between-groups comparisons is shown in the first column (Kruskal-Wallis test, * $p < 0.01$; ** $p < 0.005$; *** $p < 0.001$)

	CP	**MTP**	**Controls**
Age (years)	40.37 ± 10.36	33.53 ± 9.91	33.65 ± 13.12
Sex distribution (M:F)	12 : 8	7 : 4	23 : 15
School years*	6.62 ± 3.01	12.47 ± 2.59	NA
PANSS positive	19.26 ± 5.29	21.12 ± 3.99	NA
PANSS negative	22.00 ± 4.80	17.00 ± 4.69	NA
PANSS general	34.92 ± 17.56	33.63 ± 7.24	NA
PANSS total	76.26 ± 15.63	76.27 ± 11.37	NA
Total IQ (WAIS-III)**	86.31 ± 14.94	82.18 ± 16.76	101.93 ± 12.44
P3a artifact-free epochs	88.30 ± 9.76	80.09 ± 17.37	82.42 ± 18.52
P3b artifact-free epochs	78.65 ± 19.78	69.90 ± 18.16	84.47 ± 9.32
P3a amplitude (Cz) in μV	1.18 ± 1.14	0.68 ± 1.43	1.27 ± 1.16
P3b amplitude (Cz) in μV^{***}	1.74 ± 1.21	2.78 ± 1.28	3.39 ± 1.59

discarded toxic use in patients and healthy controls with the information gathered in the interview and a urinalysis.

Written informed consent was obtained from the patients, their families and healthy controls after providing full written information. The research boards of the University Hospitals of Valladolid and Salamanca endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

3.2.2. Electroencephalographic recording

EEG recordings were performed while the participants underwent an auditory odd-ball task. To elicit P3a and P3b components, an odd-ball 3-stimulus paradigm was employed with a 500 Hz-tone target, a 1,000 Hz-tone distracter and a 2,000 Hz-tone standard stimulus.

Accordingly, participants heard binaural tone bursts (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) presented with random stimulus onset asynchrony of 1,000 and 1,500 ms. Random series of 600 tones consisted of target, distractor and standard tones with probabilities of 0.20, 0.20 and 0.60, respectively.

The participants were asked to press the mouse button whenever they detected the target tones, to close their eyes and avoid eye movements and muscle artifacts. Non-attended target tones were discarded. Nevertheless, for distractor and standard tones non-attended trials were included, whereas attended tones were discarded.

The EEG was recorded using a Brain Vision® (Brain Products GmbH; Munich, Germany) equipment from 17 tin sensors mounted in an electrode cap (Electro-Cap International, Inc.; Eaton, Ohio, USA), according to the revised 10/20 International System. Electrode impedance was always kept under 5 kΩ. Figure 3.1 shows an example of two raw EEG trials, from a patient with schizophrenia and a control. The stimulus onset was represented by the red line. Baseline and active task responses were obtained in the (-250,0) ms and (150,550) ms interval, respectively.

Recordings were referenced over Cz electrode, the sampling rate was 250 Hz, and the signal was recorded continuously. Data were re-referenced to the average activity of all active sensors (Bledowski et al., 2004), because common average reference is less sensitive to microsaccadic artifacts in high frequency recordings (Keren et al., 2010). P3a and P3b components were, respectively, calculated from distractor and target stimuli. Firstly, ERP grand-averages were automatically performed using Brain-Vision Analyzer® (Brain Products GmbH; Munich, Germany). Secondly, P3a and P3b were defined as the mean of ERP grand-average amplitude in the 300–400 ms interval.

Artifact rejection was conducted, following a two-steps approach. Firstly, data were imported into EEGLAB, and an independent component analysis (fast ICA method) was carried out to decompose ERPs in a total of 17 components (Delorme and Makeig, 2004). After a visual inspection of the scalp maps and their temporal activation, the components related to eyeblinks were discarded. Secondly, artifacts were automatically rejected using an adaptive thresholding method to discard EEG segments that displayed an amplitude exceeding a statistical- based local threshold. Thereafter, an off-line 1–70 Hz filter was applied. EEG recordings were then segmented into 800 ms-length epochs from -250 to 550 ms with respect to the onset of the stimulus (200 samples per epoch). The average number of selected epochs for target condition is shown in Table 3.1.

3.2.3. Spectral analysis and definition of parameters

A typical approach for characterizing electromagnetic brain recordings is based on the analysis of their spectral content. In order to describe the power spectrum proper-

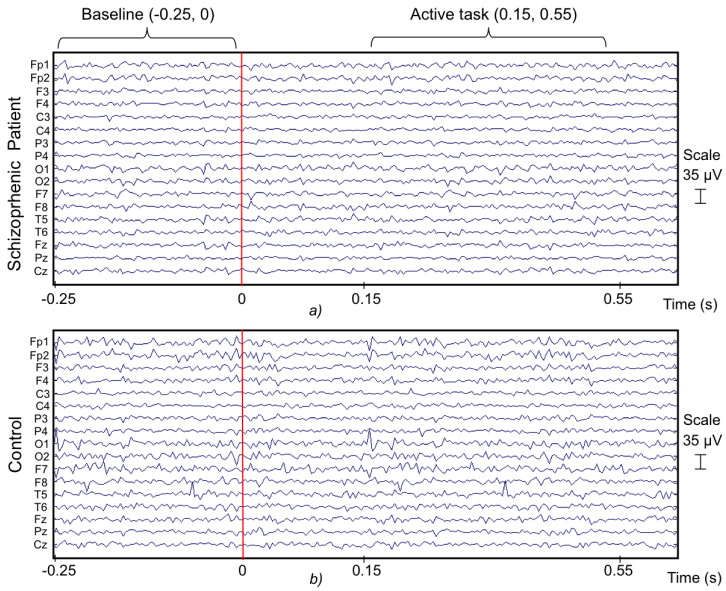

Figure 3.1: Raw EEG trials from 17 acquisition electrodes (channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T5, T6, Fz, Pz and Cz) for: **(a)** a patient with schizophrenia; and **(b)** a control participant.

ties, the PSD function was estimated. PSD represents how the power is distributed in the frequency domain. EEG recordings are non-stationary signals, whose characteristics may change over time (Blanco et al., 1995). Therefore, nonstationary signal analysis techniques, such as time–frequency distributions, may be appropriate to accurately describe their properties (Aviyente et al., 2004; Poza et al., 2008). In the present study, a sliding temporal window technique was applied to obtain the time-evolution of PSD segments. Each EEG epoch of 800 ms ($M = 200$ samples) was divided into temporal segments of 168 ms ($L = 41$ samples) with a 90 % overlapping. Then, 32 time intervals identified by i ($i = 1,\ldots,32$) were obtained, and PSD was calculated for each temporal window. Finally, the spectral content between 1 and 70 Hz was selected, and PSD was normalized (PSD_n).

$$PSD_n^{(i)}(f) = \frac{PSD^{(i)}(f)}{\sum_{f=1Hz}^{70Hz} PSD^{(i)}(f)}, i = 1, ..., 32. \tag{3.1}$$

After the normalization, it follows that $\sum_{f=1}^{70Hz} PSD^{(i)}(f) = 1$ for each i. Then, in the band of interest [1 70] Hz, PSDn can be considered as a probability distribution. This representation provides a suitable tool to apply several spectral parameters.

3.2.4. Spectral entropy

Entropy is a thermodynamic function, which was adapted to the context of information theory. Its original meaning involves uncertainty of information in terms of disorder, discrepancy and diversity (Bezerianos et al., 2003). Previous studies used SE to estimate

the irregularity in the EEG in terms of the flatness of PSD (Abásolo et al., 2006). A uniform spectrum with a broad spectral content (e.g., white noise) yields a high SE value. On the contrary, a narrow power spectrum with only a few spectral components (e.g., a sum of sinusoids) gives a low SE value [3]. Thus, SE can be considered as a disorder quantifier. To calculate SE, we applied the definition of Shannon's entropy computed over PSD_n.

$$SE^{(i)} = -\frac{1}{\log L} \sum_{f=1Hz}^{70Hz} PSD_n^{(i)}(f) \log\left[PSD_n^{(i)}(f)\right], i = 1, ..., 32. \tag{3.2}$$

where L is the number of spectral components in the [1, 70] Hz band.

3.2.5. Median frequency

An alternative way to summarize the changes in the spectral content of EEG recordings is the MF. It is defined as the frequency that comprises 50 % of the power (Poza et al., 2008). MF is calculated from PSD_n between 1 and 70 Hz. MF offers a simple way of quantifying the spectral content of PSD.

$$\sum_{f=1Hz}^{MF^{(i)}} PSD_n^{(i)}(f) = 0.5, i = 1, ..., 32. \tag{3.3}$$

3.2.6. Relative power

The RP represents the relative contribution of several oscillatory components to the global power spectrum. It is useful to analyze the changes in the spectral content of EEG recordings. It is noteworthy that several advantages can be found when comparing RP to absolute power (AP). Hence, RP is independent from the thresholds of the measurement equipment. Likewise, RP obtains lower inter-subject variability than AP (Poza et al., 2012). RP is calculated by summing the contribution of the spectral components included in the conventional EEG frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13 Hz), beta 1 (β_1, 13-19 Hz), beta 2 (β_2, 19-30 Hz) and gamma (γ, 30-70 Hz).

$$RP_{f_p}^{(i)} = \sum_{f \in f_p} PSD_n^{(i)}(f), f_p = \{\delta, \theta, \alpha, \beta_1, \beta_2, \gamma\}, i = 1, ..., 32. \tag{3.4}$$

3.2.7. Parameter baseline correction

We used a baseline correction process in order to achieve a stimulus-independent characterization. The time–frequency analysis provides a value for each temporal segment. The baseline was defined as the available 250 ms pre-stimulus recording. Thus, the values of the previous parameters in the [-250 0] ms interval were averaged to obtain a "pre-stimulus parameter mean". The baseline correction was then carried out using the "percent change from baseline method" (Roach and Mathalon, 2008). For that purpose, firstly, the pre-stimulus parameter mean is subtracted from the response value for each participant (mean of the values in the [250 550] ms interval), and then the result is divided by the pre-stimulus parameter mean.

3.2.8. Statistical analyses

Sex distribution, age, completed courses, IQ, cognitive performance (BACS) and P3a and P3b amplitudes were compared between patients and controls using non-parametric tests.

As a general rule, to minimize the possible influence of chronicity and treatment upon the study parameters, we planned to compare those parameters between patients and controls (p level corrected for multiple comparisons) and then testing whether: (a) the same pattern appeared in the comparison between MTP and controls; and (b) no differences were found between both patients groups.

To explore differences in SE between patients and controls, the significance maps of both within- and between groups were assessed (Figures 3.1 and 3.2). In a first step, the significance of SE difference within each group was assessed, comparing the mean SE values from baseline [-250 0] ms and active [150 550] ms windows, with Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$ electrodes $= 0.0029$). Then, between-groups differences were assessed in: (1) baseline SE values; and (2) SE difference from baseline to active windows, which were expressed as the SE percent of change (calculated as $[\frac{SE-SE^{BL}}{SE^{BL}}]$, where SE represents the spectral entropy in the active condition and SE^{BL} its value at baseline; negative values indicates a SE decrease in the active condition). These differences were tested with Mann–Whitney U tests (Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; trend $\alpha = 0.0058$). The analyses were supplemented by comparing SE values between both groups of patients, and between MTP and controls, again using Mann–Whitney U tests (uncorrected in this case, given the confirmatory purpose of this subtest).

Classification performance of SE between patients and controls was evaluated by a receiver operating characteristics (ROC) analysis. For that purpose, a linear discriminant analysis (LDA) and a LDA with a leave-one-out cross-validation (LOO—CV) procedure were assessed. LOO–CV procedure provides a nearly unbiased estimate of the true error rate of the classification procedure (Simon et al., 2003). Average value of all the electrodes was used in the classification analyses. Classification mean rate were shown in terms of the area under ROC curve (AUC), sensitivity (percentage of patients with a correct classification), specificity (proportion of controls properly recognized) and accuracy (total fraction of well-classified patients and healthy participants). Similar analyses were repeated for the comparisons between MTP versus controls, and MTP versus CP.

The corresponding SE values at each sensor were calculated to be subsequently used in statistical analysis (see below) and to depict the magnitude of the differences in SE changes between groups.

To explore the basis of possible SE differences, we planned to assess the statistical significance of the between groups differences in the variation of MF (significance maps, Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; Figure 3.4) and the relation between SE and MF differences (using pair-wise Pearson's r correlations between SE and MF differences at each electrode location; Suppl. Tables 3.1 and 3.2). We also assessed between-groups differences in baseline MF values. This analysis was completed by comparing RP differences between baseline and active condition in each band, using Wilcoxon signed-rank tests ($\alpha = 0.00049$; 0.05/102; 17 electrodes and 6 bands).

Finally, to assess the clinical relevance of possible differences in SE, stepwise multivariate linear regression was used. PANSS positive, negative and total scores were used as dependent variables, and SE values at each sensor were introduced as predictive variables.

3.3. Results

Patients and controls did not differ in age or sex distribution, but they differed in completed courses and total IQ (Table 3.1). P3b, but not P3a amplitudes, were reduced in the patients (Table 3.1).

3.3.1. Spectral entropy

3.3.1.1. Baseline values

Figure 3.2 shows the mean SE topographic distribution in the baseline window for each group. SE at baseline did not differ between the groups.

3.3.1.2. Spectral entropy differences

From baseline to active windows, SE showed a statistically significant and widespread decrease in the control group. The SE decrease was almost absent in MTP and was more spatially restricted in the stable patients (Figure 3.3a).

The comparison of SE differences (baseline to active windows) between patients and controls revealed a significantly lower difference in the former over parietal and central regions, predominantly left-sided and extending to the left frontal electrodes. This pattern was similar in chronic and MT patients as separately compared with controls, without statistically significant differences between patients groups (Figure 3.3c).

Additionally, ROC curves were used to assess the ability of SE values to discriminate patients from control participants. Two methods were applied: LDA with and without LOO-CV. The highest accuracy was achieved by LDA (76.8 %, accuracy; 71.1 %, sensitivity; 83.9 %, specificity; 0.789, AUC). Lower classification statistics were reached by LDA with LOO–CV (72.4 %, accuracy; 74.2 %, sensitivity; 71.0 %, specificity; 0.789, AUC). Supplementary figures of this original article show ROC curves, for both classification methodologies, to discriminate between: patients and controls, MTP and controls, and CP and MTP.

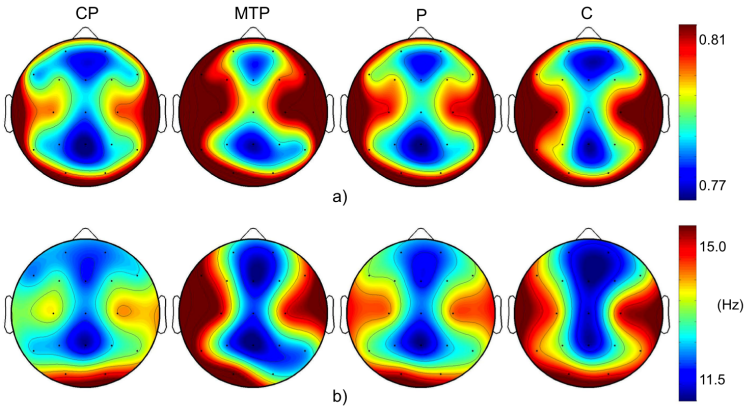

Figure 3.2: Baseline SE (a) and MF (b) maps in the three groups. There were no significant differences at $p < 0.05$ level between patients and controls, between any group of patients and controls, or between patient subgroups. *CP* chronic stable patients, *MTP* minimally treated patients, *P* patients; *C* controls.

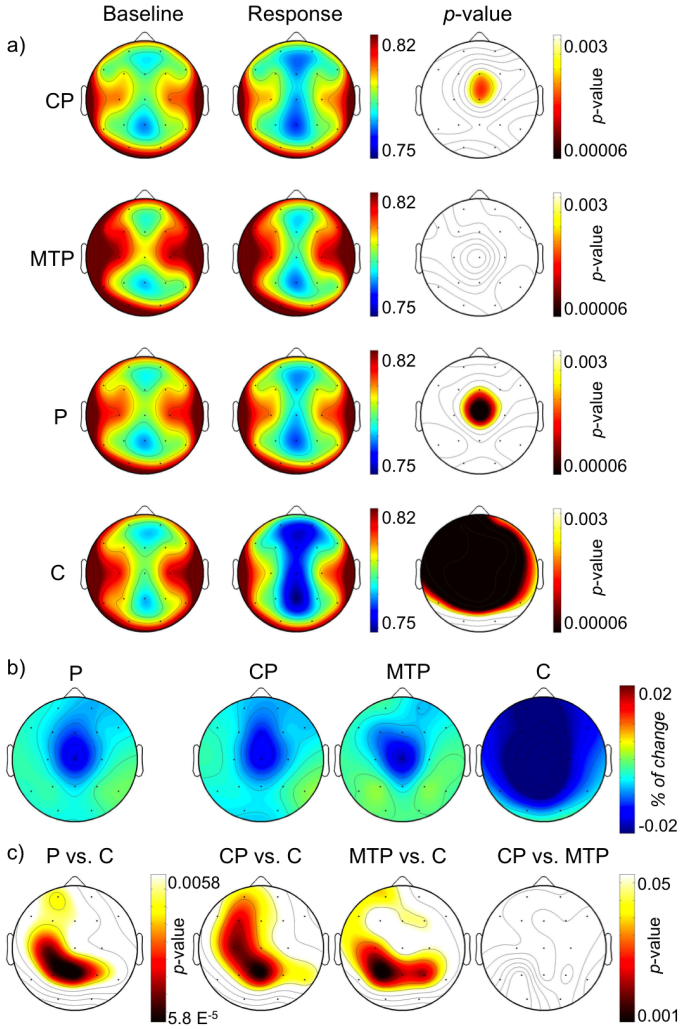

Figure 3.3: (*a*) SE maps at baseline and active window in the three groups (p values of the within groups differences are shown in the right column); (*b*) maps depicting the difference between active and baseline SE values; (*c*) topographic maps depicting the statistical results of the between-groups differences between active and baseline variation of SE values.

Equivalent analyses have been carried out for distractor non-attended trials. SE showed a statistically significant decrease in the control group, whereas SE changes were absent in MTP and CP. The comparison of SE differences between patients and controls did not show significant differences.

3.3.1.3. Association with clinical scores

In the patients, the difference in SE between active and baseline segments at C3 was significantly and directly associated with positive PANSS scores ($R^2 = 0.279$; $p = 0.013$; $b = 0.545$, $t = 2.75$), and total PANSS scores ($R^2 = 0.223$; $p = 0.035$; $b = 0.472$,$t =$

2.27). Given that the more positive SE values represent less SE decrease, the smaller this decrease was from baseline to active epochs, the higher clinical scores. This association was confirmed in MTP for total PANSS scores (R^2= 0.673; p = 0.01; b = 0.575, t = 3.01).

3.3.1.4. SE differences after haloperidol in healthy participants

An equivalent analysis was performed to the signal recorded in five healthy participants, before and 24 h after a 2 mg single dose of haloperidol. We did not detect any significant effect of haloperidol in the healthy participants. Supplementary figures of this original article show the mean SE values obtained pre- and posttreatment.

3.3.2. Median frequency

3.3.2.1. Baseline values

MF at baseline did not differ between any group of patients and controls (Figure 3.2).

3.3.2.2. Differences in median frequency

In controls, there was a decrease in MF values across the entire cortex (-1 Hz approximately), while patients showed a smaller or no difference in MF (Figure 3.4a).

The comparison of MF differences between patients and controls revealed a significantly lower decrease in the patients in approximately the same area that showed a lower SE difference in this group (Figure 3.4c). Again, the pattern of differences as compared-with controlswas similar in both groups of patients, and no differences were detected between them. Values of MF at each sensor are shown in Suppl. Table 3.2.

In patients as well as in controls, MF and SE differences were highly correlated at each electrode (in all cases, $r > 0.6, p < 0.001$).

3.3.3. Relative power

Delta and theta band RP increased in patients and controls ($p < 0.00049$) from baseline to active conditions, but this increase was lower in the patients group than controls. There was a widespread RP decrease for the high frequency bands in controls during the active condition, again smaller in the patients.

3.4. Discussion

Healthy controls showed statistically significant and widespread SE and MF decreases from baseline to active window during an odd-ball task. The same differences were significantly smaller in patients, and they correlated with clinical scores in this group. Secondary analyses revealed that the power increase observed in theta and delta bands was smaller in the patients in the active window as compared with baseline. A smaller decrease in high frequency oscillations was also observed in the patients in the active window.

To the best of our knowledge, the few SE studies published so far in schizophrenia have not explored changes with cognitive processing. The reported absence of significant SE differences in the resting state between medicated patients and controls (Sabeti et al., 2009) is consistent with the lack of baseline differences in our sample. Likewise, in resting conditions, increased entropy specific to the gamma band has been reported in

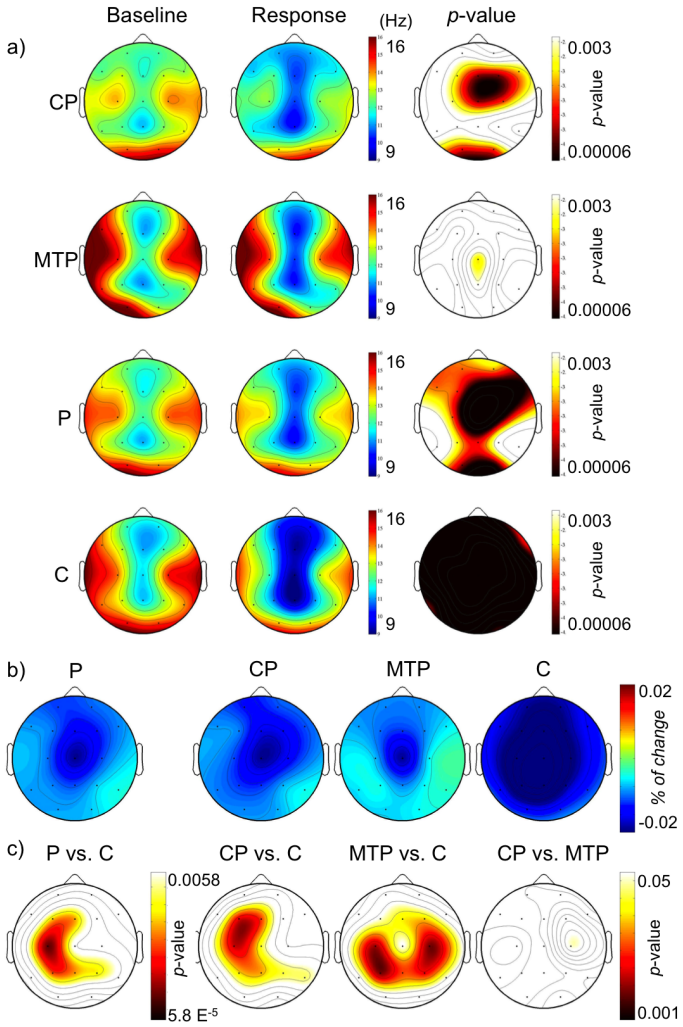

Figure 3.4: (*a*) MF topographic maps at baseline and active window in the three groups (values shown in Hz; p values of the within groups differences are shown in the right column); (*b*) maps depicting the difference between active and baseline MF values; (*c*) *p* values topographic maps depicting the significance of the between-groups differences between active and baseline variation of MF values.

schizophrenia (Schoen et al., 2011). Our data demonstrate that significantly altered SE may be found in schizophrenia in the difference in EEG signal distribution in relation to cognitive processing. In this regard, SE may be a valuable parameter for this kind of analysis, since it was less altered in patients than in controls with the processing of target stimuli. According to our data, this approach may be more sensitive to differences between patients with schizophrenia and controls than the comparison of resting SE values. Indeed, classification analyses revealed a significant discrimination between our patients and controls based on SE change that also held when only MTP patients were considered.

Two classification methodologies have been evaluated, LDA with and without LOO–

CV. In the case of LDA with LOO–CV, the data of one participant are excluded from the training set one at a time and then classified on the basis of the threshold calculated from the data of all other participants (Gómez et al., 2009). Despite the fact that the classification statistics decrease with this procedure, it provides a nearly unbiased estimate of the true error rate of the classification method (Simon et al., 2003).

MF and SE differences were highly correlated in all groups, suggesting that the SE decrease in controls was contributed by a slowing of the EEG signal during the active part of the test. In our controls, the RP comparisons indicate a decrease in high frequency bands, which was lower in the patients and likely underlie their smaller MF difference. This result is coherent with the lower reduction in gamma power observed during a P300 test in patients with schizophrenia [28], as well as with previous reports of higher gamma noise power in schizophrenia during a P300 task (Diez et al., 2013; Suazo et al., 2012; Winterer and Weinberger, 2004). Noise power represents the amount of gamma activity not related to task performance (*i.e.*, the power difference in this band between the total and the averaged signals). It is likely that such a smaller modulation of fast oscillations is reflected on a lower entropy decrease in our patients. Taken together with this, the lower SE and MF difference in our patients suggest a relatively rigid and disorganized cortico-cortical transmission during task performance in schizophrenia, which may in part relate to a hyper-active baseline state.

The lower decrease in SE observed in our patients is probably also influenced by a lower increase of theta and delta oscillations during the active window as compared with controls. Previous results revealed higher theta amplitudes in healthy participants during target processing in a similar odd-ball task (as compared to non-target) (Doege et al., 2009). Similarly, delta and theta event-related spectral perturbation (the amount of power change from baseline) was lower in patients with schizophrenia but not schizotypal personality disorder as compared to controls during a P300 test (Shin et al., 2010). In this context, our data give further support to a reduced response in these bands during cognitive activation in the schizophrenic brain. Slow theta (von Stein and Sarnthein, 2000) and beta (Kopell et al., 2000) oscillations have a role in the synchronization between relatively distant regions, while gamma band may be more involved in the short-range communication (Kopell et al., 2000; Womelsdorf et al., 2007). Besides, the dominant frequency of a neuronal assembly is dependent on its size (*i.e.*, on the number of participating neurons), the lower frequencies involving larger assembly sizes [33]. Slow bands oscillations have been proposed to subtend cortico-cortical interactions (Devrim et al., 1999). Recent researches using functional (Fair et al., 2009; Supekar et al., 2009) and diffusion magnetic(Hagmann et al., 2010) resonance suggest a shift from functional segregation (*i.e.*, more local functioning) to integration across development. In this framework, the lower change (*i.e.*, the lesser increase in slow bands RP) in our patients during the active window suggests a cortical functioning similar to that expected in earlier developmental stages.

The direction of the association between SE percent of change (active minus baseline divided by baseline SE) and clinical scores was positive in patients, suggesting that the lower changes in SE during the P300 task were associated with a higher clinical severity (*i.e.*, patients with smaller SE decrease in the active condition would have larger PANSS scores). Our patients did not show any impaired behavioral performance in the test, suggesting that the decreased SE difference did not influence the performance of a simple task. However, more complicated tasks, such as those running in real life (understanding others intentions, integrating information sources and so on) might be hampered in the patients as a consequence of the more rigid cerebral function revealed by their lower SE decrease. Speculatively, in this context, the direct association between SE and positive symptoms may arise as a consequence of an impaired capacity for processing

real-life stimuli. Such a problem may in turn have a relation with the aberrant salience proposed in schizophrenia (Kapur, 2003), in whose framework the discrimination of target (*i.e.*, relevant) stimuli from background activity may be impaired. Therefore, this may be expressed as a reduced difference in the spectral composition between baseline and active conditions of an odd-ball paradigm, as well as in higher positive symptoms such as delusions and hallucinations. In a previous study, resting gamma entropy was unrelated to symptoms (Schoen et al., 2011), suggesting that the smaller capacity for SE difference may correlate to the clinical profile, rather than its baseline increase.

It is possible that smaller SE differences in our patients were contributed by the treatment received. However, this possibility is unlikely the main reason for that altered SE, since there was no SE difference between MT and chronic patients. In addition, pre- and post-haloperidol SE differences between baseline and active condition in healthy controls did not show significant results. Moreover, a comparison of resting EEG entropy values in patients with schizophrenia between pre- and post-treatment states revealed that antipsychotics reduced entropy in frontal regions and did not affect its values in temporal regions (Takahashi et al., 2010). Hence, the small entropy reduction from baseline to active conditions found in our study is unlikely secondary to the treatment received. Although multi-scale entropy was used in that study (Takahashi et al., 2010), instead of SE, a high degree of correlation between both measurements can be assumed. In the same direction, it seems likely that neuroleptic-naïve patients show higher EEG complexity values than healthy controls and their chronic treated counterpart one. In any case, similar studies in neuroleptic-naïve cases are needed to adequately address this point. Moreover, although our cases showed the usual P3b amplitude reduction in schizophrenia, they did not show the P3a reduction also found in this syndrome (Jahshan et al., 2012; Mondragón-Maya et al., 2013; Rissling et al., 2013). This issue could be related to the relatively small sample size, in particular of MTP.

Some limitations in our study merit further consideration. Firstly, the sample size is small especially in patients' subtypes. Thus, a larger database including recordings from both patients' subtypes is needed to confirm the performance of the methods used in the current research. Secondly, all patients have been diagnosed as paranoid schizophrenia; due to the fact that it is the most prevalent schizophrenia subtype. Finally, SE has certain limitations; the spectral-based method is sensitive to spike or artifacts. Nevertheless, it should be taken into account that a two-step artifact rejection approach was applied, minimizing their impact.

As a conclusion, SE may be a useful parameter for the study of cognitive processing abnormalities in schizophrenia. The reduced SE difference during the processing of a target stimulus in patients was correlated with clinical severity and may be informative of the underlying altered cortical functions in this syndrome.

Chapter 4

Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task

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Abstract: The analysis of the interaction between novelty and relevance may be of interest to test the aberrant salience hypothesis of schizophrenia. In comparison with other neuroimaging techniques, such as functional magnetic resonance imaging, electroencephalography (EEG) provides high temporal resolution. Therefore, EEG is useful to analyze transient dynamics in neural activity, even in the range of milliseconds. In this study, EEG activity from 31 patients with schizophrenia and 38 controls was analyzed using Shannon spectral entropy (SE) and median frequency (MF). The aim of the study was to quantify differences between distractor (*i.e.*, novelty) and target (*i.e.*, novelty and relevance) tones in an auditory oddball paradigm. Healthy controls displayed a larger SE decrease in response to target stimulus than in response to distractor tones. SE decrease was accompanied by a significant and widespread reduction of MF (*i.e.*, a significant slowing of EEG activity). In comparison with controls, patients showed a significant reduction of changes in SE in response to both target and distractor tones. These differences were also observed in patients that only received a minimal treatment prior to EEG recording. Furthermore, significant changes in SE were inversely correlated to positive and total

symptoms severity for schizophrenia patients. Our findings support the notion that schizophrenia is associated with a reduced response to both novelty and relevance during an auditory P300 task.

4.1. Introduction

The analysis of bioelectrical changes from baseline to the processing stages of an auditory discrimination task using EEG recordings may help to better understand the dynamic information processing abnormalities observed in schizophrenia (Uhlhaas et al., 2010). In particular, exploring aberrant salience correlates in psychosis might be useful (Inouye et al., 1991). Some studies suggest that salience could be altered in schizophrenia (Cortinas et al., 2008). Specifically, a heightened response to novel but irrelevant stimuli (Cortinas et al., 2008) and/or a decreased response to relevant stimuli (Gur et al., 2007) has been associated with this syndrome. Therefore, comparing the response to novelty and relevance between a group of patients with schizophrenia and healthy controls should be of interest to the study of this illness. Salience detection is a short-lived process (Monville et al., 2006). Both novelty (Grondin et al., 2003) and salience (Gralewicz et al., 2003) detection occur in the few hundred milliseconds following stimulus presentation. Thereby, due to its temporal resolution, EEG may be a useful tool to study their respective contributions to schizophrenia.

Auditory ERP oddball paradigms are adequate methods for studying novelty and relevance. For that purpose, they include standard (*i.e.*, frequent), distractor and target (*i.e.*, infrequent) tones. Target and distractor tones are randomly interspersed among a series of standard tones. Distractor tones usually have the same frequency as target tones and a pitch between the target and standard tones. Nevertheless, unlike target tones, distractor tones do not require a response. Hence, distractor tones only possess a novelty component, since they are irrelevant for the task. However, target tones possess both novelty and relevance. A classical approach to analyzing evoked ERP components is to perform the grand-average across trials in the time domain. In the widely used oddball paradigm, the participant is instructed to respond to the target and ignore the distractor tones. Event-related cerebral activity can be observed by averaging in the time domain, while cerebral activity not related to the event is canceled, allowing for the assessment of amplitude and latency of the corresponding ERP. The P3a ERP component is related to novelty. Thus, it is determined from the grand-average amplitude of the responses to the distractor stimuli. On the other hand, P3b is also elicited by infrequent tones but, unlike P3a, it is task relevant. Thereby, P3b is computed from the grand-average amplitude of the responses to the target stimuli (Demiralp et al., 2001; Polich, 2007).

Previous studies indicate that salience detection may be impaired in schizophrenia. This impairment should be reflected in a reduced response to the relevant stimuli of an oddball task (where the participant is instructed to respond only to the target stimuli). Indeed, during the performance of this task, a reduced cerebral activity has been found after the relevant stimuli onset in schizophrenia (Bramon et al., 2004). That reduced activity was supported by a decrease in P3b (*i.e.*, the response to the relevant stimuli) amplitude (Bramon et al., 2004). However, an overall reduced response to novelty may also contribute to salience detection impairment. In oddball tasks, the response to novelty but not relevance can be assessed by means of the P3a potential. This potential arises after the presentation of the distractor stimuli to which the participant should refrain from responding (*i.e.*, irrelevant). A reduced P3a amplitude has also been found in schizophrenia (Hermens et al., 2010; Rissling et al., 2013). It has been observed in first episodes (Kaur et al., 2011) and high-risk participants (Kaur et al., 2011; Mondragón-Maya et al., 2013).

Classical ERP components analyses have several limitations, like the lack of simultaneous information about the time and spectral dynamics of oscillatory components (Roach and Mathalon, 2008; Shannon, 1948). For this reason, time–frequency analyses are carried out. Spectral parameters can yield additional information about time–frequency components of the response to novelty and relevance. Firstly, the median frequency (MF) is a classical technique that has been used to analyze the distribution of the spectral content of a signal. It summarizes the

whole spectral content by means of a measure of the frequency that comprises 50 % of signal power (Poza et al., 2007). Secondly, the Shannon SE has been computed to gain further insights into the characterization of the power spectrum. SE quantifies the degree of disorder of a signal. It is a measure derived from the original notion suggested by Shannon (Shannon, 1948), who defined entropy as the average amount of information of a probability distribution. This concept was extended to EEG power spectral density by Inouye et al. (Inouye et al., 1991). Thus, a high SE value implies a flat, uniform power spectrum with a broad spectral content (*i.e.*, a more complex signal), whereas a low SE indicates a power spectrum with a narrower frequency range (*i.e.*, a more regular signal). In an auditory oddball approach, SE is useful for assessing differences in information content and signal variability average across time. Hence, it can be helpful for the study of cognitive processing substrates. Likewise, SE may contribute to improve our understanding of the altered cortical processing mechanism in mental illness, especially when considering task-related differences between baseline and stimulus response conditions (Bachiller et al., 2014).

To date, MF and SE have been barely used in schizophrenia research. In this regard, Sabeti et al. (Sabeti et al., 2009) assessed their discriminatory ability in comparison with other parameters. They did not find any differences in SE between a group of patients and controls during resting-state activity. However, using a SE-based method, an increased connection entropy in the gamma band was described in patients with schizophrenia (Schoen et al., 2011). In a recent study, our group described a widespread decrease of SE across electrodes in response to the target tone of an auditory oddball task in healthy controls (Bachiller et al., 2014). In that work, patients with schizophrenia showed smaller changes in SE than controls in response to the target tone (Bachiller et al., 2014). Moreover, changes in SE were associated to clinical severity (Bachiller et al., 2014).

In the present research, we further explored the alterations in stimulus processing, likely associated with aberrant salience in schizophrenia. To that end, we studied the changes in SE between baseline and response to both distractor and target tones during a P300 task. Furthermore, we analyzed the responses to relevant (P3b) and novel but irrelevant (P3a) stimuli of participants from our previous study (Bachiller et al., 2014), in order to compare the differences in responses (*i.e.*, changes in SE) to novelty and relevance.

4.2. Materials and methods

4.2.1. Participants

The cohort of participants enrolled in the study was formed by 31 patients with schizophrenia and 38 healthy controls. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013) criteria and were divided into 20 chronic stably treated patients (CP) and 11 minimally treated patients (MTP). Prior to their inclusion, MTP did not receive any previous treatment (first episode patients, $n = 8$) or they had dropped their medications for longer than 1 month. Owing to an acute psychotic state of MTP group, a small amount of haloperidol (2–4 mg) was administered with a wash-out period of approximately 24 h before EEG acquisition. The objective was to minimize the likely bias of only including patients able to cooperate with the EEG recording during an acute psychotic episode and without any previous treatment. The stable patients were previously treated with atypical antipsychotics: risperidone (12 cases, 2–6 mg/day), olanzapine (5 cases, 5–20 mg/day), quetiapine (2 cases, 300–600 mg/day), aripiprazole (1 case, 10–15 mg/day) and clozapine (4 cases, 100–350 mg/day). Four patients received two different antipsychotics. Doses and drugs were unchanged during the 3 months preceding EEG recordings.

The clinical status of the patients was scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The intelligence quotient (IQ) was acquired using the Spanish version of the Wechsler Adult Intelligence Scale 3rd edition (WAIS–III). Demographic and clinical characteristics for both groups are shown in Table 4.1.

The control group was composed of age- and gender-matched participants. They were recruited through newspaper advertisements and remunerated for their cooperation. To discard

Table 4.1: Demographic; clinical, cognitive and EEG parameters. Values are shown as mean (standard deviation, SD); P300 amplitudes are shown in microvolts (μV); *CP*, chronic stable patients, *MTP*, minimally treated patients; *NA* not applicable; *M* male; *F* female. Results of between-groups statistical analyses are shown in the first column (Kruskal-Wallis test, * $p < 0.01$; ** $p < 0.005$; *** $p < 0.001$)

	CP	**MTP**	**Controls**
Total participants (N)	20	11	38
Age (years)	40.37 ± 10.36	33.53 ± 9.91	33.65 ± 13.12
Sex distribution (M:F)	12 : 8	7 : 4	23 : 15
School years*	6.62 ± 3.01	12.47 ± 2.59	NA
PANSS positive	19.26 ± 5.29	21.12 ± 3.99	NA
PANSS negative	22.00 ± 4.80	17.00 ± 4.69	NA
PANSS total	76.26 ± 15.63	76.27 ± 11.37	NA
Total IQ (WAIS-III)**	86.31 ± 14.94	82.18 ± 16.76	101.93 ± 12.44
Number of artifact-free epochs	78.65 ± 19.78	69.90 ± 18.16	84.47 ± 9.32
P3a amplitude (Pz) in μV	2.26 ± 1.17	2.63 ± 1.23	2.53 ± 1.36
P3b amplitude (Pz) in μV^{**}	1.74 ± 1.21	2.78 ± 1.28	3.39 ± 1.59

major psychiatric antecedents (personal or familial) and treatments, they were previously assessed by a semi-structured psychiatric interview by one researcher (V. Molina).

The exclusion criteria can be summarized as follows: (*i*) total IQ below 70; (*ii*) a history of any neurological illness; (*iii*) cranial trauma with loss of consciousness; (*iv*) past or present substance abuse, except nicotine or caffeine; and (*v*) the presence of any other psychiatric process or drug therapy and treatment with drugs known to act on the central nervous system. We discarded toxic use in patients and healthy controls with the information gathered in the interview and a urine analysis.

Written informed consent was obtained from patients, their families and healthy controls after providing full written information. The research boards of the Hospitals of Valladolid and Salamanca endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

4.2.2. Electroencephalographic recording

EEG data were continuously recorded from 17 electrodes using a BrainVision ® (Brain Products GmbH; Munich, Germany) amplifier system. Electrodes were mounted in an electrode cap (Electro-Cap International, Inc.; Eaton, Ohio, USA) at Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz. They were placed according to the revised 10/20 international system. Electrode impedance was always kept under 5 kΩ. Participants were instructed to sit comfortably, relaxed and with their eyes closed to avoid muscle and eye movements. Thirteen minutes-length ERP recordings were acquired at a sampling rate of 250 Hz, while the participants underwent a three-stimulus auditory oddball task. The tones (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) were presented with different frequencies: a 500 Hz-tone target; a 1,000 Hz-tone distractor; and a 2,000 Hz-tone standard stimulus. Random series of 600 tones consisted of target, distractor and standard tones with probabilities of 0.20, 0.20 and 0.60, respectively. The participants were asked to press a button whenever they detected the target tones. P3a and P3b components represent the evoked response, which is associated with event-related changes phase-locked to the stimulus onset (Roach and Mathalon, 2008). They were defined as the mean of ERP grand-average amplitude

in the 300–400 ms interval from distractor and target stimuli, respectively.

The recordings were referenced over Cz electrode. Data were re-referenced to the average activity of all active sensors (Bledowski et al., 2004), since common average reference is less sensitive to microsaccadic artifacts in high-frequency recordings (Keren et al., 2010). Then, each ERP recording was filtered using a 1–70 Hz finite impulse response (FIR) filter and a 50 Hz notch filter. Artifact rejection was conducted following a two-steps approach. Firstly, an independent component analysis (ICA) was carried out to decompose ERPs in a total of 17 components (Delorme and Makeig, 2004). After a visual inspection of the scalp maps and their temporal activation, the components related to eye-blinks were discarded. Secondly, artifacts were automatically rejected using an adaptive thresholding method to remove EEG segments that displayed amplitudes exceeding a statistically based local threshold criterion. EEG recordings were then segmented into 800 ms-length epochs from -250 ms to 550 ms with respect to the onset of the stimulus (200 samples per epoch). The average number of selected epochs for target condition is shown in Table 4.1.

4.2.3. Spectral analysis and definition of parameters

Electromagnetic brain recordings can be characterized by the analysis of their spectral content. Nevertheless, EEG recordings are nonstationary signals, whose characteristics may change over time (Blanco et al., 1995). Nonstationary signal analysis techniques, such as time-frequency distributions, may be appropriate to accurately describe their dynamic properties (Aviyente et al., 2004; Poza et al., 2008). In this work, the short-time Fourier transform (STFT) was used to assess the timeÐfrequency maps of ERP signals. STFT is a sliding temporal window technique used to obtain the time evolution of the PSD. Each 800 ms-length ERP epoch ($M = 200$ samples) was divided into temporal segments of 168 mslength ($L = 41$ samples) with a 90 % overlapping. Thus, we obtained 32 time intervals identified by i ($i = 1, ..., 32$) (Blanco et al., 1995). Finally, the spectral content between 1 and 70 Hz was selected, and PSD was normalized to a scale from 0 to 1, leading to the normalized PSD (PSD_n).

$$PSD_n^{(i)}(f) = \frac{PSD^{(i)}(f)}{\sum_{f=1Hz}^{70Hz} PSD^{(i)}(f)}, \quad i = 1, ..., 32. \tag{4.1}$$

After the normalization, it follows that $\sum_{f=1}^{70Hz} PSD^{(i)}(f) = 1$ for each i. Consequently, PSD_n can be considered as a probability distribution in the band of interest [1 70] Hz. This representation provides a suitable tool for the application of several spectral parameters. Figure A1 shows four examples of normalized spectrograms for distractor and target conditions, corresponding to a healthy control and a patient with schizophrenia. That figure depicts the stimulus response percent of change from baseline.

4.2.4. Spectral entropy

Entropy is a thermodynamic function whose original meaning involves uncertainty of information, in terms of disorder, discrepancy and diversity (Bezerianos et al., 2003). Entropy was adapted to the context of information theory by Shannon (Shannon, 1948). Hence, SE can be defined as a disorder quantifier. A uniform spectrum with a broad spectral content (e.g., white noise) yields a high SE value. On the contrary, a narrow power spectrum with only a few spectral components (e.g., a sum of sinusoids) gives a low

SE value (Inouye et al., 1991). To calculate SE, we applied the definition of Shannon's entropy computed over PSD_n (Poza et al., 2008).

$$SE^{(i)} = -\frac{1}{\log L} \sum_{f=1Hz}^{70Hz} PSD_n^{(i)}(f) \log \left[PSD_n^{(i)}(f)\right], i = 1, ..., 32. \tag{4.2}$$

where L is the number of spectral components in the [1, 70] Hz band.

4.2.5. Median frequency

Median frequency provides an alternative way to summarize the changes in the spectral content of EEG recordings. It is defined as the frequency that comprises 50 % of the power (Poza et al., 2007). MF is calculated from PSDn between 1 Hz and 70 Hz.

$$\sum_{f=1Hz}^{MF^{(i)}} PSD_n^{(i)}(f) = 0.5, \quad i = 1, ..., 32. \tag{4.3}$$

4.2.6. Parameter baseline correction

Baseline correction was carried out in order to obtain a stimulus-independent characterization. The time-frequency analysis provides a SE and a MF value for each temporal segment. The baseline and the stimulus response were defined as the available [-250 0] and [150 550] ms intervals, respectively. The baseline correction was then carried out using the "percent change from baseline method" (Roach and Mathalon, 2008). For that purpose, a pre-stimulus parameter mean was firstly obtained as the average of baseline values. Then, the pre-stimulus parameter mean was subtracted from the stimulus response values, and the result was divided by the pre-stimulus parameter mean. Finally, values were averaged in order to obtain a baseline-corrected parameter for each participant.

$$SE = \left(\frac{SE^{(i)}|_{i \in response} - SE^{(i)}|_{i \in baseline}}{SE^{(i)}|_{i \in baseline}} \right), \quad i = 1, ..., 32. \tag{4.4}$$

where $\langle \cdot \rangle$ denotes the temporal average in the baseline and response windows.

Figure A2 depicts MF and SE baseline-corrected values for distractor and target conditions, corresponding to a healthy control and a patient with schizophrenia. This figure illustrates time-varying differences between the response to distractor and target stimulus.

4.2.7. Statistical analyses

The statistical analyses were carried out in a four steps approach: (1) demographic, clinical and EEG parameters analysis; (2) exploratory analysis; (3) electrode-level statistical analysis; and (4) clinical correlation analysis.

Initially, sex distribution, age, completed courses, IQ, and P3a and P3b amplitudes were compared between patients and controls.

Thereafter, data distribution was assessed by an exploratory analysis. The Kolmogorov-Smirnov and Levene tests were used to check for normality and homoscedasticity, respectively. The results indicate that parametric test assumptions did not hold.

To explore the electrode-level differences between patients and controls, both within- and between-groups significance maps were computed. In a first step, within group differences were assessed using Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$

electrodes = 0.0029) for the target and the distractor tones, comparing SE and MF values from baseline [-250 0] ms and stimulus response [150 550] ms windows. In a second step, between-groups differences for SE and MF baseline corrected values were assessed by means of Mann-Whitney U-tests (Bonferroni corrected, $\alpha = 0.05/17 = 0.0029$; trend $\alpha = 0.0058$). The analyses were complemented in a second step by further statistical comparisons between both groups of patients (*i.e.*, CP and MTP) using Mann-Whitney U-tests (uncorrected in this case, given the confirmatory purpose of this subtest). In order to minimize the possible influence of chronicity and treatment on spectral parameters, SE and MF were compared between patients and controls (p level corrected for multiple comparisons). Thereafter, we assessed whether: (a) the same pattern appeared in the comparison between MTP and controls, and (b) no differences were found between both patients groups. Additionally, stimulus responses to distractor and target tones were compared in a third step. Wilcoxon signed-rank tests (Bonferroni corrected, $\alpha = 0.05/17$ electrodes = 0.0029) were performed to assess within-group differences for baseline-corrected SE and MF responses to both stimuli.

Finally, correlations between spectral parameters and clinical relevance were evaluated by means of stepwise multivariate linear regressions. PANSS positive, negative and total scores were used as dependent variables and SE values at each sensor were introduced as predictive variables. In addition, the relationship between antipsychotic dose in mg of chlorpromazine (CPZ) equivalents/day, and change of MF and SE was assessed using Spearman's rho coefficients.

4.3. Results

Table 4.1 summarizes demographic, clinical and EEG parameters, as well as between-group comparisons. Nonsignificant differences were found in age or sex distribution between patients and controls. Total IQ and P3b amplitude was significantly lower in patients in comparison with controls. On the contrary, P3a amplitude did not differ significantly between patients and controls.

4.3.1. Within-group differences

4.3.1.1. Healthy controls

Healthy controls showed a global SE decrease (except at occipital electrodes) from baseline to target stimulus response (Figure 4.1a). Likewise, controls displayed a statistically significant and global MF decrease in all electrodes (Figure 4.2a). In response to the distractor tone (Figure 4.1b), controls showed a statistically significant SE decrease, localized over central, left parietal and posterior frontal regions. In addition, controls displayed a statistically significant and widespread MF decrease (Figure 4.2b). In this group, the assessment of the differences between responses to distractor and target tones revealed a statistically significant larger SE and MF decrease in response to target (Figure 4.3), including central, frontal and parietal sensors.

4.3.1.2. Patients

Patients showed a statistically significant SE decrease from baseline to target response, mainly localized around Pz (Figure 4.1a). A SE decrease was not observed in the MTP group considered alone. A MF decrease was observed in response to target over central and right frontal sensors, but not in the MTP group considered alone (Figure 4.2a).

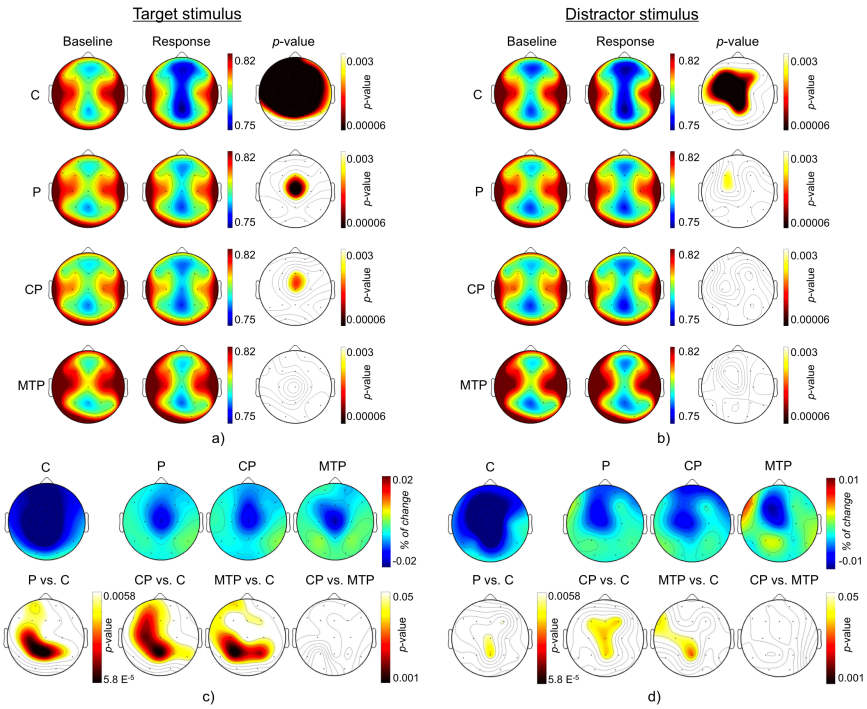

Figure 4.1: *SE* topographic maps for target (a, c) and distractor (b, d) stimuli. (**a**) *SE* topographic maps at baseline, active response to target tone and within-groups statistical analyses; (**b**) *SE* topographic maps at baseline, active response to distractor tone and within-groups statistical analyses; (**c**), (**d**) topographic maps depicting the difference between active and baseline SE values for each group and between-groups statistical analyses for target and distractor tones, respectively. *SE* spectral entropy, *P* patients, *CP* chronic patients, *MTP* minimally treated patients, *C* controls.

In response to the distractor tone (Figure 4.1b), patients did not show any statistically significant difference in SE (not for all patients or for the MTP group considered alone). On the other hand, patients with schizophrenia exhibited a MF decrease over anterior central sensors, though this result was not observed in the MTP group considered alone (Figure 4.2b).

In the patients group, statistically significant differences between target and distractor responses were observed when analyzing changes in SE. Distractor SE was significantly smaller than target SE over a localized region around Pz (similar results were obtained for both CP and MTP groups). The MF decrease in patients was significantly larger in the target response than in the distractor response over parieto-central and right frontal electrodes (Figure 4.3).

4.3.2. Differences between patients and controls

The between-group analyses of SE response to target revealed a significantly smaller SE response in patients with schizophrenia than in controls (both for CP and for MTP groups assessed separately), over posterior and central regions, and extending to left parietal and left frontal sensors (Figure 4.1c). Patients also showed a significantly smaller MF change in response to target than controls over posterior, central and left parietal

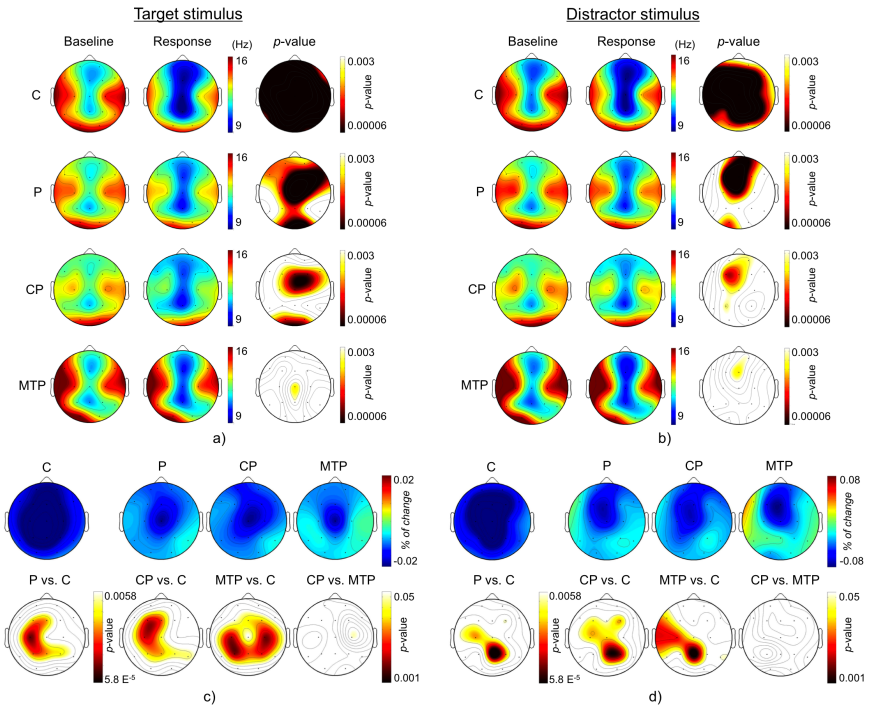

Figure 4.2: *MF* topographic maps for target (a, c) and distractor (b, d) stimuli. (**a**) *MF* topographic maps at baseline, active response to target tone and within-groups statistical analyses; (**b**) *MF* topographic maps at baseline, active response to distractor tone and within-groups statistical analyses; (**c**), (**d**) topographic maps depicting the difference between active and baseline *MF* values for each group and between-groups statistical analyses for target and distractor tones, respectively. *MF* median frequency, *P* patients, *CP* chronic patients, *MTP* minimally treated patients, *C* controls.

regions (also including right parietal sensors in the MTP group; Figure 4.2c). A slight SE change in response to distractor was observed. Although statistically significant differences were obtained, the change in SE was smaller in patients with schizophrenia than in controls, over posterior and central regions. MF decrease in response to distractor was significantly smaller for patients than controls over Pz (Figures 4.1d, 4.2d).

4.3.3. Clinical relevance

Changes in SE from baseline to target were associated with positive and total PANSS scores (*i.e.*, the smaller the SE decrease from baseline to target, the higher the clinical scores). This finding was in agreement with the results reported in a previous study (Bachiller et al., 2014).

A similar pattern was observed when the SE response to distractor was analyzed. Hence, the difference in SE between distractor and baseline segments at C3 was chosen as a direct predictor of positive ($R^2 = 0.263$; $p = 0.021$; $b = 0.513$, $t = 2.53$) and total ($R^2 = 0.242$; $p = 0.028$; $b = 0.492$, $t = 2.39$) PANSS scores in the stepwise regression (Figure 4.4).

Finally, the relations between mean dose, and change in SE and MF were not statistically significant ($q < 0.15$).

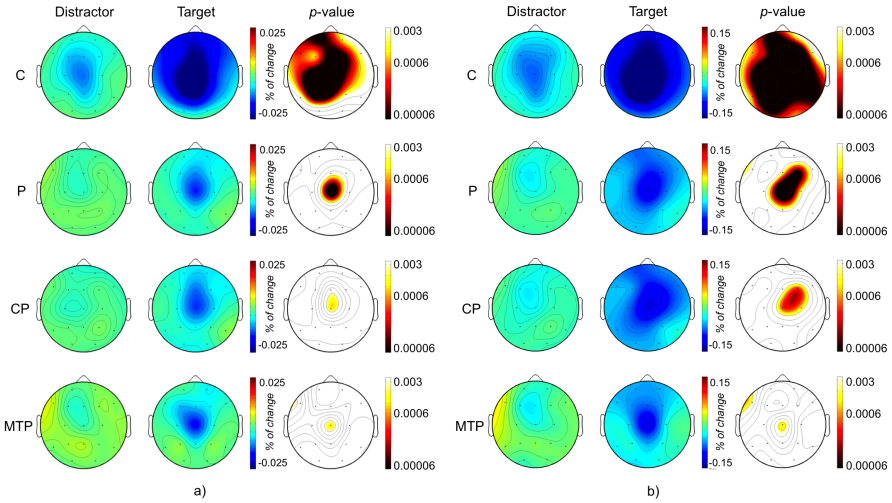

Figure 4.3: Comparison of the percent of change in *SE* (**a**) and *MF* (**b**) from baseline to active window for each group. Each row depicts the averaged percent of change from baseline in each group for distractor and target tones, as well as the within-group differences between both conditions. *SE* spectral entropy, *MF* median frequency.

4.4. Discussion and conclusions

In the present study, we found that bioelectrical responses to both novelty and relevance during an auditory oddball task were attenuated in patients with schizophrenia, especially in the MTP group. In addition, we observed that the amount of modulation with both target and distractor tones was correlated with clinical symptoms. Specifically, patients with schizophrenia with slight SE changes in response to both distractor and target tones exhibited increased severe positive and total symptoms.

In one hand, the response to the distractor stimuli involves novelty detection. On the other hand, the response to the target stimuli is associated with novelty and relevance detection, as well as with response to relevance. Healthy controls showed a larger modulation of the oscillatory activity in response to the target than patients, which suggests a more intense and/or widespread activation of cerebral resources in response to relevance. In this group, both MF and SE displayed a larger response to target in comparison with distractor, over central, parietal and frontal regions (Figure 4.3). This result would indicate that relevance detection was associated with a slowing of the spectrum in these areas. In particular, both MF and SE showed a significant change with target, but not with distractor tones, over orbitofrontal sensors. This finding seems coherent with the proposed role for inferior frontal areas in relevance detection in healthy participants (Hattori et al., 1993). Moreover, the large response to target tones for healthy participants would agree with an increased coherence of relatively distant regions underlying salience detection, which is in turn consistent with functional magnetic resonance imaging (fMRI) data (Ardekani et al., 2002; Casey et al., 2001). However, the activity modulation was significantly smaller in patients under both conditions (in particular in the MTP group) than in controls, which would suggest that response to both novelty and salience is flattened in schizophrenia. Nevertheless, this attenuated response may still contribute to aberrant salience (*i.e.*, by conferring less relevance to those stimuli that under normal conditions should be perceived as more salient). Other researchers

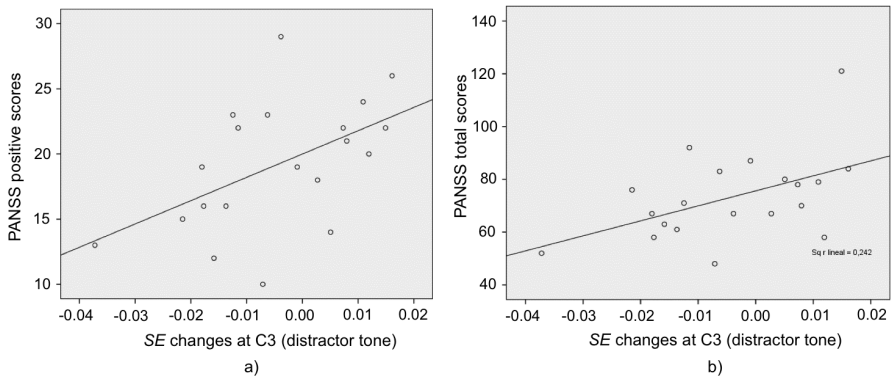

Figure 4.4: Scatterplots showing the association between *SE* changes in response to distractor tones during a P300 task and positive (**a**) and total (**b**) PANSS scores. SE changes represent the proportion of change ((*SE* active-*SE* baseline)/*SE* baseline). Thereby, more positive values imply less entropy decrease during the active condition (target or distractor). These associations are similar to those found with the responses to target tones in a previous study *SE* spectral entropy.

reported reduced connectivity in distributed networks underlying salience processing in schizophrenia (Rozas and Garcia, 1997), which is in agreement with the reduced response observed in our patients. Orbito-frontal and anterior cingulate areas are key components of the salience network (Olsson et al., 1995). In our study, sensors over these regions were conspicuously inactive in response to target tones, indicating a salience detection malfunction in schizophrenia.

The large and extended entropy decrease in controls for both conditions can be associated with an irregularity decrease of the EEG signal during the processing of target and (to a lesser degree) distractor tones. SE decrease was accompanied by a similar MF decrease, which suggests an increasing contribution of low-frequency bands to the EEG spectrum. The absence of significant P3a amplitude differences between patients and controls could be related to the weak statistically significant results obtained by SE for distractor tones. In addition, it may be associated with an improved ability of SE and MF to detect relevant neural activity differences when compared to amplitude-based methods. In healthy participants, P3a has been associated with a transitory increase of theta oscillations (Demiralp et al., 2001; Polich, 2007), which seems consistent with the observed MF decrease. Transitory coordination of EEG activity among distant regions could be mediated by theta rhythms (von Stein and Sarnthein, 2000). The observed MF decrease may support this fact, as well as previous fMRI studies that obtained a correlation between target detection in auditory oddball tasks and a spatially distributed cortical and subcortical activation (Ardekani et al., 2002; Casey et al., 2001).

In a previous fMRI study, brain activity from CP with schizophrenia was acquired during a three-tone auditory oddball task (Laurens et al., 2005). Their findings indicated that perfusion was increased in both patients and controls during novel stimuli as compared to nontarget baseline over limbic-paralimbic and association cortices, as well as subcortical structures [26]. These results are in agreement with the EEG spectrum modulation across all electrodes observed in our study. Moreover, also in accordance with our findings, the results obtained by Laurens et al. (Laurens et al., 2005) showed a widespread hypoactivation in response to novelty in patients. Nevertheless, they did not detect statistically significant differences in target versus novel stimuli processing, which

may be due to the limited temporal resolution of fMRI. Certainly, if any differences between target and distractor processing are circumscribed to a short temporal window, they could go undetected with fMRI.

The reduced response observed in our study is consistent with a hypodopaminergic state in the cortex, as proposed in schizophrenia (Davis et al., 1991; Okubo et al., 1997). Indeed, met/met homozygotes for the catechol-O-methytransferase (COMT) gene (with smaller efficacy in degrading synaptic dopamine and, thus, with a longer duration of dopamine in the synapses) showed an enhanced P3a amplitude at Fz (Heitland et al., 2013). It could be possible that a cortical hypodopaminergia underlies the reduced response to relevance and novelty in our patients. Nevertheless, this does not imply that hypodopaminergia is common to all patients with schizophrenia.

Potential limitations of the study merit further discussion. All patients with schizophrenia were receiving antipsychotic treatment that may have flattened their response. Clearly, our data need to be replicated in untreated and preferably neuroleptic-naïve patients. However, medication is unlikely the only reason for the present findings, since: (*i*) SE and MF modulation was smaller in MTP than in CP, and (*ii*) in our previous study (Bachiller et al., 2014), we found that the administration of single doses of haloperidol did not modify SE or MF response to target in a group of healthy participants. Likewise, it is noteworthy that the cohort of subjects enrolled in the study was limited. The statistical power analyses indicated that this sample size is sufficient for obtaining statistically significant results. Nevertheless, a large database would be helpful to confirm our findings.

In summary, patients with schizophrenia showed less SE change in response to both distractor and target tones than healthy controls. Furthermore, changes in SE were related to clinical symptoms. These results support the notion that schizophrenia is associated with a decreased response to both relevance and novelty, which in turn might contribute to the aberrant salience in this syndrome through a hampered differentiation between background and salient stimuli.

Chapter 5

Auditory P3a and P3b neural generators in schizophrenia: An adaptive sLORETA P300 localization approach

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Abstract: The present study investigates the neural substrates underlying cognitive processing in schizophrenia patients. To this end, an auditory 3-stimulus oddball paradigm was used to identify P3a and P3b components, elicited by rare-distractor and rare-target tones, respectively. Event-related potentials (ERP) were recorded from 31 schizophrenia patients and 38 healthy controls. The P3a and P3b brain-source generators were identified by time-averaging of low-resolution brain electromagnetic tomography (LORETA) current density images. In contrast with the commonly used fixed window of interest (WOI), we proposed to apply an adaptive WOI, which takes into account subjects' P300 latency variability. Our results showed different P3a and P3b source activation patterns in both groups. P3b sources included frontal, parietal and limbic lobes, whereas P3a response generators were localized over bilateral frontal and superior temporal regions. These areas have been related to the discrimination of auditory stimulus and to the inhibition (P3a) or the initiation (P3b) of motor response in a cognitive task. In addition, differences in source localization between schizophrenia and control groups were observed.

Schizophrenia patients showed lower P3b source activity in bilateral frontal structures and the cingulate. P3a generators were less widespread for schizophrenia patients than for controls in right superior, medial and middle frontal gyrus. Our findings suggest that target and distractor processing involves distinct attentional subsystems, both being altered in schizophrenia. Hence, the study of neuroelectric brain information can provide further insights to understand cognitive processes and underlying mechanisms in schizophrenia.

5.1. Introduction

Alterations in cognitive processing in schizophrenia have long been assessed using EEG recordings (Roach and Mathalon, 2008). In particular, it is usual to obtain the ERP as the average of EEG epochs time-locked to repeated external stimulus or events. Reduced P300 amplitude during an auditory oddball paradigm is one of the most consistent findings in schizophrenia (Bramon et al., 2004); however, the neural bases of this amplitude reduction are incompletely understood. In this regard, the analyses focused on the localization of neural generators can contribute to elucidate possible sources of altered information processing in schizophrenia (Mulert et al., 2004).

The oddball paradigm is a common experimental design used in ERP analyses to obtain the P300 wave. The 3-stimulus variant of the auditory-oddball paradigm is characterized by infrequent-distractor stimuli interspersed randomly into a sequence of frequent-standard and rare-target. This paradigm allows the examination of cognitive processing as response to both relevant and irrelevant stimuli (Polich, 2007). The resulting P300 wave includes two components: the P3a, evoked by distractor stimuli for which no subject-response is expected; and the P3b, elicited by target stimuli for which the subject is instructed to respond. The neural processing as a response to auditory distractor tones has been related to bottom-up attentional mechanisms; hence, P3a may be generated whether sufficient attentional focus is engaged. In contrast, P3b seems to be related to conscious top-down target processing, likely contributing to processing the stimulus information and performing cognitive response (Polich, 2007; Strobel et al., 2008). In previous reports, we found a blunted ERP modulation in schizophrenia as response to both target (Bachiller et al., 2014) and distractor (Bachiller et al., 2015a) tones during an oddball paradigm. Thus, the analysis of the differences in neural pattern generators between schizophrenia patients and healthy controls becomes an interesting research topic to clarify the neural substrate of reduced P300 amplitude in schizophrenia.

Source imaging techniques may help to detect neural generators that contribute to the scalp recorded ERPs, resulting in an acceptable compromise between spatial and temporal resolutions. The inverse solution (*i.e.* the computation of 3-D intracerebral images of electric neuronal activity based on scalp-recorded EEG) would provide useful information on the time course and localization of brain functions (Pascual-Marqui et al., 2002). There is no unique solution to the inverse problem; nevertheless, the low-resolution brain electromagnetic tomography (LORETA) is one of the most reliable methods for localizing ERP electrical activity and it is associated with relatively low error rates (Jung et al., 2012; Pascual-Marqui et al., 2002). LORETA has been widely used for source localization in psychiatric disorders, such as schizophrenia or depression (Kawasaki et al., 2004; Mientus et al., 2002). Moreover, auditory P3a and P3b source localization has been previously addressed in healthy controls using LORETA and functional magnetic resonance imaging (fMRI). P3a generators are localized in anterior cingulate, frontal area and parietal cortices (Polich, 2007; Strobel et al., 2008; Volpe et al., 2007), whereas P3b sources include amore distributed network, involving superior and medial temporal,

posterior parietal, hippocampal, cingulate and frontal structures (Polich, 2007; Strobel et al., 2008; Volpe et al., 2007; Wronka et al., 2012).

It is noteworthy that the previous LORETA findings are influenced by one important technical shortcoming: although ERP analyses show a considerable inter-subject variability of P300 latency (Campanella et al., 1999), LORETA source imaging studies commonly used a large fixed post-stimulus window of interest (WOI), like [250 500] ms (Higuchi et al., 2008; Kawasaki et al., 2007; Sumiyoshi et al., 2006), [280 450] ms (Wang et al., 2003, 2010), [240 420] ms (Pae et al., 2003), [227 383] ms (Volpe et al., 2007), or [400 700] ms (Wronka et al., 2012).

In this study we proposed a new LORETA approach based on P300 wave (*P300 latency adaptive WOI*) to properly localize P300 brain-source generators in each subject. To the best of our knowledge, this is the first study that analyzes the sources of both P3a and P3b in schizophrenia using LORETA. Hence, this research is aimed at: (*i*) analyzing the performance of the adaptive WOI method in comparison to conventional fixed WOI analysis; and (*ii*) applying the adaptive WOI method to analyze the differences of auditory P3a and P3b underlying cortical sources between schizophrenia patients and healthy controls.

5.2. Materials and methods

5.2.1. Subjects

Thirty-one patients with paranoid schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV-TR, criteria) and 38 healthy controls were recruited. Schizophrenia group was composed by 20 chronic stably treated patients, 7 fist-episode patients and 4 patients who had dropped their medications for a period longer than 6 months. Chronic patients were previously treated with atypical antipsychotics. First-episode patients have not been received previous antipsychotic treatment, except for a brief time interval of less than 72 h prior to EEG acquisition. No medications were administered to the patients during the 12 h preceding the EEG recording. Controls were initially assessed by a semi-structured psychiatric interview to discard major psychiatric antecedents and treatments. Detailed description of treatments and doses, as well as exclusion criteria are detailed in previous reports (Bachiller et al., 2015a,b). Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Socio-demographic and clinical characteristics for both groups are shown in Table 5.1.

The research boards of the Hospitals of Valladolid and Salamanca (Spain) endorsed the study according to The Code of Ethics of the WorldMedical Association (Declaration of Helsinki).Moreover, written informed consent was obtained from patients, their caregivers and healthy volunteers.

5.2.2. EEG recording procedure

EEG recordings were performed while subjects underwent a 3-stimulus auditory-oddball paradigm. Participants heard a random series of 600 binaural tones (90 dB; 50 ms duration; 5 ms rise and fall-time) consisting of standard (2000 Hz tone), distractor (1000 Hz tone) and target tones (500 Hz tone) with probabilities of 0.6, 0.2 and 0.2, respectively (Bachiller et al., 2015a). For each subject, 13 min of EEG activity and stimulus markers were continuously recorded using a 17-channel (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T5, T6, Fz, Pz and Cz) EEG system (BrainVision®, Brain Products GmbH; Munich, Germany). Electrodes were placed according to the revised 10/20 International System. Participants were relaxed and with their eyes closed. EEG

Table 5.1: Socio-demographic and clinical characteristics of the cohort of subjects enrolled in the study. Values are shown as "mean ± standard deviation, *SD*". Post-stimulus P300 latency was calculated over a target response using a 9-sample moving average. P3a and P3b amplitudes were obtained from distractor and target responses, respectively. Significance of between-group comparisons is shown in the first column (Kruskal–Wallis test, * $p < 0.05$; ** $p < 0.001$). *aWOI* adaptive window of interest, *CP* chronic patients, *MTP* minimally treated patients, *M* male, *F* female, *NA* not applicable.

	Schizophrenia patients	**Controls**
Age (years)	36.25 ± 9.62	33.35 ± 12.26
Gender (M:F)	21 : 10	23 : 15
PANSS positive	19.19 ± 4.81	NA
PANSS negative	19.52 ± 5.69	NA
PANSS total	73.19 ± 15.94	NA
Duration of the illness (months)	79.73 ± 103.37	NA
Number of artifact-free epochs	88.85 ± 16.15	84.47 ± 9.32
P300 latency at Pz (ms)	435.23 ± 67.82	413.05 ± 72.95
aWOI length (ms)	124.26 ± 61.66	117.47 ± 47.53
aWOI lower limit (ms)	375.48 ± 61.66	357.79 ± 66.33
aWOI upper limit (ms)	499.74 ± 85.76	475.26 ± 91.94
P3a amplitude (Pz) in μV^{**}	0.70 ± 0.82	1.62 ± 1.21
P3b amplitude (Pz) in μV^{*}	2.16 ± 1.18	3.10 ± 1.47

data were recorded at a sampling frequency of 250 Hz and referenced over Cz electrode. Electrode impedance was always kept under 5 kΩ. Each EEG recording was off-line re-referenced to the common average (Bledowski et al., 2004) and digitally filtered using a [0.5 40] Hz finite impulse response filter. Then, a three-step artifact rejection method was applied. Firstly, an independent component analysis was performed to decompose EEG signals (Delorme and Makeig, 2004). After a visual inspection of the scalp maps and their temporal activation, components related to eye blinks were discarded. In a second step, continuous EEG data were segmented from –100 ms before target stimulus onset to 900 ms after onset. In a third step, artifacts were automatically rejected using an adaptive thresholding method (Bachiller et al., 2015a). Finally, the responses to distractor and target tones were baseline-corrected by subtracting the 100 ms pre-stimulus mean and they were averaged across time-locked trials to obtain ERP data for each channel (Pae et al., 2003).

5.2.3. Identification of ERP components

The P300 wave is an ERP component commonly used to assess the neural underpinnings of cognition (Polich, 2007). P300 amplitude is obtained from ERP data as the most positive voltage between 250 and 550 ms, whereas P300 latency is defined as the time point from stimulus onset at which the peak amplitude is found (Polich, 2007). A P300 latency variability has been found across different subjects, which may be related to inter-subject anatomical variability and differences in cognitive attentional processing (Campanella et al., 1999; Polich and Herbst, 2000). In addition, it has been previously shown that P300 latency varies with the discriminability of relevant stimuli: the most difficult is to identify the stimuli, the greater the latency (Furdea et al., 2009; Sellers and Donchin, 2006; Squires et al., 1977). Indeed, this result can be also observed in our database: Figure 5.1a shows a large P300 latency variability for healthy controls and schizophrenia patients. An adaptive WOI takes into account changes in peak la-

tency across subjects. Therefore, the selection of the WOI can be critical to characterize neural generators (Kim et al., 2014).

In spite of such latency variability, most of the previous P300 source studies applying LORETA have been carried out using a fixed WOI. Recent researches proposed the use of two different fixed WOIs, one for schizophrenia patients and other for healthy controls (Jung et al., 2012; Kim et al., 2013, 2014). Nevertheless, this methodology does not take into account the P300 variability among subjects within each group. In order to overcome this limitation, and therefore to improve P3a and P3b detection and source localization procedures, we propose an algorithm for identifying a subject-specific WOI based on N200–P300 waves. The N200 wave is a negative voltage observed as a response to a visual or an auditory task. It reflects the detection of some type of mismatch between stimulus features (Folstein and Van Petten, 2008).

The proposed subject-specific algorithm was divided into two steps. Firstly, the ERP wave was filtered by a moving average of 9 samples (36 ms), a smoothing procedure commonly used in P300 detection (Furdea et al., 2009; Sellers and Donchin, 2006). Then, a subject-adaptive WOI threshold was established using the 75% rise time from N200 amplitude to P300 amplitude (*i.e.* the time to reach 75% of the P300 peak amplitude (Mooney and Prather, 2005)).

$$WOI_{threshold} = N200_{Amp} + 0.75 \cdot (P300_{Amp} - N200_{Amp}) \,. \tag{5.1}$$

Adaptive WOI interval was obtained as the time points where the ERP amplitude increases up to $WOI_{threshold}$ before P300 and decreases down to $WOI_{threshold}$ after P300. Figure 5.1 displays P300 latency values and adaptiveWOI limits for all subjects. In addition, it shows how adaptive WOI is better fitted to the P300 component than a fixed WOI.

5.2.4. sLORETA

Bioelectrical ERP neural sources distribution was assessed using standardized LORETA (sLORETA) software, which estimates a particular solution of the non-unique EEG inverse solution (Pascual-Marqui et al., 2002). sLORETA software divides the brain into a total of 6239 cubic voxels with 5 mm resolution and estimates the source current density (*i.e.* the sum of electric neuronal activity on each defined voxel) (Pascual-Marqui et al., 2002). In particular, sLORETA source current density are calculated from scalp-recorded ERP using a realistic head model from Montreal Neurological Institute (MNI) (Mazziotta et al., 2001), in which the 3-D solution space was restricted to only the cortical gray matter (Lancaster et al., 2000). Compared to previous versions of LORETA, sLORETA is superior in temporal resolution and has fewer localization errors (Kim et al., 2014). Thus, sLORETA has been used in several studies to investigate brain sources during the generation of ERP components, such as P300 (Jung et al., 2012; Kim et al., 2013, 2014; Sumiyoshi et al., 2009).

In order to consider P300 latency changes across subjects, P3a and P3b source images for each participant were averaged using the time window defined by their subject-adaptive WOI. Figure 5.1d shows an example of differences in brain activation patterns for fixed and adaptive WOI.

5.2.5. Statistical analysis

Statistical differences between P3a and P3b sLORETA images were assessed by t-tests, computed for log-transformed sLORETA current density at each voxel (Volpe et al.,

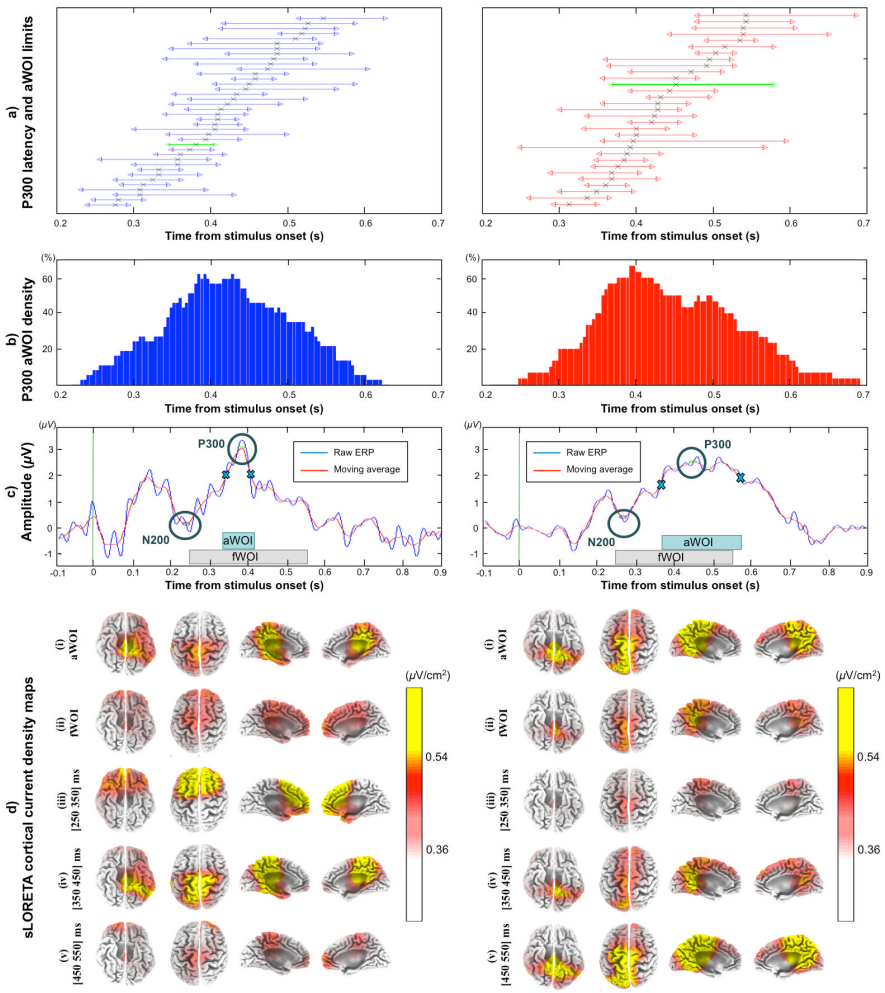

Figure 5.1: Latency and adaptive WOI (*aWOI*) for each subject. Healthy controls were displayed at left column and schizophrenia patients at right column. A large latency and *aWOI* variability across subjects can be observed. **(a)** P300 latency values (in seconds) are represented using a black "X" and *aWOI* limits are depicted using an arrow. Each arrow represents a particular subject ($n = 38$ for healthy controls and $n = 31$ for schizophrenia patients). They were sorted along Y-axis according to P300 response latency. Green arrows represent *aWOI* limits for the two subjects displayed in the Figure 5.1c. **(b)** P300 aWOI density distribution for each group. The bar plot displays a probability map for each group. It represents the percentage of subjects (in %) whose adaptiveWOI is considered for each post-stimulus time sample. **(c)** Baseline corrected ERP and 9-samples moving average waveforms at Pz electrode for a healthy control (left) and a schizophrenia patient (right). The P300 and N200 components, as well as fixed WOI (*fWOI*) and aWOI ranges, are highlighted. In addition, the figure shows the comparison between the length of aWOI and conventional fWOI [250 550]ms post-stimulus. (d) sLORETA cortical current density maps are represented for: (*i*) *aWOI*; (*ii*) [250 550]ms *fWOI*; (*iii*) [250 350] ms-window; (*iv*) [350 450] ms-window; (*v*) [450 550] ms-window. Source activity for *fWOI* is more distributed over the brain than for *aWOI*, since sLORETA averaging over a *fWOI* includes some source information non-related to P300 component. Furthermore, detailed 100 ms-length window analyses show how the source density changes over time.

2007). Schizophrenia patients were compared to healthy controls in order to identify the effect of illness in neural generators. Within-group differences between P3a and P3b were evaluated using voxel-by-voxel paired-sample t-tests,whereas voxel-by-voxel independent t-tests were conducted to analyze between-group statistics. To correct for multiple comparisons, two nonparametric permutations tests (NPT) based on the theory of randomization were applied: (i) voxel intensity and (ii) cluster size (Nichols and Holmes, 2002). Voxel intensity NPT calculates a critical t-value by means of a random sample of all the possible permutations to estimate the distribution of the maximum t-statistic. Based on the hypothesis that the activated/deactivated brain region is expected to occur in a cluster of voxels, rather than in isolated voxels, cluster size NPT is a version of voxel intensity test, which allows the calculation of the critical cluster size to be considered significant. Both NPTs provide a corrected p-value (p_{cor}), which is used to identify statistically significant results.

5.3. Results

Table 5.1 presents the grand-average ERP amplitude and latency values, as well as the adaptive WOI length and the corresponding aWOI limits for each group. Statistically significant differences between groups (Kruskal–Wallis test, $p < 0.05$) were only obtained for P3a ($p = 0.0007$) and P3b ($p = 0.0036$) amplitudes. Although a large P300 latency and an adaptive WOI variability across subjects have been observed (Figure 5.1), non-statistical differences between groups were obtained.

Based on the observation of normalized grand-averages of auditory P3a and P3b brain sources for schizophrenia patients and healthy controls (Figure 5.2), P3a response sources were mainly localized in bilateral frontal (superior, medial and inferior gyrus) and right superior temporal lobes. On the other hand, P3b sources were observed over a large distributed network, including cingulate gyrus, as well as bilateral frontal lobe and parietal lobe (Figure 5.2).

Figure 5.3 depicts sLORETA t-statistics maps for within-group comparisons between distractor and target stimulus type. Both groups exhibit a greater P3b source current density than P3a response. Statistical differences were located mainly in bilateral limbic lobe and parietal structures (voxel intensity NPT, $p_{cor} < 0.05$). Furthermore, a P3b

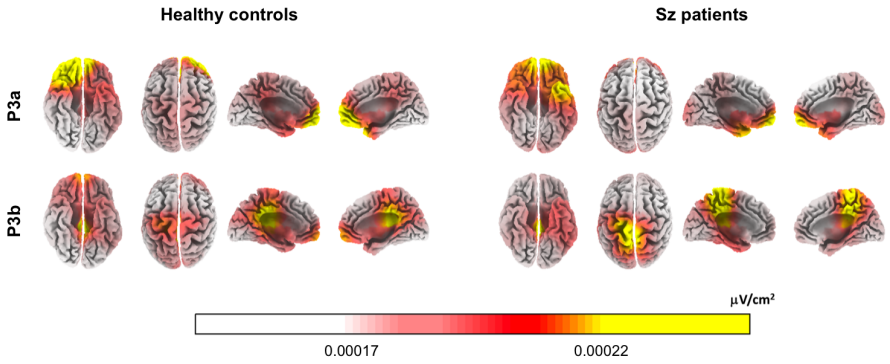

Figure 5.2: Grand-average of normalized cortical current density in healthy controls (left) and schizophrenia patients (right) as a response to distractor (P3a) and target (P3b) tones. In order to reduce inter-subject variability, sLORETA current density at each voxel is normalized by the sum of current density across all voxels. Therefore, the sum of normalized voxel densities will be the unit.

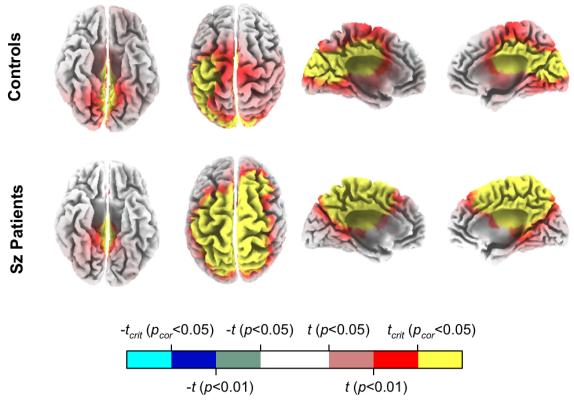

Figure 5.3: Three dimensional sLORETA maps of voxel-by-voxel paired sample t-statistics for healthy controls and schizophrenia patients. The cortical current density of P3b and P3a components is compared for each subject. The scale shows negative (blue) and positive (yellow) t-values for which alpha is statistically significant after voxel intensity NPT correction for multiple comparisons. An increase of P3b source activity from P3a is represented in yellow and vice versa.

source current density increase was observed for schizophrenia patients mainly in bilateral parietal and limbic lobes, as well as superior and medial frontal regions (Figure 5.3, Table 5.2).

A smaller source current density in schizophrenia patients in comparison with controlswas obtained for both components: P3a and P3b. Nevertheless, differences in neural activation patterns depended on stimulus tone. Figure 5.4 shows the statistically significant t-values distribution for P3a and P3b (cluster size NPT, $p_{cor} < 0.05$). In particular, P3b source current density was significantly smaller for schizophrenia patients than for controls in superior, middle and medial frontal gyrus, and cingulate gyrus. On the other hand, reduced P3a in schizophrenia patients was mainly observed in frontal areas (Table 5.3).

5.4. Discussion

The aim of the present studywas to provide further insights into the neural correlates of target (P3b) and distractor (P3a) processing in schizophrenia. A 3-tone auditory-oddball paradigm was used to characterize P3b and P3a brain sources and to compare them between schizophrenia patients and controls.

Firstly, regarding the validity of the proposed P300 latency adaptive WOI algorithm, our research shows how the selection of the WOI influences the sLORETA findings. A wide fixed WOI has been commonly used to solve the problem of P300 latency variability (Kim et al., 2014). However, sLORETA image averaging over a fixedWOI can include several activities strictly non-related to the P300 component. A fixed WOI commonly obtains a smoother source current density that includes a large source activity in medial and superior frontal structures. This frontal activation may be caused by the inclusion of N200 component in the fixed WOI. As shown in Figure 5.1d, an adaptive WOI allows focusing on the brain-source generators of P300 component. Consequently, we can conclude that an adaptive WOI may improve P300 source localization procedures.

Table 5.2: Results of within-group (P3b vs P3a) analyses. Critical t-value (t_{crit}) was estimated for each comparison applying a statistical threshold ($p < 0.01$) to voxel intensity NPT. Gyrus and BA are only displayed when they obtained statistically significant differences after multiple comparisons correction (voxel intensity NPT, $t > t_{crit}$). Bold names of gyrus and BA represent, respectively, the gyrus and the BA that contain the maximum voxel statistical t-value. NS indicates that non-significant differences are found.

	***p*-value voxel intensity threshold**	**Critical *t*-value**	**Gyrus**	**BA**
Healthy controls	0.01	4.426		BA3
			Paracentral Lobule	BA7
			Postcentral Gyrus	BA18
			Precuneus	BA19
			Cuneus	BA23
			Cingulate Gyrus	BA24
			Posterior Cingulate	BA30
				BA31
Schizophrenia patients	0.01	4.975	Medial Frontal Gyrus	
			Superior Frontal Gyrus	BA3
			Paracentral Lobule	BA4
			Precentral Gyrus	BA5
			Postcentral Gyrus	**BA6**
			Superior Parietal Lobule	BA7
			Precuneus	BA8
			Sub-gyral	BA23
			Cingulate Gyrus	BA24
			Posterior Cingulate Gyrus	BA31

5.4.1. P3a and P3b neural generator patterns

Our results using an adaptive WOI suggest that common brain areas are activated as a response to target (P3b) and distractor (P3a) tones (Figure 5.2), including right superior temporal gyrus and bilateral frontal lobe. This finding is in agreement with previous reports (Bledowski et al., 2004; Strobel et al., 2008; Volpe et al., 2007). Prior research has demonstrated that discrimination between standard and non-standard infrequent stimuli reflects frontal lobe activation, sensible to attentional allocation (Goldstein et al., 2002; Polich, 2007; Volpe et al., 2007). Our findings also concern regions distinctly activated by distractor and target stimuli. Likewise, differences in P300 brain-source generators are coherent with previous studies in healthy subjects: P3a generators were identified over frontal structures and P3b source activation over a distributed network, including frontal, temporal, limbic and parietal lobes (Anderer et al., 2003; Volpe et al., 2007; Wronka et al., 2012). It is noteworthy that these different patterns may have functional significance. P3b is originated as a temporo-parietal mechanism that performs memory and executive control functions (Polich, 2007; Polich and Criado, 2006). On the contrary, P3a reflects the inhibition of a response engaged automatically with the detection of the stimulus deviance (Goldstein et al., 2002). In this sense, frontal lobe activity related to the hippocampus can be associated with the distractor-triggered inhibitory processes (Polich, 2007).

Table 5.3: Results of between-group brain-source generator analyses. Cluster size NPT were carried out to obtain the critical size of the cluster of voxels and their associated statistical p_{cor} value. Gyrus and BA are only displayed when they obtained statistically significant differences after multiple comparisons correction (*i.e.* they formed a greater cluster of voxels than the critical size). Bold names of gyrus and BA represent, respectively, the gyrus and the BA that contain the maximum voxel statistical t-value. *NS* indicates that non-significant differences are found.

	p_{cor} **cluster size**	**Critical size (number of voxels)**	**Gyrus**	**BA**
P3a	0.038	587	**Superior Frontal Gyrus**	**BA6**
			Middle Frontal Gyrus	BA8
			Medial Frontal Gyrus	BA9
			Cingulate Gyrus	BA24
				BA32
P3b	0.033	617	Medial Frontal Gyrus	BA11
			Anterior Cingulate	BA10
			Superior Frontal Gyrus	BA25
			Rectal Gyrus	BA31
			Orbital Gyrus	BA32
			Cingulate Gyrus	**BA33**

5.4.2. Between-group differences

We found statistically significant differences in the activation of brain sources between patients and controls for both P3a and P3b. We are aware of only one study addressing brain source localization of auditory P3a in schizophrenia (Takahashi et al., 2013). Its results revealed widespread deficits in schizophrenia patients (including frontal, temporal and parietal lobes) with post-central maximum. Our patients showed a lower P3a source activation in frontal (BA6, BA8, BA9) and cingulate regions (BA24, BA32) (Figure 5.4, Table 5.3). Accordingly, within-group differences (P3b vs. P3a) pointed out the role of these areas in auditory 3-stimulus oddball characterization (Table 5.2). In this regard, superior and middle frontal (BA6, BA9), cingulate (BA32) and posterior cingulate gyrus (BA23) were commonly involved in auditory P3a generation for healthy controls (Strobel et al., 2008; Volpe et al., 2007). Interestingly, P3a current density reduction for schizophrenia patients in comparison with controls was mainly observed in the right hemisphere of superior, medial and middle frontal cortex (Figure 5.4, Table 5.3). A right lateralization has been associated with the detection of behaviorally relevant or unexpected stimuli (Strobel et al., 2008). Right hemisphere is crucially involved in neural processes underlying adaptive responses to novelty, mainly in perceptual and attention paradigms (Strobel et al., 2008). According to our results, this adaptive function may be hampered in schizophrenia patients. It might hypothetically contribute to aberrant salience in this syndrome through a decreased response to relevance (Kapur, 2003).

In comparison to controls, P3b source activation was smaller in schizophrenia patients over superior and medial frontal gyrus (BA10, BA11), orbital frontal gyrus (BA11), bilateral anterior cingulate gyrus (BA33) and cingulate gyrus (BA31, BA32, BA25). Our findings are consistent with previous auditory 2-tone oddball studies focused on P3b source localization in schizophrenia. Sabeti et al. (Sabeti et al., 2011) described a hypoactivation for schizophrenia patients ($n = 20$) in the cingulate area. Kim et al. (2014) showed decreased cingulate (BA31) activation and a negative correlation with negative symptoms in the posterior cingulate (BA31) for schizophrenia patients ($n = 34$). Like-

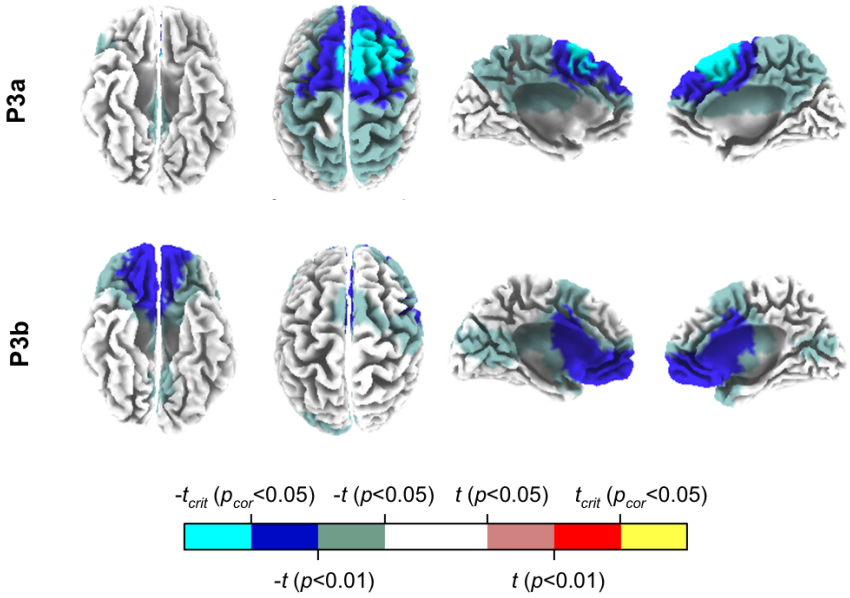

Figure 5.4: Differences in brain activation patterns between schizophrenia patients and healthy controls using voxel-by-voxel independent t-statistics. The scale shows negative (blue) and positive (yellow) t-values for which alpha is statistically significant after cluster size NPT correction for multiple comparisons. Negative t-values represent larger source activity in control group than in schizophrenia patients and vice versa.

wise, Mucci et al. (Mucci et al., 2007) reported a P3b current density reduction in 18 schizophrenia patients compared to 20 controls during a 3-tone oddball paradigm in bilateral frontal and cingulate areas. These studies and our results support the role of cingulate on information processing deficits in schizophrenia. Furthermore, the decreased P3b source activation in Brodmann areas 10 and 11 obtained by schizophrenia patients is consistent with the left middle frontal decrease of current density observed in 16 schizophrenia patients by Higuchi et al. (Higuchi et al., 2008). Interestingly, in spite of the aforementioned decrease of P3b sources in frontal areas for schizophrenia patients, the differences between P3b and P3a were larger in patients than in controls (Figure 5.3). This result may indicate an inefficient hyperactivation during the processing of target stimuli. Moreover, our findings showed a left-lateralized P3b increase in comparison with P3a for controls, in contrast to the bilateral temporal increase for schizophrenia patients (Figure 5.3). These findings agree with previous auditory oddball reports for healthy controls. A statistically significant P3b increase in left BAs 7 and 19 was previously reported ($n = 32$) (Volpe et al., 2007), as well as a P3b increase in left precuneus (BA19) ($n = 28$) (Wronka et al., 2012). It is noteworthy that target response involves the activation of associative cortices involved in attentional, perceptual and memory processes (Volpe et al., 2007). In this regard, Corbetta and Shulman (Corbetta and Shulman, 2002) pointed out that left parietal cortex might be involved in assembling associations that link the appropriate stimuli to the response for a given task.

Taken together with previous literature, our findings suggest a relevant role of frontal and cingulate hypoactivation in the deficient response of schizophrenia patients in P300 paradigms (Bramon et al., 2004). Neuropathological (Benes, 2009; Hashimoto et al., 2008) and functional (Guerrero-Pedraza et al., 2012; Lynall et al., 2010) abnormalities

in these regions have been associated with schizophrenia. They might underlie their decreased activation during the task performance. The frontal lobe has been related to the performance of discriminatory tasks (Pae et al., 2003), whereas the cingulate has been assumed to be involved in both the effortful initiation of motor response and the inhibition of motor responses (Liddle et al., 2001). Therefore, deficient capacities for discrimination, inhibition and/or initiation of responses may mediate the role of cingulate and frontal regions in P3b source activity.

5.4.3. Limitations and future work

Some limitations of this research merit further consideration. It would be interesting to evaluate sources of brain activity over a larger database of first-episode patients and relatives. The comparison between chronic and first-episode patients may contribute to characterize the effect of antipsychotic treatment in the neural generators.Moreover, results were limited by the technical constraints associated with sLORETA analysis. However, the effects of these limitations were reduced by using randomization and NPT procedures. Finally, future studies will complement the obtained sLORETA patterns analyzing detailed time-course source activation, effective and functional connectivity at the source level, and cross-frequency neural coupling.

5.4.4. Conclusions

In summary, this research supports the use of an adaptive WOI to accurately localize the P300 brain-source generators. Furthermore, we found that cortical source generators during an auditory-oddball task are altered in schizophrenia patients. P3a and P3b source differences between groups were mainly obtained in areas related to stimulus discrimination capacity and motor response tasks. Hence, the study of sLORETA neural current density can improve the pathophysiological characterization of schizophrenia.

Chapter 6

A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia

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Abstract: *Objective.* The aim of this research is to explore the coupling patterns of brain dynamics during an auditory oddball task in schizophrenia. *Approach.* Event-related electroencephalographic (ERP) activity was recorded from 20 schizophrenia patients and 20 healthy controls. The coupling changes between auditory response and pre-stimulus baseline were calculated in conventional EEG frequency bands (theta, alpha, beta-1, beta-2 and gamma), using three coupling measures: coherence, phase-locking value and Euclidean distance. *Main results.* Our results showed a statistically significant increase from baseline to response in theta coupling and a statistically significant decrease in beta-2 coupling in controls. No statistically significant changes were observed in schizophrenia patients. *Significance.* Our findings support the aberrant salience hypothesis, since schizophrenia patients failed to change their coupling dynamics between stimulus response and baseline when performing an auditory cognitive task. This result may reflect an impaired communication among neural areas, which may be related to abnormal cognitive functions.

6.1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) of the American Psychiatric Association (American Psychiatric Association, 2013), schizophrenia is a psychiatric disorder characterized by positive and negative symptoms, frequently accompanied by impaired cognitive processing. Schizophrenia usually starts in late adolescence or early adulthood and may become a chronic condition. It has been proposed that the longer the period of untreated psychosis, the worse the outcome (Marshall et al., 2005). Therefore, schizophrenia patients should be identified and treated as early as possible. It is considered a relevant socioeconomic problem for health care systems. Thereby, schizophrenia accounts for an approximately 20% decrease in life expectancy compared with the general population (Laursen et al., 2014).

Schizophrenia has been identified as a dysconnection syndrome, which is associated with a reduced capacity to integrate information between different brain regions (Friston, 1998; Stephan et al., 2009). In addition, it has been related to an aberrant assignment of salience to external objects and internal representations (Kapur, 2003). During the performance of a cognitive task, schizophrenia patients tend to pay more attention to non-salient events and less to salient events (Kapur, 2003). Relevance attribution likely involves diverse cerebral regions and their interconnections. As a consequence, many efforts have been devoted to identifying abnormalities in the cortical connections and their relation to schizophrenia symptoms and cognitive performance (Uhlhaas and Singer, 2010).

The disconnection and aberrant salience hypotheses of schizophrenia may, at first glance, seem unrelated. However, recent formulations of the disconnection hypothesis, in terms of predictive coding and hierarchical Bayesian inference, suggest that aberrant salience can be understood in terms of aberrant precision. Precision corresponds to the salience or confidence in sensory cues and boosts sensory signals (prediction errors) that are considered to convey interesting information. Crucially, in biologically plausible predictive coding schemes, precision is encoded by the gain of neuronal populations reporting prediction errors. This means that aberrant precision corresponds to abnormalities of cortical gain control that follow from a disconnection at the synaptic level – secondary to neuromodulatory failures (Adams et al., 2013). This is important from our perspective because one of the key determinants of gain control is synchronous activity (e.g., synchronous gain). Furthermore, the top-down control of precision or gain is thought to mediate attention that also implicates fast synchronous activity (e.g., (Engel et al., 2001; Landau and Fries, 2012). In summary, we hypothesized that schizophrenia patients would show a failure to contextualize stimulus processing through a failure to optimize the synchronous gain of neuronal populations, leading to a functional disintegration or disconnection. The physiological correlates of this disconnection would be expressed in terms of a failure to modulate synchronous activity; particularly when asked to attend to target stimuli.

Neural oscillations are the main mechanism for enabling coordinated activity during normal brain functioning. Impairments in these oscillations may contribute to pervasive network dysfunction in schizophrenia (Uhlhaas and Singer, 2010). Oscillations in low frequency ranges (delta, theta and alpha) modulate long-range synchronization (Sauseng et al., 2004; von Stein et al., 2000), whereas high frequency ranges (beta and gamma) reflect synchronization in both local cortical networks (Womelsdorf et al., 2007) and large-scale networks (Uhlhaas, 2013). Impaired neural oscillations in schizophrenia may lead to functional disconnections between and within cortical regions (Friston, 1998). Most schizophrenia studies used structural magnetic resonance imaging (MRI), functional MRI or diffusion tensor imaging to study brain organization (Gur and Gur, 2010; Kubicki

et al., 2007; Molina et al., 2010; Shenton et al., 2001). On the other hand, EEG provides high temporal resolution and allows for the assessment of the spatio-temporal patterns of neural activity and their interactions in the time range of milliseconds (Meehan and Bressler, 2012; Uhlhaas, 2013). In this regard, ERP analyses are used to gain further insights into the neural mechanisms underlying cognitive dysfunctions (Uhlhaas et al., 2008). ERP coupling patterns based on time-frequency representations could provide a more sensitive measure to describe schizophrenia alterations than resting-state EEG analysis (Uhlhaas, 2013; Uhlhaas and Singer, 2006). In particular, schizophrenia aberrant attribution of salience may be evidenced by task-related functional connectivity anomalies (Palaniyappan et al., 2012). Thereby, the examination of neural integration mechanisms may be useful for characterizing schizophrenia pathophysiology.

In this study, all coupling parameters are measures of functional connectivity, defined as the statistical dependence between remote physiological activities. Functional neural coupling has been commonly analyzed looking at the relationships between specific sensors by means of measures of connectivity and synchrony between two signals (Bruns and Eckhorn, 2004; Uhlhaas, 2013; Varela et al., 2001). This should be contrasted with effective connectivity, which is defined as the directed or causal inference of one system over another and can be assessed by direct modification of the former (e.g., via trascranial magnetic stimulation). Our focus on various measures of functional connectivity is motivated by the notion that disconnectivity in schizophrenia is accompanied by a failure to modulate synchronous activity, which is one aspect of functional connectivity.

In this regard, ERP coherence and phase synchronization have been previously used to characterize schizophrenia neural coupling (Bob et al., 2008; Ford et al., 2002). They provide an effective measure for the integration of neural ERP response (Uhlhaas, 2013). In particular, transitory phase synchronization of brain activity plays an important role in neural synaptic connections (Uhlhaas et al., 2010). Perception, memories, emotions and other complex mental processes seem to be partially supported by the transient synchronization of synaptic activity across the brain (Fell and Axmacher, 2011). Nevertheless, different coupling patterns have been found depending on the applied measure (Uhlhaas, 2013). Some studies reported reduced functional connections in patients, using coherence or phase synchronization, but they revealed a lack of agreement (Hinkley et al., 2010; Stephan et al., 2009). Several studies reported reduced functional connections in patients between frontal and temporal cortical areas (Ford et al., 2002) and connections involving parietal and occipital cortex (Spencer et al., 2003). Tauscher et al (Tauscher et al., 1998) revealed a reduced local coherence for adjacent electrodes in frontal area, but they did not obtained differences for inter-hemispheric coherence analysis. Certainly, further studies are still required to appropriately assess neural functional connectivity patterns associated with schizophrenia.

In order to obtain a comprehensive time-dependent characterization of neural coupling in schizophrenia, in this study WC and PLV have been calculated. They are useful to explore the relationship between the auditory oddball responses in different frequency bands, in terms of connectivity and synchrony. Furthermore, these connectivity and synchrony parameters have been complemented by a similarity measure: the ED. Similarity measures have been proposed to assess the statistical distance between probability distributions (Rosso et al., 2006). Applied to brain activity, ED provides an alternative description of neural interactions. It has been previously used to characterize neural patterns from different brain disorders, such as epilepsy (Rosso et al 2006), Alzheimer's disease (Bruña et al., 2012) or cerebral ischemia (Geocadin et al., 2000). In sum, WC, PLV and ED provide three different conceptual frameworks to study neural coupling. Hence, they will be useful to test our working hypothesis that aberrant salience in schizophrenia is related to several deficits in processing task relevant information. On

the basis of this idea, two research questions have been addressed: (*i*) can the proposed methodology be useful to provide further insights into the underlying brain dynamics associated with schizophrenia?; (*ii*) can a global pattern of ERP coupling changes between the auditory response and pre-stimulus baseline be defined to characterize normal and schizophrenia neural dynamics? In conclusion, we hoped to show that our complementary functional connectivity measures could disclose coupling changes induced by attended stimuli in control subjects and an attenuation of this induced functional connectivity in schizophrenia.

6.2. Materials

6.2.1. Selection of subjects

Forty subjects were selected to participate in the study. The inclusion and exclusion criteria can be summarized as:

- Inclusion criteria: (*i*) total intelligence quotient (IQ) greater than 70; (*ii*) collaborative subjects in EEG recordings; and (*iii*) written informed consent obtained from patients, their caregivers and healthy volunteers.
- Exclusion criteria: (*i*) a case history including any neurological illness; (*ii*) a history of cranial trauma with loss of consciousness longer than one minute; (*iii*) past or present substance abuse, except nicotine or caffeine; and (*iv*) for the patients, presence of any other psychiatric process, and (*v*) for the controls, any psychiatric diagnosis present or past, or current treatment with drugs known to act on the central nervous system.

Twenty stably treated patients with paranoid schizophrenia were included in the study. They were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th revised edition (DSM-IV-TR) criteria. The clinical status of the patients was scored using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). The Spanish version of the Wechsler adult intelligence scale, 3th edition (WAIS–III), was used to assess IQ. In addition, cognitive assessment was performed using the Spanish version of the brief assessment of cognition in schizophrenia (BACS) scale (Segarra et al., 2011). Twenty age- and gender-matched healthy controls were recruited through newspaper advertisements and remunerated for their cooperation. To discard major psychiatric antecedents (personal or family background), semi-structured psychiatric interviews were previously performed. Demographic and clinical characteristics are shown in Table 6.1. The research boards of the University Hospitals of Valladolid and Salamanca (Spain) endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

6.2.2. EEG recordings

Data recording was performed using a 17-channel EEG system (BrainVision®, Brain Products GmbH; Munich, Germany). Electrodes were placed in accordance with the revised international 10/20 system at Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz. Electrode impedance was always kept under 5 kΩ. Subjects were sat, relaxed and with their eyes closed. They were asked to stay awake and to avoid blinking. EEG recordings were performed while the participants underwent an auditory oddball task. Random series of 600 tones (whose duration was 50 ms, rise and fall time

Table 6.1: Demographic and clinical characteristics. Values are shown as: mean ± standard deviation, SD. *NA* represents *not applicable*.

	Schizophrenia Patients	**Controls**
Age (years)	35.45 ± 12.07	33.35 ± 12.26
Gender (M:F)	14 : 6	14 : 6
PANSS positive	18.87 ± 4.39	NA
PANSS negative	20.93 ± 5.76	NA
PANSS total	74.47 ± 17.70	NA

being 5 ms and intensity being 90 dB) consisted of target (500 Hz tone), distractor (1000 Hz tone) and standard (2000 Hz tone) tones with probabilities of 0.20, 0.20 and 0.60, respectively. ERP signal and stimulus markers were recorded continuously. Only attended target tones were considered in the analyses. Our focus on the attended target tones can be motivated in terms of the aberrant precision hypothesis, given that the control of precision has been linked in computational studies to attentional gain control (Adams et al., 2013).

For each subject, 13 min of auditory response ERP activity were acquired at a sampling frequency of 250 Hz. Recordings were referenced over Cz electrode. Data were rereferenced to the average activity of all active sensors (Bledowski et al., 2004), since common average reference is less sensitive to microssacadic artifacts in high frequency recordings (Keren et al., 2010). Then, each ERP recording was filtered using a 50 Hz notch filter and a finite impulse response filter with a Hamming window and band-pass frequencies between 1 and 70 Hz. To minimize the presence of oculographic and myographic artifacts, a three-steps artifact rejection was carried out (Bachiller et al., 2014). Firstly, an independent component analysis was performed to decompose ERP signals. Components related to eye-blinks were discarded according to a visual inspection of the scalp maps and their temporal activation. In a second step, continuous ERP data were segmented into 1 s-length trials ranging from –300 ms before target stimulus onset to 700 ms after onset (250 samples per trial). Finally, artifacts were automatically rejected using an adaptive thresholding method to discard ERP trials, whose amplitude exceeded a statistical-based local threshold. The numbers of selected trials for target condition were 80.85 ± 20.62 (mean ± standard deviation, SD) and 88.75 ± 10.12 in schizophrenia patients and controls, respectively.

6.3. Methods

6.3.1. Continuous wavelet transform

Information processing in the brain is reflected in dynamical changes of the electrical activity in time, frequency and space (Rosso et al 2006). Time-frequency EEG analyses provide additional information about neural synchrony, not apparent in the ongoing EEG (Roach and Mathalon, 2008). In the present study, continuous wavelet transform (CWT) was used to compute the time-frequency maps. A wavelet is a zeromean function characterized by its localization in time (Δt) and frequency (Δf) (Torrence and Compo, 1998). Different waveforms can be considered to be a wavelet. In this study, the complex Morlet wavelet is used as *mother wavelet*. It is a gaussian-windowed sinusoidal wave that provides a biologically plausible fit to the signal being modeled (Roach and Mathalon,

2008). Complex Morlet wavelet is defined as follows (Mørup et al., 2006)

$$\psi(t) = \frac{1}{\sqrt{\pi \cdot \Omega_b}} \cdot exp\left(j2\pi\Omega_c t\right) \cdot exp\left(\frac{-t^2}{\Omega_b}\right), \tag{6.1}$$

where Ω_b is a bandwidth parameter and Ω_c is a wavelet center frequency parameter. In this analysis, both were chosen to be 1, in order to obtain a good relation between Δt and Δf at low frequencies (Hirano et al., 2008). A family of wavelets was formed by compressed and stretched versions of the *mother wavelet* (Mallat, 2008). The CWT of each ERP trial, $x(t)$, is defined as the convolution of $x(t)$ with a scaled and translated version of the "mother wavelet"

$$W_x(k,s) = \frac{1}{\sqrt{s}} \cdot \int_{-\infty}^{+\infty} x(t) \cdot \psi^*\left(\frac{t-k}{s}\right) dt, \tag{6.2}$$

where s represents the scaling factor, k is the time interval and $*$ denotes the complex conjugation. The scaling factor was set to include frequencies from 1 to 70 Hz, in 0.5 Hz intervals. This approach was introduced by Tallon-Baudry et al (Tallon-Baudry et al., 1996) and it allows to explore in detail the frequency domain. The wavelet energy is a simple way to represent the magnitude of EEG oscillations at specific scales. Hence, the wavelet scalogram (WS) summarizes the distribution of the signal energy in the time-frequency plane (Mallat, 2008). The WS is calculated as the squared modulus of the CWT coefficients

$$WS_x(k,s) = |W_x(k,s)|^2. \tag{6.3}$$

On the contrary to Fourier analysis, CWT has a variable time-frequency resolution (Mallat, 2008). The longest time windows were applied to the lowest frequencies, whereas the shortest time windows were applied to the highest frequencies (Roach and Mathalon, 2008). A Heisenberg box was introduced by the use of the Heisenberg uncertainty principle. It is defined as a rectangle whose width depends on the time-frequency resolution, but its area remains constant (Mallat, 2008). In this study, the width of the Heisenberg box was chosen to be two times the time (Δt) and frequency resolution (Δf) (Tallon-Baudry et al., 1996). Additionally, ERP signals have an important limitation: they are finite and short-time recordings. To take this issue into account, the CWT edge effect was introduced as a variation of wavelet energy caused by a discontinuity at the edge (Torrence and Compo, 1998). Hence, a cone of influence (COI) can be defined, in which edge effects can be ignored (Torrence and Compo, 1998). In this study, 1 s-length target trials were decomposed into the baseline, defined as the available 300 ms pre-stimulus recording, and the response, which was evaluated in the [150 450] ms window (Bachiller et al., 2014). Therefore, it is possible to evaluate their respective COIs by establishing the edges in the baseline [–300 0] ms and response [150 450] ms windows. Figure 6.1 shows two examples of scalograms where the baseline and response COI are represented.

Time-frequency analysis was evaluated in the conventional EEG frequency bands: delta (δ, 1–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta-1 (β_1, 13–19 Hz), beta-2 (β_2, 19–30 Hz) and gamma (γ, 30–70 Hz). The Heisenberg box approach was used to select the CWT coefficients corresponding to each frequency band. CWT coefficients were only considered when their associated Heisenberg boxes were completely included in the COI. Thereby, δ-band was not analyzed, since it is associated with a wavelet duration of hundreds of milliseconds. For instance, at 2 Hz this leads to a spectral bandwidth ($2\Delta f$) of 0.64 Hz and a wavelet duration ($2\Delta t$) of 500 ms. Hence to be correctly analyzed, a window length longer than 300 ms is needed for both response and baseline intervals.

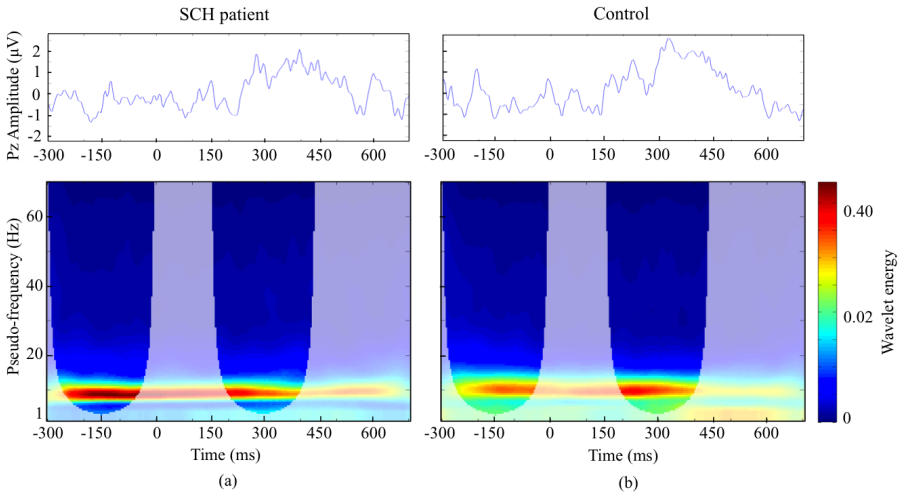

Figure 6.1: Averaged raw ERP and scalograms at Pz electrode for: (**a**) a schizophrenia patient; (**b**) a healthy control. The schizophrenia patient shows the wavelet energy concentrated in a narrow band at low frequencies. In addition, the scalogram shows a decrease of energy in the stimulus response from baseline in this band. On the other hand, the control subject shows a less concentrated wavelet energy and exhibits a slight increase of energy in the response from baseline at low frequencies. The transparency outline represents the limits of the COI, where edge effects can be ignored. **SCH**, schizophrenia.

6.3.2. Connectivity, synchrony and similarity measures

Brain organization cannot be fully understood if coupling between brain regions is not analyzed (Varela et al., 2001). Functional neural coupling involves the identification of different regions that reflect a temporal correlation while subjects are performing a cognitive task (Varela et al., 2001). Several approaches have been developed to study these neural connections. In this research, we focused on three complementary coupling measures derived from the CWT representation: (*i*) WC, (*ii*) PLV and (*iii*) ED.

6.3.2.1. Wavelet coherence

Coherence has been commonly used in neuroscience to quantify the interdependencies among the neurophysiological signals measured at different electrodes (Bruns and Eckhorn, 2004; von Stein and Sarnthein, 2000). ERP coherence is based on the assumption that the same patterns of physiological activity are repeated at the same latency from trial to trial (Lachaux et al., 2002). From the CWT of two signals $x(t)$ and $y(t)$, the wavelet cross-spectrum (WCS) at time interval k and scale s can be defined as (Lachaux et al., 2002)

$$WCS_{xy}(k,s) = \langle W_x(k,s) \cdot W_y^*(k,s) \rangle, \tag{6.4}$$

where $\langle \cdot \rangle$ denotes the average across trials.

Then, the WC between signals $x(t)$ and $y(t)$ is calculated dividing their WCS by their scalograms (Lachaux et al., 2002)

$$WC_{xy}(k,s) = \frac{|WCS_{xy}(k,s)|}{[WS_x(k,s) \cdot WS_y(k,s)]^{1/2}}. \tag{6.5}$$

WC values range from 0 to 1. WC becomes 1 when the signals are perfectly coupled and 0 when they are linearly independent (Bruns and Eckhorn, 2004). Finally, a frequency-dependent WC was calculated by averaging the CWT coefficients for each frequency band

$$WC_{band}(k) = \langle WC_{xy}(k,s)\rangle|_{s\in band}, \quad band = \{\theta, \alpha, \beta_1, \beta_2, \gamma\}. \tag{6.6}$$

6.3.2.2. Phase-locking value

PLV is a highly sensitive measure of neural synchronization in the EEG, useful to quantify the stability of phases between pairs of electrodes (Lachaux et al., 1999). In contrast to WC, PLV reflects the relationship between the phases of two signals, while their amplitudes may be uncorrelated (Bob et al., 2008). For that reason, PLV does not depend on stationarity and it is sensitive to small amplitude oscillations (Spencer et al., 2003).

To calculate PLV, it is necessary to constrain the frequency spectrum to a narrow bandwidth and extract the instantaneous phase of every signal (Lachaux et al., 1999).CWT approach can be used to perform filtering and phase extraction in one operation (Bob et al., 2008). From the instantaneous phases $\varphi_x(k,s,n)$ and $\varphi_y(k,s,n)$ of two ERP signals $x(t)$ and $y(t)$, the instantaneous phase difference can be defined by

$$\Delta\varphi_{xy}(k,s,n) = \varphi_x(k,s,n) - \varphi_y(k,s,n), \tag{6.7}$$

where n represents each trial. Finally, PLV evaluates the variability of the phase differences across successive trials, as follows

$$PLV_{xy}(k,s) = \frac{1}{N_t}\,|\sum_{n=1}^{N_t} e^{\left(\Delta_{\varphi_{xy}}(k,s,n)\right)}|, \tag{6.8}$$

where N_t is the total number of artifact-free trials. PLV is a normalized index, ranging from 0 (non-phase locked, random activity) to 1 (perfect phase synchrony) (Le Van Quyen et al., 2001). Analogously to WC, the PLV was calculated for each frequency band

$$PLV_{band}(k) = \langle PLV_{xy}(k,s)\langle|_{s\in band}, \quad band = \{\theta, \alpha, \beta_1, \beta_2, \gamma\}. \tag{6.9}$$

6.3.2.3. Euclidean distance

Distance between statistical models is widely used in signal processing applications, such as segmentation, pattern recognition, coding or classification (Basseville, 1989). The concept of distance between two probability distributions was initially developed by Mahalanobis (Mahalanobis, 1936). Since then, several types of distance measures have been suggested to describe the similarity between probability distributions (Ullah, 1996). In this study, we propose the use of ED to quantify the differences between the spectral content in the normalized scalogram of two different EEG electrodes. ED has been successfully applied to characterize electromagnetic brain signals in different disorders (Bruña et al., 2012; Rosso et al., 2006). The normalized ED between signals $x(t)$ and $y(t)$ on each frequency band is then defined as (Ullah, 1996)

$$ED_{band}(k) = \sum_{s\in band}\left[\frac{WS_{n,x}(k,s) - WS_{n,y}(k,s)}{2}\right]^{1/2}, \quad band = \{\theta, \alpha, \beta_1, \beta_2, \gamma\}. \tag{6.10}$$

where $WS_{n,x}$ and $WS_{n,y}$ represent the normalized scalograms from the signals $x(t)$ and $y(t)$, respectively.

ED is a normalized dissimilarity measure, where values of 0 and 1 correspond to the highest and lowest similarity, respectively. Therefore, to obtain a direct relation with the WC and PLV, $\overline{ED}$ =1–ED is considered.

6.4. Results

The coupling measures were calculated for all subjects in each frequency band, obtaining a time-frequency dependent measure from –300 ms to 700 ms. In ERP studies, it is interesting to capture event-related changes in brain activity. To this end, a baseline correction is carried out by means of the baseline [–300 0] ms and response [150 450] ms COI windows, previously defined. There are a variety of baseline correction methods. The z-score approach is commonly used, since it takes into account the variability of the baseline values (Roach and Mathalon, 2008). It is noteworthy that the corrected z-values will be positive when there is a coupling increase of auditory response from baseline and they will be negative due to a coupling decrease. In addition, two statistical analyses were performed: (i) within-groups analyses evaluate coupling changes between the baseline and the response in each frequency band by means of Wilcoxon signed-rank tests; and (ii) between-groups analyses show the differences in the pattern of coupling z-values for pathologic and control groups using Mann-Whitney U-tests.

6.4.1. Global analysis

As a first step, to study the global changes in EEG coupling, z-values were averaged over all electrode connections. Then, a single value per coupling parameter, band and subject was obtained. Figure 6.2 depicts the boxplots corresponding to the averaged z-values for each group. Afterwards, statistical analyses were performed to delimitate the frequency bands that showed statistically significant results. Initially, an exploratory analysis was used to check normality and homoscedasticity by means of the Kolmogorov-Smirnov test and Levene tests, respectively. It revealed that data did not meet parametric test assumptions. Within-groups statistical differences were evaluated by means of Wilcoxon signedrank tests ($\alpha = 0.05$). The results are summarized in Table 6.2; it highlights those functional connections that survived false discovery rate correction (FDR). Controls obtained a statistically significant increase of coupling between the baseline and the response in θ-band and a decrease in α, β_1 and β_2 bands. On the other hand, patients did not show statistically significant differences. These findings suggest that schizophrenia patients were not able to change their coupling patterns when performed an oddball auditory target detection task, whereas controls exhibited significant changes in the response from the baseline.

Between-groups analyses showed coupling differences between patients and controls. In detail, between-groups differences correspond to an interaction between changes in coupling and group. Mann–Whitney U-tests ($\alpha = 0.05$) were performed to assess the statistical differences. The results are summarized in Table 6.2. Controls obtained a statistically significant increase in coupling when compared with patients in θ-band. Nevertheless, controls obtained a more statistically significant decrease than schizophrenia patients in β_2-band.

6.4.2. Electrode coupling analyses

In a second step, spatial analyses were performed to explore the topographic changes in the ERP coupling patterns for the frequency bands that obtained statistically significant differences between both groups (*i.e.*, θ and β_2). Besides, γ-band has been

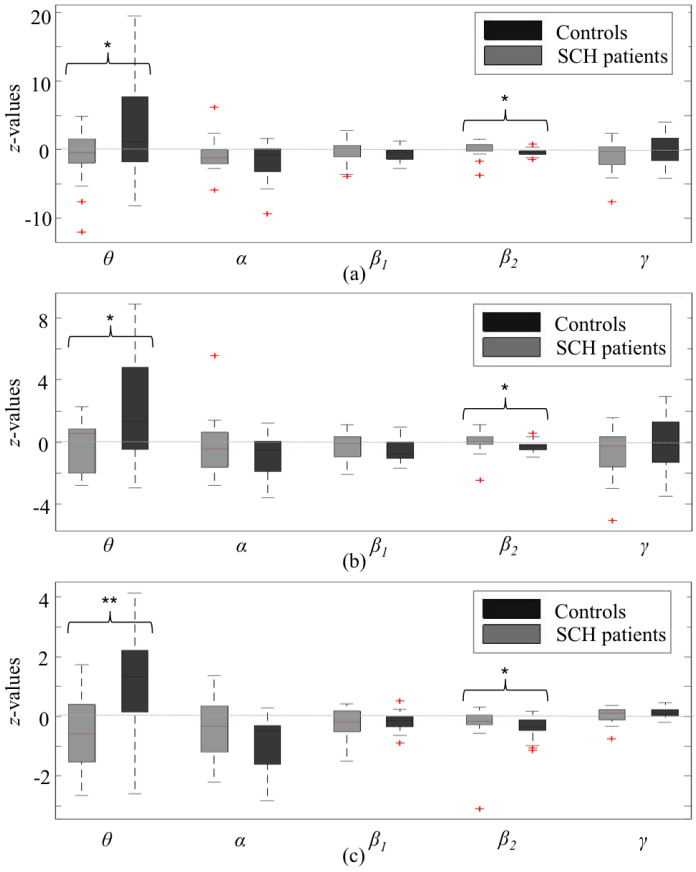

Figure 6.2: Boxplots displaying coupling z-values averaged over all pairs of connections at each frequency band. Positive values indicate an increase in the stimulus response compared to the baseline, whereas negative values indicate a decrease. (**a**) WC. (**b**) PLV. (**c**) ED. Statistical analyses were performed using Mann–Whitney U-tests ($^{*}p < 0.05$, $^{**}\mathrm{p} < 0.01$). **SCH**, schizophrenia.

included since neural coupling in this band seems to play an important role to understand schizophrenia (Uhlhaas and Singer, 2010). Coupling parameters were computed for all pairs of electrodes. Detailed results for coupling z-values between the baseline and response windows are shown in Figure 6.3 (θ-band), Figure 6.4 (β_2-band) and Figure 6.5 (γ-band). Note that we did not apply a FDR correction for multiple comparisons in these topographically specific results. This is because we have already established a significant difference in terms of the average connections and report the current results as standardized effect sizes, which characterize their regional specificity. In these figures, left and central columns depict the coupling z-values for each group. Connections across pairs of electrodes were only displayed whether they obtained statistically significant within-groups differences between the stimulus response and the baseline (Wilcoxon signed–rank test, Statistically significant between-groups results at each frequency band are displayed in the right column of Figures 5.3, 5.4 and 5.5. They were assessed by means of Mann–Whitney U-tests ($\alpha = 0.05$).

Ä

Coupling analyses in θ-band show a widespread increase from baseline to response

Table 6.2: Results of Wilcoxon signed-rank tests and Mann–Whitney U-tests for the averaged coupling parameters. p-values have been FDR-corrected and statistically significant results ($p < 0.05$) have been highlighted.

		Wilcoxon signed-rank test		**Mann–Whitney U-test**
Parameter	**Band**	**Schizophrenia Patients**	**Controls**	**Schizophrenia vs. Controls**
WC	θ	$p < 0.1$	p=0.0402	p=0.0963
	α	$p < 0.1$	p=0.0730	$p < 0.1$
	β_1	$p < 0.1$	$p < 0.1$	$p < 0.1$
	β_2	$p < 0.1$	p=0.0467	p=0.0963
	γ	$p < 0.1$	$p < 0.1$	$p < 0.1$
PLV	θ	$p < 0.1$	p=0.0281	p=0.0963
	α	$p < 0.1$	p=0.0992	$p < 0.1$
	β_1	$p < 0.1$	p=0.0289	$p < 0.1$
	β_2	$p < 0.1$	p=0.0281	p=0.0963
	γ	$p < 0.1$	$p < 0.1$	$p < 0.1$
$\overline{ED}$	θ	$p < 0.1$	p=0.0015	p=0.0963
	α	$p < 0.1$	p=0.0010	$p < 0.1$
	β_1	p=0.0187	$p < 0.1$	$p < 0.1$
	β_2	$p < 0.1$	p=0.0010	$p < 0.1$
	γ	$p < 0.1$	p=0.0045	$p < 0.1$

in the control group, whereas patient group exhibits a slight decrease of coupling measures, specially in frontal region (Figure 6.3). This behavior was shown for all coupling parameters, WC, PLV and $\overline{ED}$. Within-groups analyses show that the control group obtained higher within-groups statistically significant connections than patients, mainly among electrodes on central and parietal areas. Significant differences between patients and controls are observed in the connections between frontal and central regions, central and occipital regions, central and right-temporal regions and several inter-hemispheric connections. On the other hand, β_2-band is characterized by a decrease of coupling changes from baseline to response in both groups (Figure 6.4). Controls show a global decrease, while schizophrenia patients are characterized by stable coupling patterns. The distribution of z-values in controls reveals a significant coupling decrease from baseline to response in the connections among electrodes on frontal, central and parietal regions. Between-groups statistical analyses show significant differences, particularly between prefrontal and frontal regions, frontal and central regions, central and parietal regions and the connections between right-occipital region and several electrodes from frontal, central and parietal regions. Despite exploratory results did not show statistically significant differences in the global analysis (figure 2 and table 2), electrode coupling analyses have provided some significant patterns for γ-band (Figure 6.5). Patients exhibit a γ-coupling decrease from baseline to response, mainly between frontal and parietal cortical areas. On the contrary, controls show a slight increase from baseline to response in the connections with the central region. Significant differences between patients and controls are observed in the connection between electrodes in frontal and parietal regions (Figure 6.5).

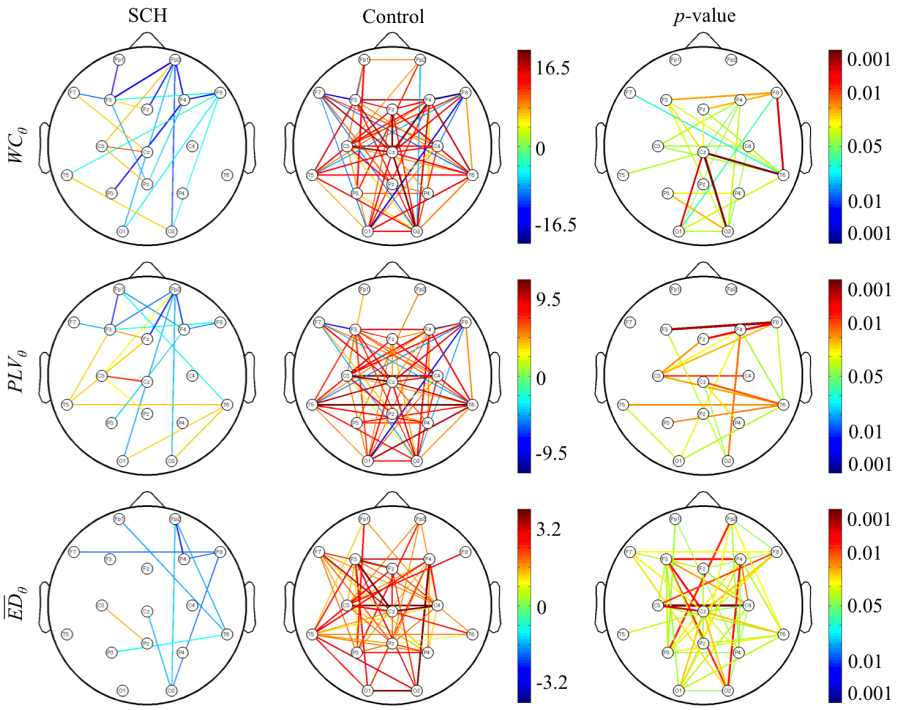

Figure 6.3: Spatial analyses of θ-coupling between all pairs of electrodes for WC, PLV and $\overline{ED}$. Left and central columns depict z-values for schizophrenia patients and controls, where connections were only shown if they obtained statistically significant differences between the stimulus response and the baseline (Wilcoxon signed-rank test, $z > 1.96$; $p < 0.05$). Right column displays statistically significant p-values between-groups (Mann–Whitney U-tests, $\alpha = 0.05$). A color map was applied; in left and central columns, hot colors are associated with a coupling increase during auditory response in comparison to baseline and cold ones are assigned to a decrease. In the right column, hot colors represent smaller z-values in schizophrenia patients than controls and cold ones higher z-values in schizophrenia patients than controls. **SCH**, schizophrenia.

6.5. Discussion

The aim of this study was to characterize the neural dynamics associated with schizophrenia. For this purpose, three coupling measures were calculated for 20 schizophrenia patients and 20 healthy controls. Our findings suggest that schizophrenia patients are not able to change their brain coupling as controls, when attending to target stimuli during an auditory oddball task. Therefore, neural coupling in schizophrenia did not show statistically significant differences between the auditory stimulus response and the baseline condition. In contrast, controls exhibited several changes in the coupling patterns, specially in θ and β_2 bands.

6.5.1. Dynamical properties associated with schizophrenia

The first research question pointed out in the introduction posed the issue about whether the proposed methodology provides further insights into the underlying brain dynamics associated with schizophrenia. Most of EEG functional connectivity studies are

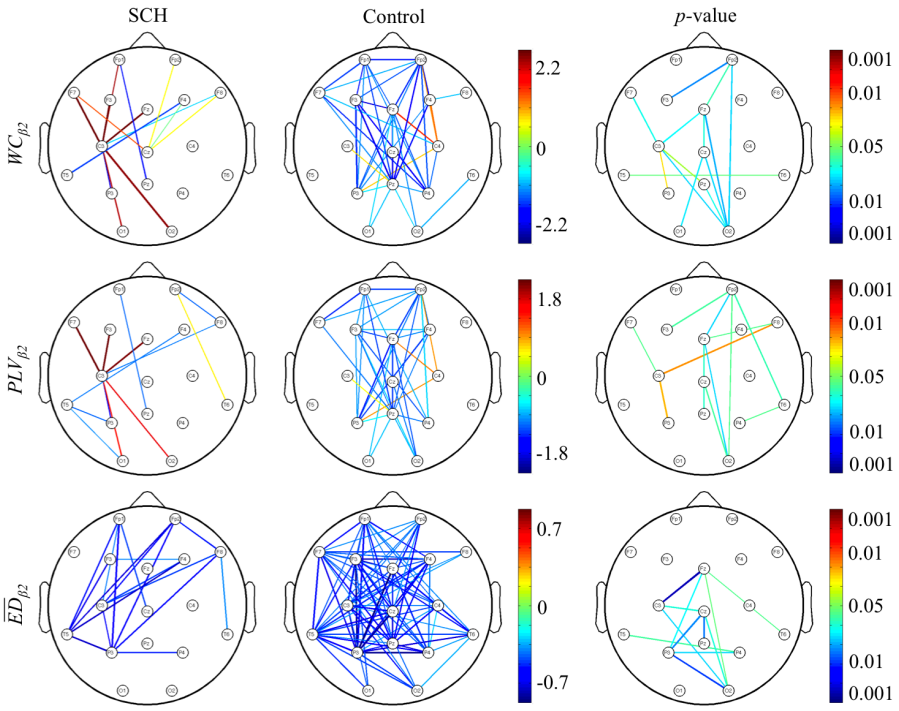

Figure 6.4: Spatial analyses of β_2-coupling between all pairs of electrodes for WC, PLV and $\overline{ED}$. Left and central columns depict z-values for schizophrenia patients and controls, where connections were only shown if they obtained statistically significant differences between the stimulus response and the baseline (Wilcoxon signed-rank test, $z > 1.96$; $p < 0.05$). Right column displays statistically significant p-values between-groups (Mann–Whitney U-tests, $\alpha = 0.05$). A color map was applied; in left and central columns, hot colors are associated with a coupling increase during auditory response in comparison to baseline and cold ones are assigned to a decrease. In the right column, hot colors represent smaller z-values in schizophrenia patients than controls and cold ones higher z-values in schizophrenia patients than controls. **SCH**, schizophrenia.

conducted at resting-state. Nevertheless, to understand the complex relations of brain dynamics, both rest and task states should be evaluated (Turk-Browne, 2013). The ERP paradigm appears then as an appropriate approach to understand how cognitive processes are performed in the brain, since it provides high temporal resolution that allows the assessment of neural events (Turk-Browne, 2013; Uhlhaas, 2013).

ERP data were usually analyzed using a local activation approach. Several researches focused on determining the P300 amplitude and latency, the evoked power or other spectral parameters associated with ERPs on each electrode (Bachiller et al., 2014; Hirano et al., 2008; Roach and Mathalon, 2008; Schmiedt et al., 2005). However, the study of the interactions between pairs of electrodes can provide further insights to understand the underlying neural mechanisms (Stam and van Straaten, 2012; Turk-Browne, 2013). In this regard, the analysis of the amplitude and phase of neural oscillations is crucial for schizophrenia pathophysiology characterization. The amplitude of brain oscillations has been related to the discharges of assemblies of neurons (Uhlhaas et al., 2008), whereas phase locking has been associated with neural firing (Varela et al., 2001). In addition,

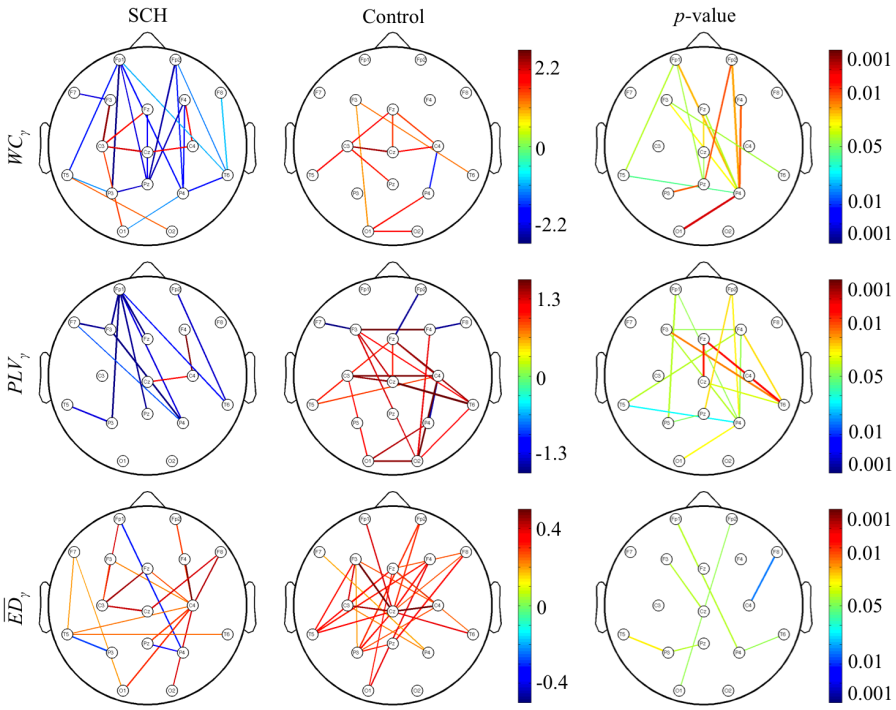

Figure 6.5: Spatial analyses of γ-coupling between all pairs of electrodes for WC, PLV and $\overline{ED}$. Left and central columns depict z-values for schizophrenia patients and controls, where connections were only shown if they obtained statistically significant differences between the stimulus response and the baseline (Wilcoxon signed-rank test, $z > 1.96$; $p < 0.05$). Right column displays statistically significant p-values between-groups (Mann–Whitney U-tests, $\alpha = 0.05$). A color map was applied; in left and central columns, hot colors are associated with a coupling increase during auditory response in comparison to baseline and cold ones are assigned to a decrease. In the right column, hot colors represent smaller z-values in schizophrenia patients than controls and cold ones higher z-values in schizophrenia patients than controls. **SCH**, schizophrenia.

recent researches have been observed a strong correlation between phase and amplitude of neural oscillations at different frequencies (Canolty and Knight, 2010; Jensen and Colgin, 2007). Schizophrenia has been associated with a reduction of the amplitude from the oscillatory activity, as well as with a widespread deficit in the generation and synchronization of rhythmic activity (Uhlhaas et al., 2008). Therefore, in order to address the underlying brain dynamics associated with schizophrenia, we propose the analysis of ERPs neural coupling by means of three complementary measures, which consider both amplitude and phase effects.

WC and PLV have been used to assess connectivity and synchrony, respectively. Connectivity evaluates time-interdependencies between neurophysiological signals (Hinkley et al., 2010), whereas synchrony provides an effective measure for the integration of neural responses in distributed cortical networks (Varela et al., 2001). Thereby, they could constitute high sensitive measures for functional dysconnectivity of local and large-scale networks in schizophrenia (Uhlhaas, 2013). As showed in Figures 5.3 and 5.4, connectivity and synchrony patterns are related, but these measures are not equivalent. Indeed,

if two signals are synchronized, they are correlated, whereas coherence does not necessarily show the presence of synchronization (Rosenblum et al., 2001). Connectivity and synchrony have been previously used to analyze the functional dynamics associated with schizophrenia. Different coupling patterns were found depending on the frequency band considered. Reduced coupling from response to baseline was obtained for high frequencies, whereas a coupling increase has been showed in θ-band (Ford et al., 2002; von Stein and Sarnthein, 2000). In addition, WC and PLV were correlated with psychotic symptoms reflected by PANSS (Bob et al., 2008).

On the other hand, statistical distances establish a new way to explore neural coupling, introducing the concept of similarity between the spectral content of two signals in the probability space. $\overline{ED}$ and other statistical distances have been previously used as disequilibrium or irregularity measures (Bruña et al., 2012; Rosso et al., 2006). Nevertheless, there is a lack of studies that applied statistical distances to address the similarity between the spectral content of ERP recordings. Our results showed that similarity is better suited than connectivity and synchrony to focus on local-range interactions. As showed in Figures 5.3 and 5.4, $\overline{ED}$ obtained the largest z-values and the smallest p-values for short distance links in θ and β_2 bands. On the contrary, synchrony obtained statistically significant results for large-distance links, even for several links between electrodes in different hemispheres. These results can be explained because similarity depends on the oscillations amplitude (Rosso et al., 2006). Therefore, it may be more appropriate to measure short-distance coupling and low frequency bands.

Finally, it is noteworthy that the use of CWT can improve the understanding of neural dynamics. Wavelet analysis is better suited than Fourier and Hilbert approach for non-stationary signals, since it provides a more detailed description of the ERP time-frequency properties (Mørup et al., 2006). Thereby, CWT approach has been proposed as a natural choice for the estimation of coupling between non-stationary signals (Lachaux et al., 2002). In addition, using CWT, filtering and phase extraction were performed in one operation (Bob et al., 2008), obtaining equivalent results to those obtained by means of Hilbert transform (Le Van Quyen et al., 2001).

6.5.2. Coupling changes pattern characterization

The second research question addressed the characterization of normal and schizophrenia neural coupling patterns. It is well known that neural oscillations are a fundamental mechanism for enabling coordinated activity during normal brain functioning (Singer, 1999). Thereby, several EEG researches support the hypothesis that distinct frequencies are involved in different computational and functional interactions (Meehan and Bressler, 2012; Uhlhaas, 2013; von Stein and Sarnthein, 2000). In this research, our findings revealed the main differences in θ and β_2.

Starting with θ-band, our analyses showed a statistically significant increase of neural coupling in controls in comparison to schizophrenia patients. The z-value differences between patients and controls are consistent with previous studies. Schmiedt et al (Schmiedt et al., 2005) obtained an increase of evoked θ-activity in controls engaged in a cognitive task, opposite to schizophrenia patients, which did not show any change. In addition, von Stein and Sarnthein (von Stein and Sarnthein, 2000) highlighted the role that θ-band neuronal synchronization plays in the interaction between frontal and posterior cortex during a cognitive task. Indeed, the deficit in θ-coupling changes in schizophrenia patients may be related to aberrant salience hypothesis. In this regard, several researches have associated schizophrenia with an impairment in θ-phase resetting, a gray matter reduction and a functional connectivity deficit in a defined salience network (Palaniyappan et al., 2011; White et al., 2010).

In the case of β_2-band, our findings suggest that schizophrenia patients are not able to change their coupling between the auditory response and pre-stimulus baseline. The abnormal salience in schizophrenia may be related to a decrease neural response to relevant stimuli and to an excessive response to irrelevant tones (Kapur, 2003). Thereby, schizophrenia patients failed to respond to relevance. On the contrary, control group decreases their β_2-coupling response from baseline. Several authors suggested enhanced β_2-band synchronization in healthy controls at rest, but then it is attenuated during the cognitive response (Kilner et al., 2000; Uhlhaas et al., 2008). In agreement with previous studies, our findings showed several statistically significant differences in fronto-parietal connections, which have been related to cognitive tasks that involve higher executive functions (Meehan and Bressler, 2012). For example, human functional MRI studies showed correlated activity between both areas in β_2-band during a cognitive task (Meehan and Bressler, 2012). The analysis of coupling in beta band may be an important signature of neurocognitive network interaction. Beta-coupling is involved in long-range coordination of distributed neural activity and the synaptic connections between neurons in local cortical circuits (Meehan and Bressler, 2012; Uhlhaas and Singer, 2010). In this way, von Stein and Sarnthein (von Stein and Sarnthein, 2000) suggested that phase synchronization of β_2-oscillations plays a more important role than γ-synchronization on the long-distance coordination, which takes place in neurocognitive networks.

Lastly, γ-band oscillations play an important role in brain dynamics. They have been related to several brain functions, such as perception, attention, memory, consciousness and synaptic plasticity (Uhlhaas et al., 2008). In agreement with previous studies, our findings suggest that schizophrenia patients decrease their γ-coupling activity between response and baseline (Slewa-Younan et al., 2004a), whereas controls exhibit a γ-coupling increase (Ford et al., 2007). Abnormal γ-band activity has also been related to disturbed corollary modulation of sensory processes (Uhlhaas et al., 2008). Thereby, abnormal corollary discharge mechanism might be related to impaired neural γ-synchrony in patients with schizophrenia (Uhlhaas, 2013; Uhlhaas et al., 2008). In addition, there is also a relation between abnormal γ-band and impairments in higher cognitive processes, such as executive processes and working memory (Uhlhaas et al., 2008).

6.5.3. Limitations of the study and future research lines

Some limitations of this research merit consideration. Firstly, δ-band was not analyzed in this study. As we explained in 3.1 subsection, this band is influenced by edge effects due to its time resolution requirements (Torrence and Compo, 1998). Thereby, future studies are needed to assess δ-coupling. Secondly, successive ERP trials have been used to compute coupling parameters. As a consequence, the induced and evoked activity has not been independently analyzed. Further work is necessary to obtain an appropriate coupling parameter that allows separating evoked and induced activity without loosing temporal resolution. Thirdly, the oscillations in cortical networks coexist in multiple frequency bands. There are several evidences that neural activity comprises interactions between oscillations at different frequencies (Le Van Quyen and Bragin, 2007). Cross-frequency coupling provides a plausible mechanism for the neural coordination during perception, cognition and action functions (Canolty and Knight, 2010). In particular, it has been primary observed between low and high frequency oscillations when subjects were performing different cognitive tasks (Kirihara et al., 2012; Sauseng et al., 2008). As a consequence, future studies should be performed to evaluate cross-frequency neural coupling. Finally, on the basis of the connections network, established by WC, PLV and $\overline{ED}$, a complex network analysis could be addressed. We feel that it may provide very valuable insights on the structural and functional organization of neural networks

in schizophrenia.

From the perspective of predictive coding, our results are entirely consistent with the aberrant precision hypothesis of psychosis. Our data support a failure in chronic schizophrenia patients to show an attention-dependent modulation of synchronous activity in specific frequency bands. This may reflect a failure to establish the appropriate levels of synaptic gain or precision mediating the salience of stimuli that are subsequently processed and seems coherent with a synaptic disconnection that may contribute to false inference in schizophrenia.

6.6. Conclusions

In summary, we found that neural coupling is altered in schizophrenia patients during an auditory oddball task. Our results suggest that schizophrenia patients show abnormalities in θ and β_2 bands. Specifically, controls increase their coupling between stimulus response and baseline in θ, whereas the opposite behavior is observed in β_2. On the other hand, schizophrenia patients are not able to change their coupling dynamics, which may be related to aberrant salience in this pathology. Technically, in this research, $\overline{ED}$ was introduced for studying neural coupling patterns in terms of similarity. Our findings support the notion that $\overline{ED}$ provides original insights in comparison with the two classical connectivity and synchrony measures (WC and PLV). Further studies will address the frequency coupling between different bands and a complex network analysis.

Chapter 7

Investigating ERPAC patterns of brain activity: Evidence of alpha-to-gamma hierarchical organization elicited by an auditory oddball task

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Cross-frequency coupling (CFC) is an emerging area of neural research based on the idea that neural oscillations have a complex and hierarchical organization. Particularly, phase-amplitude coupling (PAC) has been identified in a wide variety of tasks and cortical regions. Current studies usually calculate PAC across a wide time period, losing temporal information on PAC patterns. Thereby, time-varying neural mechanisms cannot be studied using conventional PAC. A recent formulation explored PAC dynamics in an event-related way (ERPAC). In this study, ERPAC is applied to the electroencephalographic auditory-oddball brain response recorded from 38 schizophrenia patients and 52 healthy controls. Our results validate the ERPAC as a meaningful approach for measuring dynamic changes in CFC. Furthermore, we show that the phase of alpha rhythm is coupled with the power of low gamma oscillations, mainly in healthy controls. However, abnormal ERPAC patterns are found in schizophrenia patients. It supports the role of excitatory/inhibitory balance in neural oscillatory hierarchy, suggesting that the CFC patterns are altered in schizophrenia.

7.1. Introduction

Transiently active ensembles of neurons, commonly known as *cell assemblies*, underlie numerous operations of the brain, from perception to encoding memories (Buzsáki, 2010). In particular, neural cell assemblies provide a conceptual framework for the integration of distributed neural activity (Varela et al., 2001). Likewise, neural oscillations are the main mechanism for enabling cell assemblies and coordinated activity during normal brain functioning (Uhlhaas and Singer, 2010). The relation between both components (i.e. the cell assemblies and neural oscillatory patterns) allows brain operations to be carried out simultaneously at multiple temporal and spatial scales (Buzsáki and Draguhn, 2004).

Several studies have demonstrated that cognitive processes involve the coordination of slow and fast brain oscillations (Engel et al., 2001; Szczepanski et al., 2014; Wang et al., 2014). The rhythms in different frequency bands can interact to each other in behaviorally meaningful ways (Canolty and Knight, 2010; Szczepanski et al., 2014). Accordingly, it has been proposed that populations of neurons oscillate together and synchronize their firing and post-synaptic potentials in a rhythmic fashion (Buzsáki and Draguhn, 2004; Szczepanski et al., 2014). This phenomenon, commonly known as CFC, indicates that neural oscillations have a complex and hierarchical organization (Kirihara et al., 2012). CFC patterns were firstly evaluated on mice and non-human primates (Lakatos et al., 2005; Lisman, 2005; Tort et al., 2009, 2008). Nowadays, evidence of CFC patterns has been demonstrated in humans using different electrophysiological signals (i.e. Local Field Potentials, LFP; electrocorticography, ECoG; EEG; and magnetoencephalography, MEG) (Tort et al., 2010). In particular, a PAC has been reported in previous studies (Allen et al., 2011; Canolty et al., 2006; Tort et al., 2010; Voytek et al., 2010). It describes the statistical dependence between the phase of a low-frequency (LF) brain rhythm and the amplitude of a high-frequency (HF) component of brain activity (Canolty and Knight, 2010). Voytek and Knight (2015b) proposed that PAC provides a bridge between local microscale and systems-level macroscale neuronal ensembles facilitating a dynamic network communication. However, the factors that contribute to these mechanisms are still not completely understood (Fell and Axmacher, 2011). It has been suggested that the phase of LF oscillations could control neuronal excitability through fluctuations of membrane potentials in a brain area, which affects the amplitude of HF oscillations in that area (Fell and Axmacher, 2011; Szczepanski et al., 2014). In fact, recent studies posed the question of whether the phase of slower oscillations drives the power of faster oscillations or, otherwise, whether the power of faster oscillations drives the phase of slower oscillations (Helfrich et al., 2015; Jiang et al., 2015).

PAC algorithms yield an averaged CFC measure across a defined time window that is bounded by the frequency of the neural oscillations considered (Canolty et al., 2006; Cohen, 2008; Voytek et al., 2010). In particular, the time window should include, at least, one full cycle of the phase signal (Tort et al., 2010). Nevertheless, several authors pointed out that PAC is sensitive to noise and more than 200 cycles are necessary to get a reliable PAC estimation (Tort et al., 2010). It implies the use of long trial time windows with an important cost of temporal resolution (Tort et al., 2009). In order to overcome this drawback, it has been proposed the use of block designs (Voytek et al., 2010) or the concatenation of time series across trials, which could be affected by edge artifacts (Kramer et al., 2008; Tort et al., 2009; Voytek et al., 2013). Moreover, it is well known that a temporally coordinated input facilitates the transmission and integration of

information within brain areas and neurons (Buzsáki, 2015). It is therefore appropriate to focus on the temporal dynamics of neural networks in the millisecond range (Varela et al., 2001). In order to solve these problems, a recent research proposed a novel approach for measuring transient PAC directly in an event-related way: the event-related PAC (ERPAC) (Voytek et al., 2013). In this study, ERPAC was estimated to assess the time-varying CFC associated to an auditory oddball cognitive task.

Additionally, dysfunctions in the generation and coordination of neural oscillations are increasingly implicated in the pathophysiology of psychiatric disorders (Mathalon and Sohal, 2015). Particularly, it has been demonstrated that schizophrenia patients exhibit impaired neural oscillatory activities during sensory and cognitive tasks (Uhlhaas and Singer, 2010). Nevertheless, the alterations of CFC patterns related to schizophrenia have not been widely addressed (Moran and Hong, 2011). Abnormalities of neural oscillations in schizophrenia have been found in all frequency bands. Hence, it could be adequate to evaluate the hierarchy between brain rhythms on schizophrenia. According to the dysconnection hypothesis, a disturbed dynamic coordination between neural oscillations contributes to the pathophysiology of schizophrenia (Friston et al., 2016; Friston, 1998; Uhlhaas, 2013). The physiological correlates of this dysconnection would be expressed in terms of a failure to modulate their neural rhythms (Uhlhaas and Singer, 2010). It is therefore reasonable to assume that CFC studies could be helpful to further understand schizophrenia brain dynamics. Finally, an important question is whether LF and HF oscillations represent independent abnormalities or whether these abnormalities in both frequency ranges are caused by a common origin (Uhlhaas and Singer, 2015). Certainly, it could be related with inhibitory interactions, because there are several lines of evidence that inhibitory interneurons are involved in the generation and the synchronization of oscillatory activity at both LF and HF (Jensen et al., 2014; Uhlhaas and Singer, 2012). In particular, HF has been related to the establishment of cell assemblies in local neural circuits, whereas LF could be associated with functional integration and segregation processes (Uhlhaas and Singer, 2012).

CFC analyses have been traditionally conducted in small databases (i.e. less than 10 subjects) (Canolty et al., 2006; Cohen, 2008; Foster and Parvizi, 2012; Voytek et al., 2010, 2013). Thereby, further studies that include larger databases are strongly encouraged in order to obtain a representative characterization of the hierarchical organization of neural oscillations. In this research, 90 EEG recordings (52 from healthy controls and 38 from schizophrenia patients) were analyzed to identify consistent CFC patterns. In particular, we used ERPAC to obtain a comprehensive understanding of the temporal organization of brain activity and the interactions between neural oscillations. The aim of this study was to investigate whether the recently defined ERPAC could provide a meaningful interpretation of the temporal hierarchical neural rhythms in schizophrenia. Based on these ideas, two research questions were addressed: (*i*) could ERPAC be a useful measure for characterizing time-varying CFC patterns of an auditory oddball paradigm?; and (*ii*) could a global pattern of ERPAC be defined to study the role of dynamic dysfunctions in schizophrenia?

7.2. Materials and methods

7.2.1. Participants

A total of ninety subjects were recruited to participate in the study: 38 schizophrenia patients (22 men and 16 women; 32.82 ± 9.01 years, mean ± standard deviation, SD) and 52 age- and gender-matched healthy controls (28 men and 24 women; 31.60 ± 9.62 years, mean ± SD). Schizophrenia patients were diagnosed according to the Diagnostic

and Statistical Manual of Mental Disorders, 5th revised edition (DSM-V) criteria. All healthy controls reported no history of neurological or psychiatric disease. The inclusion and exclusion criteria can be summarized as:

I. Inclusion criteria: (*i*) total intelligence quotient (IQ) greater than 70; (*ii*) collaborative subjects in EEG recordings; and (*iii*) written informed consent obtained from patients (or their caregivers) and healthy volunteers.

II. Exclusion criteria: (*i*) a case history including any neurological illness; (*ii*) a history of cranial trauma with loss of consciousness longer than one minute; (*iii*) past or present substance abuse, except nicotine or caffeine; and (*iv*) for the patients, presence of any other psychiatric process, and (*v*) for the controls, any psychiatric diagnosis present or past, or current treatment with drugs known to act on the central nervous system.

The research board of the Clinical University Hospital of Valladolid (Spain) endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Moreover, written informed consent was obtained from patients, or their caregivers, and healthy volunteers. Demographic, clinical and behavioral characteristics are shown in Table 7.1.

7.2.2. EEG recordings

ERP recordings were acquired using a 33-channel EEG system (BrainVision®, Brain Products GmbH; Munich, Germany). Active electrodes were placed in accordance with the revised International 10/10 System. EEG data were recorded at a sampling rate of 500 Hz and referenced over Cz electrode. Electrode impedance was always kept under 5 kΩ. Subjects were sat with their eyes closed in a noiseless room. They were asked to stay awake, relaxed and to avoid movements. For each subject, 13 min of EEG activity and stimulus markers were continuously recorded while subjects underwent a 3-stimulus auditory-oddball paradigm. Participants heard a random series of 600 binaural tones (90 dB; 50 ms duration; 5 ms rise and fall-time) consisting on standard (2000 Hz tone), distractor (1000 Hz tone) and target tones (500 Hz tone) with probabilities of 0.6, 0.2 and 0.2, respectively (Bachiller2015b). All participants responded to a target tone by a mouse click with their right hand. It is important to note that only attended target tones were considered in this study (i.e. target tones followed by a mouse click).

7.2.3. EEG data analysis

In this section, we explain the preprocessing stage, which includes: average re-reference, artifact rejection, filtering and segmentation processes. Furthermore, we analyze the spectral characteristics of EEG data and their relation with the timing of stimulus onsets. In particular, we focused on analyzing time-frequency maps, the evoked amplitude and the phase consistency across trials.

7.2.3.1. Signal preprocessing

Initially, peripheral electrodes (TP9, TP10, PO9 and PO10) were discarded due to their low signal-to-noise (SNR) ratio. Then, the data were put into a common average reference, since it is less sensitive to microsaccadic artifacts in HF recordings and contributes to avoid spatial bias due to the choice of single intracranial reference electrode (Boatman-Reich et al., 2010). The artifact rejection algorithm was inspired by

Table 7.1: Demographic, clinical and behavioral characteristics. Values are shown as mean ± standard deviation, SD. *NA* represents *not applicable*. CPZ stands for Chlorpromazine.

	CP	**MTP**	**Controls**
Age (years)	35.95 ± 8.65	$29.33. \pm 8.27$	31.60 ± 9.62
Gender (Male:Female)	11 : 9	11 : 7	28 : 24
PANSS positive	19.26 ± 5.29	21.12 ± 3.99	NA
PANSS negative	22.00 ± 4.80	17.00 ± 4.69	NA
PANSS total	76.26 ± 15.63	76.27 ± 11.37	NA
Treatment dosage (CPZ equivalents)	433.18 ± 194.66	357.14 ± 216.82	NA
Duration of the illness (months)	64.48 ± 18.78	25.14 ± 32.75	NA
Number of artifact-free trials	64.48 ± 18.78	76.67 ± 12.93	77.04 ± 13.20
P300 amplitude at Pz (μ V)	1.51 ± 0.97	1.93 ± 1.39	2.72 ± 1.73
P300 latency at Pz (ms)	431.30 ± 75.21	421.67 ± 76.45	432.15 ± 74.50
Reaction time (ms)	582.37 ± 82.09	519.08 ± 86.60	485.36 ± 68.03

our previous studies (Bachiller et al., 2015b,c). Firstly, EEG data were decomposed by an independent component analysis (ICA). Components related to eyeblinks were discarded according to a visual inspection of the scalp maps and their temporal activation. Secondly, EEG recordings were filtered using a zero phase-lag finite impulse response (FIR) filter with a Hamming window and band-pass frequencies between 1 and 120 Hz, as well as notch filters at 50 Hz and 100 Hz. Thirdly, filtered data were segmented into 1.5 s-length trials ranging from [-500 1000] ms preceding and following auditory stimulus onset. Only attended target tones were considered in the analyses. Finally, trials contaminated with artifacts were rejected using an adaptive thresholding method (Bachiller et al., 2015b). Table 7.1 shows the average number of artifact-free trials included for each group.

7.2.3.2. Spectral characteristics of EEG data and relation with stimulus onset

To obtain meaningful PAC patterns the frequency range for the instantaneous phase should include a clear peak in a time-resolved power spectrum (Aru et al., 2015). Spectral characteristics of EEG data were evaluated using single-trial and evoked-averaging approaches (Roach and Mathalon, 2008). Single-trial time-frequency maps were estimated using the wavelet transform for schizophrenia patients and healthy controls (Figure 7.1). In particular, the methodology followed for single-trial wavelet analysis was described in Bachiller et al. (2015b). Therefore, time-frequency representations were assessed to identify the main power contribution of EEG data on low frequency bands.

The PAC is defined as a causal interaction between brain rhythms. However, a spurious PAC can arise due to common drive generated by external or internal input (*i.e.* an external event that causes the changes in both phase and amplitude) (Aru et al., 2015). Therefore, to achieve a reliable PAC, it is relevant to assess the relation among LF phase, HF amplitude and the timing of external inputs. Firstly, the effect of the frequency band on evoked activity was assessed. Event-related amplitude (Figure 7.2a) was computed for the whole spectrum, ([1 120] Hz), and only for HF band ([25 120] Hz). Secondly, single-trial spectral power was averaged over pre-stimulus baseline and post-stimulus response windows ([-500 0] and [0 500] ms, respectively) (Figure 7.2b). Finally, the relation between LF phases and the stimulus onset was evaluated using the event-

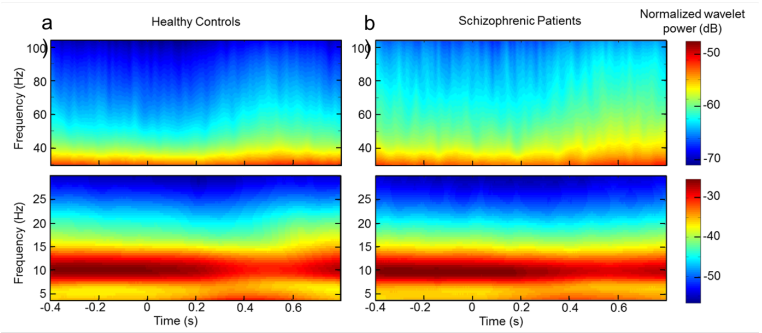

Figure 7.1: Grand-average time-frequency plots. Averaged raw EEG scalogram at electrode Pz for healthy controls group (A) and schizophrenia patients (B). The scalogram is divided into frequencies up to 30 Hz and the gamma range ([30 120] Hz). Wavelet energy is concentrated in a narrow band at low frequencies, which approximately corresponds to alpha band ([7 13] Hz). Wavelet scalogram and normalized power were obtained following the procedure described in (Bachiller et al., 2015b).

related phase-locking across trials (*ITPC*, Inter-trial Phase Coherence) (Tallon-Baudry et al., 1996). *ITPC* is a normalized measure of Ôphase consistencyÕ, or phase-locking with respect to an event onset (Roach and Mathalon, 2008). A value of zero represents total phase independence, whereas an *ITPC* value of one can be associated with a strictly phase-locked activity (Tallon-Baudry et al., 1996). For *ITPC* analyses, each point in the Hilbert transform at each electrode and each LF band-pass was divided by the absolute value of its amplitude. *ITPC* was obtained as the modulus of this value (Tallon-Baudry et al., 1996; Voytek et al., 2013). Figure 7.2c shows the variation of *ITPC* with regard to the frequency (for pre-stimulus baseline and response time-windows) and Figure 7.2d evaluates the relation between *ITPC* at low frequencies ([5, 8] Hz) and the P300 latency.

7.2.4. CFC analysis

In this section, we explain the steps carried out to compute ERPAC. Initially, we address important analytical and methodological caveats and confounds in the CFC study. Secondly, we describe specific CFC preprocessing, including the LF and HF filters used. Then, the algorithm for ERPAC computation is explained. Finally, statistical analysis subsection introduces surrogated analysis based on permutation testing.

7.2.4.1. Methodological caveats and confounds of CFC analysis

Before describing the methodology used in this study, we detail several important analytical and methodological caveats and confounds to be taken into account for the CFC analysis (Aru et al., 2015). Previous studies that used different PAC metrics could be affected by spurious CFC (Aru et al., 2015; Hari and Parkkonen, 2015). In other words, not all cross-frequency correlations are signatures of direct interactions between different physiological processes occurring at different frequencies (Aru et al., 2015; Jedynak et al., 2015). In order to obtain a reliable CFC measure, Aru et al. (2015) brilliantly established a list of practical recommendations to minimize technical pitfalls and to underplay the problem of over-interpretation of PAC measures. The consequences of failing to take these guidelines into account could involve the computation of a misleading PAC measure (Aru

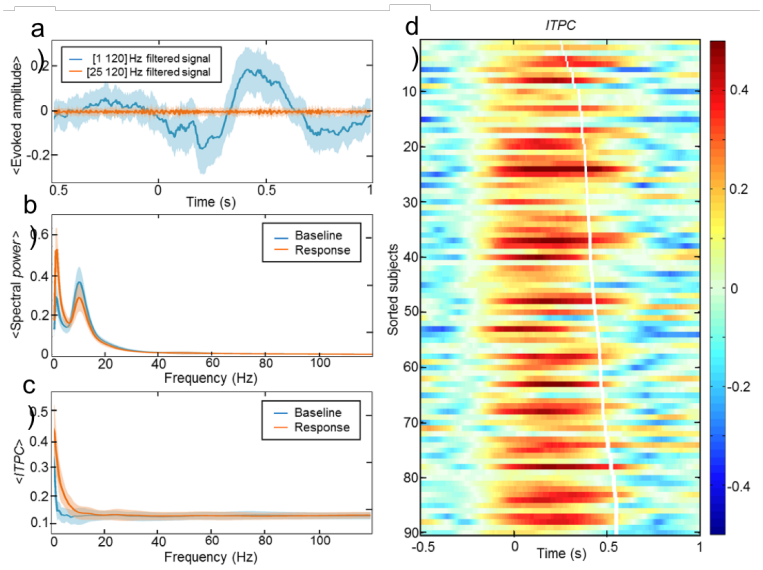

Figure 7.2: Analysis of spectral characteristics of EEG data. (A) Trial-averaged evoked amplitude at Pz electrode for the whole spectrum ([1 120] Hz), and after a high-pass filtering process ([25 120] Hz). Remarked lines depict the average values of all subjects and the shaded areas represent their standard deviation. (B) Single-trial spectral power values at Pz electrode as a function of frequency for a period preceding (blue, [-500 0] ms) or following (red, [0 500] ms) the auditory stimulus onset. (C) Inter-trial phase coherence (*ITPC*) values at FCz electrode as a function of frequency for the same pre-stimulus baseline and response time windows. (D) Baseline corrected *ITPC* changes over time for low frequencies ([5 8] Hz) at FCz electrode. Subjects were sorted based on the P300 latency (showed as a white mark). Non-statistically significant relationship was found between P300 latency and the time sample where the maximum *ITPC* value occurs (Spearman's rank correlation, $R = 0.0227$; $p = 0.8320$).

et al., 2015). Hereafter, we summarize the suggested practical recommendations into two main issues.

7.2.4.1.1. Selection of the frequency bands of interest and filter bank design

A concentration of power in a time-frequency decomposition was required for a meaningful interpretation of the phase extraction and therefore for PAC estimation (Aru et al., 2015). Furthermore, PAC analysis computes the correlation or dependency between the LF phase and the HF amplitude. The detailed selection of these frequency bands is then a remarkable stage on PAC analyses. Several filtering guidelines should be considered (Aru et al., 2015):

I. In order to prevent edge effects, filtering process should be done on the entire ERP data before segmenting the EEG data into epochs (Cohen et al., 2009).

II. It is noteworthy that a reliable phase estimation requires to constrain the frequency spectrum to a narrow bandwidth (Lachaux et al., 1999). The selection of a given narrow frequency band requires filters with excellent resolutions in both time and frequency, which do not delay phase components (Lachaux et al., 1999).

III. PAC is very sensitive to phase distortion (Foster and Parvizi, 2012). In order to prevent phase distortion, each channel must be filtered using a two-way least-squares FIR procedure. This filtering method uses a zero phase-lag forward and reverse operation (Cohen et al., 2009).

IV. HF filtering procedure affects the sensitivity of PAC metrics. The complex frequency spectrum of an amplitude-modulated signal is related to the frequency of modulation (Berman et al., 2012). Thus, a filter with appropriate bandwidth is necessary for preserving amplitude modulation (*i.e.* the bandwidth of the HF filter must be at least two times the LF modulating band) (Berman et al., 2012).

7.2.4.1.2. Non-stationarity and non-linearity misunderstandings In general, both non-stationary and non-linearity processes could exhibit spectral correlations between their spectral components that may be misinterpreted as CFC (Aru et al., 2015). In an ERP context, a significant PAC can be potentially explained by common influence of external stimulus on the phase and amplitude (i.e. the combination of phase-locking to stimulus onset at LF and increased HF amplitude is enough to obtain a significant PAC) (Aru et al., 2015). In order to avoid non-stationarity and non-linearity misunderstandings it is highly recommended to analyze the relative locking among signal phase, amplitude and the timing of external input (Aru et al., 2015). It allows evaluating whether physiological processes indeed interact and whether the measured PAC is a real LF phase modulation to the HF power. Secondly, a surrogate analysis should be performed. Of note, a suitable surrogate analysis should be designed to destroy the specific non-stationarities related to the hypothesized CFC effect (called cyclo-stationarities) and to minimize the distortion of both unspecific non-stationarities and non-linearities of the original signal (Aru et al., 2015). Surrogate design requirements will be addressed on Subsection 2.5.

7.2.4.2. Specific CFC preprocessing

After the artifact rejection stage, a specific CFC filtering processing was done. Filtering was performed on the entire ERP data in order to prevent edge effects. As we previously mentioned, phase extraction of LF oscillations requires narrow bandwidth filters (Lachaux et al., 1999), whereas the bandwidth of the HF filters must be designed to include the modulation sidebands (Berman et al., 2012). Specifically, we used the next two filter banks with a partially overlapping bandwidth:

I. For LF bands, a zero phase-lag FIR filter bank from 4 to 13 Hz, with a 1 Hz step and a 2 Hz bandwidth.

II. For HF bands, a zero phase-lag FIR filter bank from 30 to 110 Hz, with a 10 Hz step and a 26 Hz bandwidth.

7.2.4.3. ERPAC analysis

ERPAC was designed to measure transient PAC in an event-related manner and to overcome the problem of spurious CFC due to non-stationarities in ERP data (Aru et al., 2015; Voytek et al., 2013). PAC algorithms were commonly computed over a semi-arbitrary time window, whose length was bounded by the minimum frequency of LF range (Canolty et al., 2006; Tort et al., 2010). PAC computation requires a time window-length longer than, at least, a full cycle of LF rhythm (Tort et al., 2010). Hence, for the LF range used in this research, [4 13] Hz, the higher temporal resolution would

be 250 ms. However, Tort et al. (2010) also showed that PAC metric is sensitive to noise and they recommended the use of more than 200 cycles to get a reliable PAC estimation. Several methodologies were developed to meet this requirement: (*I*) using long trial windows at the cost of temporal resolution (Tort et al., 2009); (*ii*) using block designs (Voytek et al., 2010); or (*iii*) concatenating time series across trials, which could introduce spurious PAC due to edge artifacts (Kramer et al., 2008). ERPAC solves this limitation because it does not requires the use of a time window; it estimates PAC at each time point, across-trials (Dimitriadis et al., 2015; Voytek et al., 2013). Thus, ERPAC allows for obtaining a time-varying CFC measure (Voytek et al., 2013).

7.2.4.3.1. PLV-ERPAC estimation Several analysis methods targeting PAC have been proposed (for a review, see (Tort et al., 2010)). Nevertheless, phase-locking value (PLV) has been highlighted as one of the most robust and sensitive techniques for investigating CFC (Canolty et al., 2012; Penny et al., 2008; van Driel et al., 2015). PLV is an appropriate technique for estimating instantaneous phase coupling between two brain signals. Consequently, it has been widely used to investigate a multitude of different functional brain networks (Canolty et al., 2012).

PLV was introduced by Lachaux et al. (1999) as a measure of the stability of phases between pairs of electrodes in the same frequency band. The estimation of PAC patterns using PLV was firstly introduced by Vanhatalo et al. (2004). Since then, it has been employed in several PAC studies (Canolty et al., 2012; Dimitriadis et al., 2015; Foster and Parvizi, 2012; Helfrich et al., 2015; Mormann et al., 2005; Penny et al., 2008; Voytek et al., 2010). One of the main advantages of PLV for measuring PAC is that it allows removing changes in HF amplitude that are not related to the specific phase modulating frequency (i.e. LF bands) (Foster and Parvizi, 2012).

As it was explained, ERP data were filtered using two filter banks obtaining a series of LF and HF signals. Subsequently, the phase and amplitude of each band-pass signal were obtained from the analytic signal, which is a complex time series that was computed using the Hilbert transform:

$$h_x[n] = a_x[n] \cdot exp\left(i \cdot \phi_x[n]\right), x = \{LF, HF\} \tag{7.1}$$

where $a_x[n]$ and $\phi_x[n]$ are the instantaneous amplitudes and phases respectively, and x represents LF and HF filtering procedure.

PLV-PAC was calculated following the steps defined by Penny et al. (2008). Figure 7.3 illustrates PLV-PAC algorithmic steps using a single-trial ERP signal for a healthy control. Firstly, for each trial *j*, LF phase ($\phi_x[n]$) and HF amplitude (a_{HF_i}) were obtained using the complex time series from equation (1). Then, a second filtering operation is applied to extract the LF component of the HF amplitude envelope time series. Finally, the phase corresponding to HF amplitude (ϕ_{aHF_i}) is extracted by using again the Hilbert transform. Hence, PLV-PAC can be computed as:

$$PLV - PAC_{LF \rightarrow HF}[n] = \left\| \frac{1}{N} \sum_{j=1}^{N} exp\left\{ i\left(\phi_{LF_j}[n] - \phi_{aHF_j}[n]\right)\right\} \right\|, \tag{7.2}$$

where N represents the total number of artifact-free trials.

Following the ERPAC methodology defined by Voytek et al. (2013), PLV-PAC was recently revisited in an event-related manner (Dimitriadis et al., 2015). Thereby, PLV-ERPAC was computed across-trials obtaining a time-varying PAC measure (Voytek et al., 2013). ERPAC allows keeping the same temporal resolution as the original single-trial data. However, with the aim of avoiding redundancies and the limitation of a low number

of trials available for each participant, PLV-ERPAC was calculated by means of a stepping 20 ms-length window without overlapping between sequential segments (Dimitriadis et al., 2015), as follows:

$$PLV - PAC_{LF \rightarrow HF}[n'] = \left\| \frac{1}{N \cdot w} \sum_{t'=1}^{N} \sum_{j=1}^{N} exp\left\{ i \left(\phi_{LF_j}[t', n'] - \phi_{aHF_j}[t', n'] \right) \right\} \right\|, \quad (7.3)$$

index inside the 20 ms-length segment and n' is the number of non-overlapped segments. It is noteworthy that although the temporal resolution is reduced, PLV-ERPAC allows measuring the temporal variations of PAC.

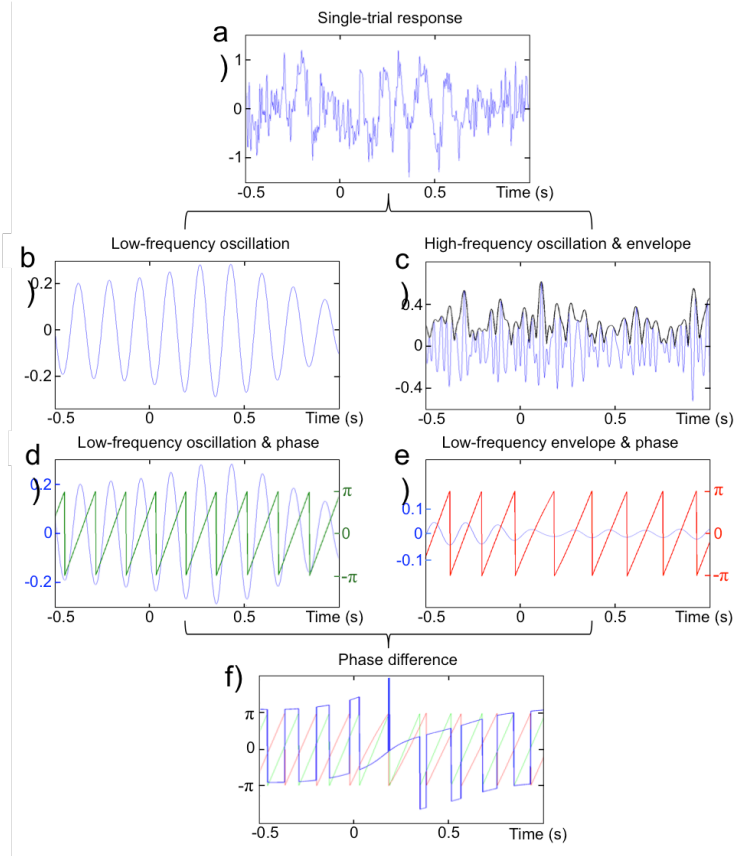

Figure 7.3: The algorithmic steps for PAC estimation. (A) Single-trial wave from the cognitive response of a control subject. (B) Single-trial after applying a LF filter ([4 6] Hz). (C) Single-trial after applying a HF filter ([25 45] Hz) (blue line) and envelope of HF amplitude (dark line). (D) Single-trial after applying a LF filter (blue line) and LF phase obtained by means of Hilbert transform (green line). (E) HF envelope after applying a LF filter (blue line) and its phase obtained by means of Hilbert transform (red line). (F) LF phase (green line), HF phase (red line) and phase difference obtained by subtracting both phase waves (blue line). Phase difference is used to assess PLV-PAC.

7.2.5. Statistical analysis

To study statistical significance at the population level, we carried out a surrogate analysis. This method is useful for determining whether CFC is greater than what would be observed by chance (Cohen, 2008). In addition, this kind of analysis is commonly performed to avoid non-stationarity and non-linearity effects (Aru et al., 2015). A suitable surrogate analysis should be designed to destroy the specific non-stationarities related to the hypothesized CFC effect (called cyclo-stationarities) and to minimize the distortion of both unspecific non-stationarities and non-linearities of the original signal (Aru et al., 2015).

Currently, most CFC studies rely on the confidence distribution approach, which used surrogate data to estimate statistical significance (i.e. p-value is based on a Z-distribution of null-hypothesis test statistics) (Aru et al., 2015; Cohen, 2014). In this work, surrogate analyses were performed based on a permutation testing procedure, whose two main advantages are: (*i*) it does not rely on previous assumptions about the distribution of the data; and (*ii*) it easily incorporates an appropriate correction for multiple comparisons (Cohen, 2014; Maris and Oostenveld, 2007; Nichols and Holmes, 2002). A surrogate procedure was conducted in order to take into account inter-trial relationship between amplitude and phase. In particular, we generated surrogate data by randomly shuffling the order of full trials, which is the most suitable procedure in an ERP approach (Aru et al., 2015; Voytek et al., 2013). This surrogate method preserves the induced changes in frequency analytic phase and amplitude, but randomizes the inter-trial relationships between them (Voytek et al., 2013). In detail, for each time point, we shuffled the order of the trial-wise LF phase values with respect to the phase of HF amplitude envelope values at that same time point and calculated the ERPAC among this shuffled data (Voytek et al., 2013).

CFC showed high variability between subjects, where stronger LF activity showed larger PAC values (Berman et al., 2015; Osipova et al., 2008). Therefore, averaging the comodulograms over all subjects could not provide a meaningful measure of ERPAC patterns. In order to solve this limitation, we applied a correction method for multiple comparisons using *pixel-based statistics* (Cohen, 2014). In order to carry out the surrogate procedure for ERPAC, we firstly generated 500 surrogate distributions and we calculated their associated Z-score statistic. Finally, statistical significance was determined using *pixel-based statistics*, which are based on computing a critical Z-value (named Z-threshold) corresponding with the 95th percentile of the largest values. This is the bound of the threshold at $\alpha = 0.05$ (one-tail) (Cohen, 2014). Based on *pixel-based statistics*, we extracted LF and HF sub-bands of interest from comodulograms where only Z-values greater than a Z-threshold could be considered statistically significant (Nichols and Holmes, 2002). The LF and HF sub-bands of interest were used to assess the differences between healthy controls and schizophrenia patients (permutation test with 10000 permutations; $\alpha = 0.05$) (Nichols and Holmes, 2002). Finally, correlations between alpha power and ERPAC values over a post-stimulus window were evaluated by means of Spearman's rank correlation.

7.3. Results

7.3.1. Spectral features at the sensor-level

As Aru et al. (2015) pointed out, the low frequency range should include a clear peak in a time-resolved power spectrum. Time-frequency representations of oscillatory activity are depicted in Figs. 1 and 2B. We observed a clear peak of spectral power at

low frequencies, which corresponds approximately with the alpha frequency band ([8 13] Hz).

In order to further characterize the event-related EEG data, we studied the time-frequency features of amplitude and phase information. Firstly, Figure 7.2a shows time-averaged evoked amplitude for the whole spectrum ([1 120] Hz) and after a HF filtering process ([25 120] Hz). Whereas evoked ERP on the whole spectrum shows typical ERP components (*i.e.* P100, N200 and P300 waves), the HF filtered ERP does not depict any event-related variation with regard to stimulus onset. Secondly, Figure 7.2c depicts frequency-dependent *ITPC* values measured for time windows preceding and following the stimulus onset ([-500 0] and [0 500] ms windows, respectively). At low frequencies, a slight increase of phase-locking in the post-stimulus window when compared with the pre-stimulus baseline can be observed. In addition, this figure shows how phase reorganization is prevalent at low frequencies. Finally, Figure 7.2d illustrates time evolution of *ITPC* at LF for each subject included in the study. It depicts that phase reorganization was taking place mainly a few milliseconds after stimulus onset. In addition, the relationship between the time-course of *ITPC* and the P300 latency for each subject was assessed. Non-statistically significant relationship was found between the time sample where the maximum *ITPC* value occurs and the P300 latency (Spearman's rank correlation, $R = 0.0227$; $p = 0.8320$).

7.3.2. ERPAC patterns: selection of LF and HF sub-bands of interest

In order to select a pair of frequency ranges of interest in the comodulogram, ERPAC was firstly computed over a wide range of frequencies for healthy controls (*i.e.* LF, [4 13] Hz; and HF, [30 110] Hz). Thereby, surrogated ERPAC on healthy subjects was used to select LF and HF sub-bands of interest where meaningful CFC patterns could be found. Besides, as previously mentioned in Subsection 2.5, statistical significance was determined using a Z-threshold obtained by means of a surrogate analysis. Figure 7.4 depicts the percentage of subjects whose surrogated ERPAC values were higher than their Z-threshold. It includes spatial and temporal information of ERPAC, showing averaged comodulograms over 200 ms-length temporal windows at F3, F4, C3, C4, T7, T8, P3, P4, O1 and O2 electrodes. It is noteworthy that Figure 7.4 shows a higher prevalence of alpha-to-gamma ERPAC over posterior brain regions than over frontal and temporal brain regions. Based on these results, we selected hereafter two frequency sub-bands: [9 13] and [17 53] Hz. They were used to identify a pathological signature in CFC of schizophrenia patients.

7.3.3. ERPAC differences between schizophrenia patients and healthy controls

The previous analysis highlighted the relevance of alpha-to-gamma ERPAC over posterior brain areas during an auditory-oddball task. The next step was then to analyze whether schizophrenia patients exhibited altered CFC patterns in comparison to healthy controls over these selected sub-bands. Figure 7.5 shows the temporal evolution of topographical ERPAC patterns and the results of between-group statistical analysis. In general, ERPAC is higher in central and posterior brain regions for both groups. In addition, it can be observed that ERPAC progressively decreases after stimulus onset. Nevertheless, neural reorganization during the auditory-oddball task is different for healthy controls and schizophrenia patients. Specifically, healthy controls exhibited statistically significant higher ERPAC values than schizophrenia patients over centro-parietal brain

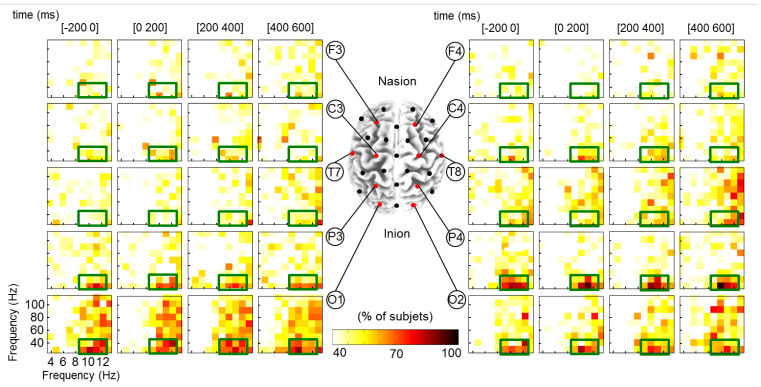

Figure 7.4: Selection of LF and HF sub-bands of interest. Comodulograms show the percentage of subjects whose surrogated ERPAC values were higher than their *pixel-based statistics* Z-threshold. It is also shown the evolution of comodulugrams along time. Only percentages higher than 40% are depicted. In order to facilitate the figure comprehension, comodulograms from only 10 channels were shown. These channels are representative from different brain regions and the two brain hemispheres.

areas after stimulus onset. In addition, schizophrenia patients depicted a statistically significant cross-frequency increase at fronto-temporal electrodes.

Finally, we tested whether the strength of the LF power in the selected sub-band of interest (*i.e.* [9 13] Hz) is correlated with the degree of CFC. A linear regression analysis showed a correlation between alpha power and ERPAC for healthy controls over the post-stimulus [0 500] ms time window. The main statistical significant correlations were obtained at right centro-parietal regions (P4, R=0.6159, p<0.0001; Pz, R=0.6093, p<0.0001; P8, R=0.5127, p=0.0001; CP2, R=0.5615, p=0.0001; CP1, R=0.4765, p=0.0003; CP6, R=0.4940, p=0.0002; C3, R=0.4933, p=0.0002; C4, R=0.4877, p=0.0002) and frontal regions (FCz, R=0.5663, p<0.0001; F3, R=0.4864, p=0.0003; FC2, R=0.5061, p=0.0001). In detail, Figure 7.6 shows a direct relationship between alpha power and ERPAC over Pz electrode. Lower statistical significant correlations were obtained between alpha power and ERPAC for schizophrenia group. They were also found at right centro-parietal region (Cz, R=0.5244, p=0.0007; P8, R=0.4723, p=0.0027; Pz, R=0.4411, p=0.0055; P4, R=0.3961, p=0.0138; P3, R=0.4148, p=0.0096).

7.4. Discussion

The aim of this study was two-fold. First, the study aimed to characterize the hierarchy of oscillations between LF and HF activity during an auditory oddball paradigm. Second, the study explored the PAC differences between healthy controls and schizophrenia patients. For this purpose, a measure of time-varying CFC, ERPAC, was computed for 52 healthy controls and 38 schizophrenia patients. Our findings suggested that low gamma amplitude is modulated by alpha phase in healthy controls, whereas schizophrenia patients exhibited statistically significant lower alpha-to-gamma ERPAC than healthy controls at centro-parietal brain regions.

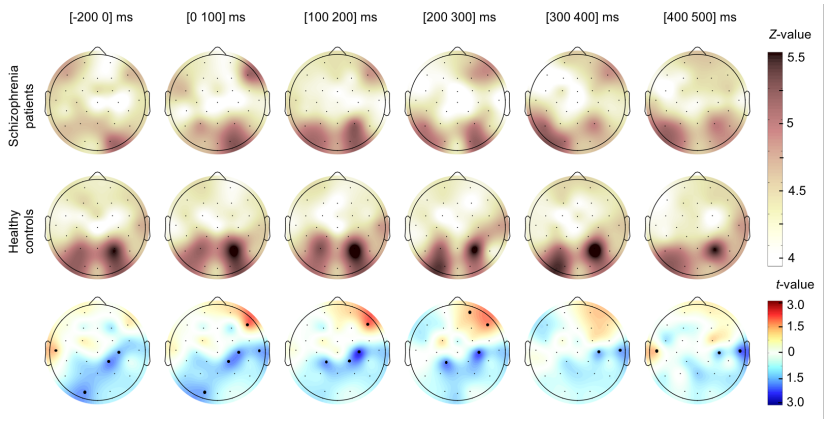

Figure 7.5: Temporal evolution of topographical ERPAC patterns. Between-group differences were assessed over [9 13] Hz and [17 53] Hz sub-bands of interest. The first and the second row depict surrogated ERPAC averages for healthy controls and schizophrenia patients, respectively. The third row summarizes statistically significant t-values between groups (permutation test with 1000 permutations, $\alpha = 0.05$). A color map was applied. Hot colors are associated with a higher ERPAC in controls than in schizophrenia patients. On the contrary, cold ones depict higher ERPAC values in schizophrenia patients. Bold dots ($\cdot$) indicate sensors showing statistically significant differences ($p<0.05$, permutation test).

7.4.1. Methodological event-related CFC assessment

The first research question pointed out in the Introduction section addressed the use of ERPAC to characterize CFC patterns associated with an auditory oddball paradigm. To obtain a physiological interpretation of CFC, it is necessary to know the set of potential mechanisms responsible for neural coupling (Aru et al., 2015). Likewise, it is important to know the methodological confounds that could make difficult to build connections between the measured CFC and the underlying neurophysiological processes.

As we have introduced, PAC analysis proceeds by first selecting two frequency bands. LF phase extraction requires narrow filters with excellent resolutions in both time and frequency. HF filter bandwidth must be large enough to preserve amplitude modulation (Berman et al., 2012). Likewise, phase-amplitude CFC could reflect unspecific non-stationary responses of driven systems not related to neural processes (Aru et al., 2015). For example, an external input that simultaneously affects the phase of a LF component and the amplitude of HF oscillations. The key issue is to distinguish whether the observed PAC is correlated with a causal interaction between brain rhythms or whether it is due to a common drive (Aru et al., 2015). This limitation can be managed, firstly, by examining the spectral characteristics of the data and, secondly, by applying a surrogate analysis that preserves the induced changes but randomizes the inter-trial relationship between LF and HF oscillations (Aru et al., 2015; Voytek et al., 2013):

1. When spectral characteristics of event-related EEG data are analyzed, both amplitude and phase information must be taken into account. Firstly, clear peaks in a time-resolved power spectrum are indispensable requisites to obtain a meaningful instantaneous phase extraction (Aru et al., 2015). In this study, we observed the highest spectral power in alpha frequency band for both schizophrenia patients and healthy controls (Figures 1 and 2b). Likewise, in agreement with previous stud-

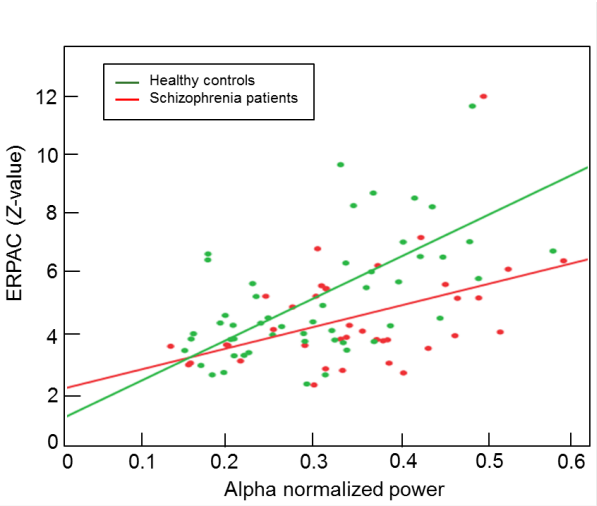

Figure 7.6: Scatterplot showing the association between alpha band normalized power and surrogated ERPAC values averaged over a post-stimulus [0 500] ms time window at Pz electrode. Green points depict healthy controls and red points depict schizophrenia patients. As a response to an auditory oddball paradigm, more positive alpha power values can be associated with higher surrogated ERPAC values in healthy controls (R=0.6093, p<0.0001) and in schizophrenia patients (R=0.4411, p=0.0055).

ies, the average alpha-band spectral power decreased after stimulus onset (Friese et al., 2013). Secondly, although evoked potentials affect a broad range of frequency components (Makeig et al., 2002), our spectral analyses showed that the evoked amplitude had no effect on HF oscillations (Figure 7.2a). This result is coherent with several researchers showing that the ERP wave is dominant at LF bands (<25 Hz) (Bachiller et al., 2015c; Polich, 2007). Thirdly, *ITPC* was computed to provide a metric of event-related phase-locking across trials for a given frequency band (Voytek et al., 2013). Our results suggested that phase was reorganized preferentially at LF (Figs. 2C and 2D). Furthermore, we obtained an increase of phase-locking across trials at LF immediately after stimulus onset. Therefore, our findings revealed a meaningful phase-locking with respect to a stimulus onset at LF, whereas there was a lack of stimulus-evoked changes in HF amplitude.

II. Surrogated analyses were applied to prevent non-stationarity and non-linearity misunderstandings, as well as to assess statistical significance (Aru et al., 2015). Performing a resampling analysis preserves the induced changes while randomizing the relative trial structure between amplitude and phase (Lachaux et al., 1999; Voytek et al., 2013). The proposed ERPAC surrogate method takes into account event-related responses. Therefore, it could be more sensitive to detect subtle time-varying CFC patterns (Voytek et al., 2013). As we introduced previously, ERPAC is well-suited to capture dynamic changes in CFC over both temporal and frequency domains (Sato et al., 2014; Voytek et al., 2013). It provides a method for assessing sub-second coupling dynamic changes in CFC caused by an external event of interest (Voytek et al., 2013).

In summary, in this study we examined the temporal profile of ERPAC at each pair of LF and HF sub-bands. In order to obtain a reliable measure of PAC, we carefully

took into account several methodological recommendations including filtering procedure, phase and amplitude extraction, and testing the effect of non-stationarities by means of a surrogate procedure.

7.4.2. Characterization of time-varying CFC patterns

7.4.2.1. Alpha-to-gamma ERPAC

CFC is proposed to reflect how neurophysiological processes in the brain can be temporally organized across different frequency bands (van Driel et al., 2015). Although recent studies partially disagreed (Helfrich et al., 2015; Jiang et al., 2015), PAC is based on the idea that the distribution of HF power values is modulated by the LF phase (Dvorak and Fenton, 2014). Thereby, it reflects the dynamical relationship between two oscillations that are generated by distinct neurophysiological mechanisms (Dvorak and Fenton, 2014).

Different CFC patterns have been reported in the literature depending on the variety of experimental conditions, species, brain regions or the particular CFC methodology (Hyafil et al., 2015). Most of the studies evaluated the PAC between theta ([4 8] Hz) and gamma ($>$ 30 Hz) (Axmacher et al., 2010; Lisman and Jensen, 2013), as well as between alpha ([8 13] Hz) and gamma ($>$ 30 Hz) (Bahramisharif et al., 2013; Berman et al., 2015; Bonnefond and Jensen, 2015; Osipova et al., 2008; Roux et al., 2013; Voytek et al., 2010). In particular, theta-gamma PAC might support sequential memory organization and long-range cortico-cortical communication (Axmacher et al., 2010; Lisman, 2005; Lisman and Jensen, 2013), whereas alpha-gamma PAC has been suggested to constitute a powerful mechanism to organize cognitive processing in sensory regions (Bonnefond and Jensen, 2015; Jensen et al., 2014; Roux et al., 2013), such as visual and sensorimotor cortex (Voytek et al., 2010; Yanagisawa et al., 2012). Based on these previous studies, a wide LF sweep was explored, including theta and alpha frequency bands. As Figures 5 and 6 show, our study reveled a statistically significant alpha-to-gamma ERPAC, mainly over parietal and occipital areas. These findings agree with previous PAC studies, since topographic results showed greater alpha-to-gamma correlation in parietal and occipital cortices in various ranges of the gamma band ([30 40] Hz, [50 70] Hz and $>$ 70 Hz). Such ERPAC has been widely observed in EEG/MEG studies (Berman et al., 2015; Bonnefond and Jensen, 2015; Chorlian et al., 2006; Osipova et al., 2008; Roux et al., 2013), as well as in ECoG investigations (Bahramisharif et al., 2013; Jiang et al., 2015; van Kerkoerle et al., 2014; Voytek et al., 2010; Yanagisawa et al., 2012). These studies suggested that alpha rhythms have a critical influence on the excitability level of neocortical networks (Berman et al., 2015; Jensen et al., 2014; Klimesch, 2012). The major effect on parietal and occipital areas could be due to the fact that posterior brain regions include a large concentration of alpha rhythm generators (Berman et al., 2015; Huang et al., 2014).

Several PAC studies have shown that alpha oscillations could play a key role in the coordination of brain activity in different frequencies (Klimesch, 2012), but the exact physiological mechanisms that generate alpha rhythms are not yet known (Klimesch, 2012). In this regard, the use of event-related PAC measures could provide novel insights for understanding the neural basis of alpha-to-gamma coupling.

7.4.2.2. Analysis of ERPAC in schizophrenia

Our second aim was to investigate whether a global ERPAC pattern could characterize brain dynamics in schizophrenia. We can assume that healthy functioning requires

a balance between the different frequencies (Northoff and Duncan, 2016). Novel measures of the brain structural and functional integrity highlighted that cognitive functions emerge from coordinated activity of distributed neural processes in the time range of milliseconds (Bullmore and Sporns, 2009; Uhlhaas, 2013; Uhlhaas and Singer, 2015). However, there is support for a frequency-dependent disbalance of relative activity levels in schizophrenia (Northoff and Duncan, 2016). Prior research on this issue was based on the premise that the substrates of cognitive dysfunctions and symptoms of schizophrenia were underpinned by alterations of brain regions and circuits (Uhlhaas, 2013). Nevertheless, their meaning and significance for the different psychopathological symptoms are yet to be defined (Northoff and Duncan, 2016; Uhlhaas and Singer, 2015).

As far as we know, the present work is the first study that evaluates cross-frequency modulation differences between schizophrenia patients and healthy controls using an event-related approach. Impaired EEG neural oscillatory activity during sensory and cognitive tasks in schizophrenia has been previously observed in all frequency bands (Mathalon and Sohal, 2015; Moran and Hong, 2011; Uhlhaas and Singer, 2010). For these reason, it remains misunderstood what is the role of each frequency band in the characterization of the pathophysiology of schizophrenia (Moran and Hong, 2011). In our study, the comparison between groups was performed over two particular sub-bands of interest: [9 13] Hz and [17 53] Hz. As shown in Figure 7.5, alpha-to-gamma ERPAC was higher for healthy controls than for schizophrenia patients over centro-parietal brain areas (Allen et al., 2011; White et al., 2010). Likewise, our results depicted a significantly increased cross-frequency modulation in comparison with healthy subjects at fronto-temporal electrodes (Allen et al., 2011; Northoff and Duncan, 2016). Analogously to previous researches, our findings showed an association between alpha power and ERPAC (*i.e.* the higher alpha power, the larger ERPAC values) (Berman et al., 2015; Osipova et al., 2008). This association suggests that strong alpha power is a prerequisite for the CFC, supporting the idea of a clear peak at LF band (Osipova et al., 2008). It is possible that higher alpha band amplitude may provide greater SNR and thus allow CFC to be more accurately estimated (Berman et al., 2015).

As we have introduced, the dysconnection hypothesis in the schizophrenia has been defined as a disturbed dynamic coordination between neural oscillations (Friston et al., 2016; Friston, 1998). Our findings could be related to the dysconnection hypothesis through an aberrant modulation of synaptic efficacy in the context of distributed and hierarchical neural processing (Friston et al., 2016). Recent work has focused on the alteration in the excitatory/inhibitory (E/I) balance parameters as one possible cause for deficits in neural oscillations (Uhlhaas, 2013). The abnormal dynamics in schizophrenia has been related to deficits in local circuits as well as abnormal large-scale networks (Uhlhaas and Singer, 2010). In the first case, disturbances of GABAergic inhibitory mechanism could be constitutive of abnormal generation of gamma band oscillations (Uhlhaas and Singer, 2015). The second scenario could implicate a hypofunctioning of N-methyl-D-aspartate (NMDA) receptors, related to excitatory function (Uhlhaas and Singer, 2015). In this sense, Friston et al. (2016) proposed that the pathophysiological key determinants of schizophrenia could lie in the interactions between NMDA receptor function and modulatory neurotransmitter systems. They speculated that an abnormal response of the NMDA receptor could involve secondary abnormalities in GABAergic neurotransmission that can be summarized as a failure to optimize the E/I balance (Friston et al., 2016). Taken together, these findings point towards an altered hierarchical organization of neural activity in schizophrenia: an abnormal frequency-dependent disbalance of relative activity levels, depicted by a decoupling between low and high frequencies (Northoff and Duncan, 2016).

7.4.3. Limitations of the study and future research lines

Several limitations of this research merit consideration. Firstly, one of the main controversies on CFC analyses concerns to the directionality of the CFC. Conventionally, it was established that LF entrainment drives HF amplitude modulation in a unidirectional manner. However, recent researchers have found a causal relationship (i.e. gamma amplitude is inhibited by alpha phase, as it is well known, but it exists a feedback mechanism in which gamma drives the alpha entrainment) (Chorlian et al., 2006; Helfrich et al., 2015; Jiang et al., 2015). Secondly, as well as gamma band is nested within lower frequencies, LF oscillations may be nested within lower frequency bands, such as delta rhythms. Likewise, these couplings depend on the specific brain region and the particular task (Voytek and Knight, 2015b). Thirdly, the use of PLV for assessing CFC has two limitations: (*I*) it provides a single scalar index rather than a probability distribution; and (*ii*) it is an inherently bivariate technique (Canolty et al., 2012). In spite of these limitations, PLV is denoted as a very sensitive method, which displayed a good robustness against phase-clustering bias (van Driel et al., 2015). Finally, further work is required to improve our comprehension of the functional role of hierarchical neural oscillations. Recent researches have related a PAC between frontal theta and posterior gamma rhythms with memory and attention tasks in humans (Friese et al., 2013; Köster et al., 2014; Szczepanski et al., 2014). As a consequence, future steps would assess pairwise CFC patterns between electrodes. In particular, it would be interesting to evaluate the role of fronto-parietal network as a response to cognitive task. Pairwise CFC analyses would provide a measure of effective connectivity that could contribute into the characterization of the schizophrenia as a dysconnection syndrome.

7.5. Conclusions

Neural oscillations have a complex and hierarchical organization. Consequently, interactions among different frequency bands can contribute to further understand brain dynamics. In this study, we applied a recently reported event-related CFC measure that allows measuring time-varying PAC patterns and capturing task-related PAC effects. Our results revealed the role of alpha-to-gamma PAC in neural cognitive processing, indicating that alpha rhythms could play a key role in the coordination of cognitive information processing. In particular, the alpha phase modulation of cortical gamma power may support the significance of the E/I balance in neural oscillatory hierarchy. Furthermore, the study of ERPAC patterns differences between schizophrenia patients and healthy controls supports the notion that hierarchical neural processes are altered in the schizophrenia.

Chapter 8

Discussion

In this Doctoral Thesis, the characterization of cognitive processes altered by the schizophrenia was addressed. Firstly, it assessed how time-frequency analyses of EEG data offer a valuable framework for the cognitive electrophysiology study of the neural mechanisms underlying cognitive processes. Secondly, this Doctoral Thesis aimed to elucidate the functional significance of the different classical frequency bands in neurocognitive mechanisms. For this purpose, a two-level analysis of EEG data was carried out. It allowed to analyze: (*i*) local activation, by means of time-frequency and neural source generators analyses; and (*ii*) EEG interactions, including pair-wise interactions and the hierarchical organization of neural rhythms.

In this Chapter, the main findings obtained with this two-level analysis in relation with human cognition will be further discussed. Finally, the main limitations of the study are presented.

8.1. Time-frequency characteristics of ERP data

Transiently active ensembles of neurons, commonly known as 'cell assemblies', underlie numerous operations of the brain from perception to encoding memory (Buzsáki, 2010). In particular, neural cell assemblies provide a conceptual framework for the integration of distributed neural activity (Varela et al., 2001). Likewise, neural oscillations are one of the largest contributing mechanisms for enabling cell assemblies and coordinated activity during normal brain functioning (Uhlhaas and Singer, 2010). The relation between both components (*i.e.* the cell assemblies and oscillatory patterns) allows brain operations to be carried out simultaneously at multiple temporal and spatial scales (Buzsáki and Draguhn, 2004).

Neurophysiological measurements, such as ERPs, have been suggested to provide a biological substrate of cognitive disturbances in schizophrenia. Traditional analyses assess ERP data in the time-domain. Researchers averaged a set of data epochs or trials time-locked to an external event, yielding among others, the P300 component (Makeig et al., 2004). However, trial averaging ignores the fact that the response to a cognitive task may vary widely across trials in amplitude, time course and scalp distribution (Jung et al., 2001). Thus, conventional averaging methods may not be suitable for investigating brain dynamics arising from complex interactions among subject's state and experimental events (Jung et al., 2001; Roach and Mathalon, 2008). In this regard, single-trial time-frequency analyses provide additional information about neural synchrony, not apparent in the evoked ERP (Makeig et al., 2004).

Chapters 3 and 4 of this Doctoral Thesis evaluate the time-frequency local activation characteristics of single-trial ERP data by means of relative power into the conventional frequency bands, spectral entropy and median frequency. Initially, spectral characteristics on the baseline window (*i.e.* short period previous to the stimulus onset) were assessed. Non-statistically significant baseline differences between groups were obtained. These findings were consistent with the absence of spectral differences in the resting state between medicated schizophrenia patients and controls (Sabeti et al., 2009). According to our results, the study of bioelectrical spectral changes from baseline window to the response one (*i.e.* processing stages of a cognitive task) may be a more sensitive measure to assess the differences between schizophrenia patients and healthy controls. RP analysis showed an increase of low frequency power from baseline to cognitive response in δ and θ frequency bands. In contrast, high frequency bands (β_1, β_2 and γ) showed a power decrease in response window with regard to baseline (Bachiller et al., 2014). However, these changes were statistically significant higher in healthy controls than in schizophrenia patients, suggesting a lack of modulation in patients group. RP changes from baseline to response windows were correlated with MF and SE, suggesting that MF and SE decrease is contributed by a slowing of the EEG signal (*i.e.* higher amplitudes for low frequencies and lower amplitudes at high frequencies). Indeed, MF and SE provide a summary of the spectral content. According to previous studies, the lower decrease in MF and SE observed in schizophrenia patients could be influenced by lower θ amplitude increase (Doege et al., 2009) and lower reduction in γ power for patients with schizophrenia than for healthy subjects during target processing (Hong et al., 2012). Likewise, a positive association between SE modulation and clinical scores was observed, suggesting that the lower changes in SE as a response to target tones were associated with a higher clinical severity (Bachiller et al., 2014). According to aberrant salience hypothesis, it may be due to an impaired capacity for processing real-life stimuli (Kapur, 2003).

Furthermore, cognitive responses to distractor and target tones were assessed in Chapter 4. The response to the distractor stimuli involves novelty detection, whereas target response is associated with novelty detection and relevance attribution (Bachiller et al., 2015a). MF and SE displayed a larger activation over central, parietal and frontal regions, as a response to target tone than to distractor stimuli (Fig 4.3). These findings agreed with the proposed role of frontal regions for relevance attribution in healthy subjects (Kapur, 2003). Furthermore, SE decrease in controls from baseline to response windows can be associated with an irregularity decrease of the ERP signal during the processing of target and distractor tones. These findings are coherent with the widespread hypoactivation observed in response to novelty in patients (Laurens et al., 2005). In addition, the neural generators of cognitive response to both, target and distractor tones, have been assessed in Chapter 5 and they will be discussed in the next section.

8.2. Neural source generator patterns

Source imaging techniques have been commonly used to detect neural generators that contribute to the ERP data as a response to a cognitive task. EEG has higher temporal resolution than other imaging techniques, such as fMRI or DTI. However, due to the inverse problem, precise inference on EEG brain generators cannot be made (Sabeti et al., 2016).

Chapter 5 detailed how P3a and P3b brain-source generators were obtained by time-averaging of sLORETA current density images over a novel adaptive WOI based on subject's P300 latency (Bachiller et al., 2015c). Previous researches demonstrated that discrimination between standard and non-standard infrequent stimuli reflects frontal lobe

activation, sensitive to attentional allocation (Goldstein et al., 2002; Polich, 2007; Volpe et al., 2007). According to prior studies, our findings suggested that there were common brain areas activated as a response to target (P3b) and distractor (P3a) tones, including right superior temporal gyrus and bilateral frontal lobe (Bledowski et al., 2004; Strobel et al., 2008; Volpe et al., 2007). Likewise, our findings also concerned regions distinctly activated by distractor and target stimuli. P3a generators were mainly identified over frontal structures, reflecting the inhibition of a response engaged automatically with the detection of the stimulus deviance (Goldstein et al., 2002). Nonetheless, P3b is originated as a temporo-parietal mechanism that performs memory and executive control functions. Therefore, its source activation is localized over a distributed network, including frontal, temporal, limbic and parietal lobes (Anderer et al., 2003; Volpe et al., 2007; Wronka et al., 2012).

Furthermore, statistically significant differences in the activation of brain sources between patients and controls were found for both P3a and P3b components. According to Takahashi et al. (2013), schizophrenia patients showed a lower P3a activation in frontal, temporal and cingulate brain regions. All of these areas are commonly involved in auditory P3a generation (Strobel et al., 2008; Volpe et al., 2007). Additionally, P3b source activation was smaller in schizophrenia patients than in healthy controls over frontal, anterior cingulate and cingulate regions. Previous researches described a hypoactivation of schizophrenia in frontal and cingulate areas (Kim et al., 2014; Mucci et al., 2007; Sabeti et al., 2011). In summary, our results suggest a relevant role of frontal and cingulate hypoactivation as a response to both distractor (P3a) and target (P3b) auditory tasks. In this regard, frontal lobe has been related to the performance of discriminatory tasks (Pae et al., 2003), whereas the cingulate has been assumed to be involved in both the effortful initiation of motor response and the inhibition of motor responses (Liddle et al., 2001). Therefore, it might hypothetically contribute to aberrant salience in this syndrome through a decreased response to relevance (Kapur, 2003)

In addition to an aberrant assignment of salience, schizophrenia has been identified as a dysconnection syndrome, which is associated with a reduced capacity to integrate neural information among brain regions (Friston, 1998; Stephan et al., 2009). Thereby, it is interesting to perform the analysis of functional connectivity among different brain regions.

8.3. Functional connectivity analysis

Neural oscillations are one of the largest contributing mechanisms for enabling coordinated activity during normal brain functioning. Impairments in these oscillations in schizophrenia may lead to functional disconnections between and within cortical regions (Friston, 1998). As a consequence, many efforts have been devoted to identifying abnormalities in the cortical connections among brain areas and their relation to schizophrenia symptoms and cognitive performance (Uhlhaas and Singer, 2010).

Brain connectivity is a broad issue, which includes the study of anatomical links (*i.e.* structural or anatomical connectivity), statistical dependencies (*i.e.* functional connectivity), or causal interactions (*i.e.* effective connectivity) between neural populations (Sporns, 2007). This Doctoral Thesis is focused on analyzing functional connectivity when subjects were performed an auditory oddball cognitive task. It accounts for the statistical association between two neuronal activities acquired by EEG data (Friston et al., 2013).

A variety of neural analysis methods to estimate functional connectivity exist (Basseville, 1989; Lachaux et al., 1999; Lopes da Silva, 2013; Stam and Reijneveld, 2007).

This Doctoral Thesis assessed dynamical neural interactions by means of three complementary methods based on amplitude and phase information: (*i*) *connectivity* evaluates time-interdependecies between neurophysiological signals (Hinkley et al., 2010); (*ii*) *synchrony* provides an effective measure for the integration of neural responses in distributed cortical networks (Varela et al., 2001); and (*iii*) *similarity* evaluates the statistical distance between probability distributions based on time-frequency representations (Rosso et al., 2006). In particular, we combined two measures previously used in neuroscience, such as the wavelet coherence and the phase-locking value, and a novel one: the Euclidean distance.

Chapter 6 evaluates event-related functional connectivity patterns based on wavelet time-scale representations. ERP analysis provides a more sensitive overview of the underlying schizophrenia neural mechanisms dysfunctions than resting-state EEG analysis (Uhlhaas, 2013; Uhlhaas and Singer, 2006). Analysis of the amplitude and phase of neural oscillations is crucial for connectivity characterization. The amplitude of brain oscillations has been related to the discharges of assemblies of neurons (Uhlhaas et al., 2008), whereas phase-locking has been associated with neural firing (Varela et al., 2001). In addition, recent researches have observed a strong correlation between phase and amplitude of neural oscillations at different frequencies (Canolty et al., 2010; Jensen and Colgin, 2007).

Several EEG researches support the hypothesis that distinct frequencies are involved in different computational and functional interactions (Meehan and Bressler, 2012; Uhlhaas, 2013; von Stein and Sarnthein, 2000). In this Doctoral Thesis, the main functional connectivity differences were found in θ, β_2 and γ bands. Our analyses showed a statistically significant increase of θ–band connectivity from task response to baseline at controls group in comparison to schizophrenia patients. This result supports the important role that θ–band neuronal synchronization plays in the interaction between frontal and posterior cortex during a cognitive task. In the case of β_2–band, our findings suggested that schizophrenia patients were not able to change their coupling between the auditory response and pre-stimulus baseline. Thereby, schizophrenia patients failed to respond to relevance (Kapur, 2003). On the contrary, the control group decreased their β_2–coupling response from baseline. In agreement with previous studies, our findings showed several statistically significant differences in fronto-parietal connections, which have been related to cognitive tasks that involve higher executive functions (Meehan and Bressler, 2012). Lastly, γ–band oscillations have been related to several brain functions, such as perception, attention, memory, consciousness and synaptic plasticity (Uhlhaas et al., 2008). In agreement with previous studies, our findings suggest that schizophrenia patients decrease their γ–coupling activity between response and baseline (Slewa-Younan et al., 2004b), whereas controls exhibit a γ–coupling increase (Ford et al., 2007). Abnormal γ–band activity in schizophrenia patients may be related to disturbed corollary modulation of sensory processes (Uhlhaas et al., 2008).

Up to now, the analyses were independently performed on each frequency band. However, several studies demonstrated that the rhythms in different frequency bands can interact to each other in behaviorally meaningful ways, suggesting that neural oscillations have a complex and hierarchical organization (Canolty and Knight, 2010; Szczepanski et al., 2014). In this regard, the next section will address the statistical dependence between the phase of a low-frequency brain rhythm and the amplitude of a high-frequency component of brain activity.

8.4. Cross-frequency coupling patterns

CFC is proposed to reflect how neurophysiological processes in the brain can be temporally organized across different frequency bands (van Driel et al., 2015). Several studies have demonstrated that cognitive processes involve the coordination of slow and fast brain oscillations (Engel et al., 2001; Szczepanski et al., 2014; Wang et al., 2014). Chapter 7 of this Doctoral Thesis raised two main objectives: (i) to characterize the hierarchy of brain oscillations between LF and HF during an auditory oddball paradigm; and (ii) to explore the role of PAC abnormalities between healthy controls and schizophrenia patients.

Firstly, conventional PAC algorithms do not allow analyzing time-varying CFC changes when subjects are performing a cognitive task (Voytek et al., 2013). For this reason ERPAC, a novel approach for measuring transient PAC, was defined. It provides a meaningful time-varying measure of CFC for real EEG data (Bachiller et al., 2017). Our findings showed the relevance of alpha–to–gamma modulation. In agreement with previous studies, topographical results showed greater alpha–to–gamma ERPAC in parietal and occipital cortices (Bahramisharif et al., 2013; Berman et al., 2015; Osipova et al., 2008; Roux et al., 2013; Voytek et al., 2010). Alpha–to–gamma PAC has been suggested to constitute a powerful mechanism to organize cognitive processing in sensory regions (Bonnefond and Jensen, 2015; Jensen et al., 2014; Roux et al., 2013), such as visual and sensorimotor cortex (Voytek et al., 2010; Yanagisawa et al., 2012). These studies suggested that alpha rhythms have a critical influence on the excitability level of neocortical networks (Berman et al., 2015; Jensen et al., 2014; Klimesch, 2012).

Secondly, the second aim is to investigate whether a global ERPAC pattern could characterize brain dynamic abnormalities in schizophrenia. Impaired EEG neural oscillatory activity during sensory and cognitive tasks in schizophrenia has been previously observed in all frequency bands (Mathalon and Sohal, 2015; Moran and Hong, 2011; Uhlhaas and Singer, 2010). It supports a disbalance interaction between the different frequencies (Northoff and Duncan, 2016). However, it remains misunderstood what is the role of each frequency band in the characterization of the pathophysiology of schizophrenia (Moran and Hong, 2011). Statistical analyses between both groups revealed that alpha-to-gamma ERPAC was higher for healthy controls than for schizophrenia patients over centro-parietal brain areas. Likewise, our results depicted a significantly increased cross-frequency modulation in comparison with healthy subjects at fronto-temporal electrodes (Allen et al., 2011; Northoff and Duncan, 2016). Likewise, our findings showed an association between alpha power and ERPAC (i.e. the higher alpha power, the larger ERPAC values) (Berman et al., 2015; Osipova et al., 2008). Our findings could be related to the dysconnection hypothesis through an aberrant modulation of synaptic efficacy in the context of distributed and hierarchical neural processing (Friston et al., 2016). Recent studies hypothesized that neuropsychiatric disorders, such as schizophrenia, are determined by disturbances if the excitatory/inhibitory (E/I) balance between neuronal rhythms (Lopes da Silva, 2013; Uhlhaas and Singer, 2012, 2015).

Taken together, these findings point towards an altered hierarchical organization of neural activity in schizophrenia: an abnormal frequency-dependent disbalance of relative activity levels, depicted by a decoupling between low and high frequencies (Northoff and Duncan, 2016).

8.5. Understanding schizophrenia disease by means of EEG

As it was introduced, two main theories have been associated with schizophrenia: (*i*) the aberrant salience hypothesis (*i.e.* aberrant attribution of salience to external

objects and internal representations); and (*ii*) the dysconnection hypothesis (*i.e.* a disturbed dynamic coordination between neural oscillations). Both theories are related. Schizophrenia aberrant attribution of salience may be evidenced by task-related functional connectivity anomalies (Palaniyappan et al., 2012). Relevance attribution likely involves diverse cerebral regions and their interconnections. In particular, an aberrant neuromodulation of synaptic activity mediates the influence of intrinsic and extrinsic connectivity (Friston et al., 2016). Therefore, in order to obtain a comprehensive characterization of schizophrenia neural abnormalities, the cognitive response to an auditory oddball task was explored using a two-level analysis: (*i*) local activation studies to explore functional segregation in the brain network; and (*ii*) EEG interactions analyses to examine functional integration across brain regions.

Firstly, time-frequency characterization of local activation showed reduced modulation between the response of cognitive task and the baseline periods in schizophrenia. According to aberrant salience hypothesis, it may be due to an impaired capacity for processing real-life stimuli (Kapur, 2003). Likewise, it was confirmed by the analysis of distractor and target cognitive responses. Spectral features displayed a larger activation over central, parietal and frontal regions, as a response to target tone than to distractor stimuli. In addition, our findings showed statistically significant differences in fronto-parietal connections, which have been related to cognitive tasks that involve higher executive functions (Meehan and Bressler, 2012). According to previous researches, our neural source generator findings described a hypoactivation of schizophrenia in frontal and cingulate areas as a response to both distractor (P3a) and target (P3b) auditory tasks (Kim et al., 2014; Mucci et al., 2007; Sabeti et al., 2011). Frontal and cingulate areas have been involved in discriminatory task and the initiation/inhibition of motor response, respectively (Liddle et al., 2001; Pae et al., 2003). Therefore, it might contribute to aberrant attribution of salience in schizophrenia through a decreased response to relevance (Kapur, 2003).

Secondly, functional connectivity between pairs of electrodes agreed with the identification of schizophrenia as a dysconnection syndrome, which is associated with a reduced capacity to integrate information among different brain regions. Functional connectivity analyses revealed that θ, β_2 and γ neuronal synchronization play an important role in the interaction between frontal and posterior cortex during a cognitive task. It suggests that schizophrenia patients may be related to disturbed corollary modulation of sensory processes (Uhlhaas et al., 2008).

Finally, the cognitive electrophysiology literature addresses a wide range of spatial and temporal scales. Several researches support the idea that spatio-temporal multiscale interactions are a critical principle that underlies cognitive functions and consciousness (Breakspear and Stam, 2005; Le Van Quyen, 2011; Varela et al., 2001). However, it is unknown how these multiscale dynamics are related to cognitive processes (Cohen and Gulbinaite, 2014). In this regard, CFC provides a useful tool for assessing multiscale interactions (Lisman and Jensen, 2013; Young and Eggermont, 2009). In this Doctoral Thesis, CFC analyses revealed that alpha–to–gamma PAC constitutes a powerful mechanism to organize cognitive processing in sensory regions (Bonnefond and Jensen, 2015; Jensen et al., 2014; Roux et al., 2013).

In addition, recent researches hypothesized that neuropsychiatric disorders are determined by disturbances of the balance between excitation-inhibition functions (Lopes da Silva, 2013; Uhlhaas and Singer, 2012). These disturbances hypothetically contribute to aberrant salience through a decreased response to relevance (Kapur, 2003). Our findings could support this excitatory-inhibitory dysfunction, since schizophrenia patients have shown a hypoactivation in cingulate areas (involved in the effortful initiation and the inhibition of motor responses), as well as reduced alpha–to–gamma PAC (supporting the

idea that inhibitory neurotransmission is implicated in the generation of high-frequency oscillations). In summary, our findings supports the aberrant salience and dysconnection hypotheses: schizophrenia patients show a failure to contextualize stimulus processing through a failure on neuronal firing synchronization at specific frequency bands, leading to a functional disintegration or dysconnection (Uhlhaas et al., 2010).

8.6. Limitations of the study

This Doctoral Thesis showed the utility of EEG data analysis for characterizing the neural dynamics underlying cognitive processing in schizophrenia. However, some limitations of this research merit further consideration. The first one is related to the sample size. In spite of using two different databases involving a relatively high number of subjects, a larger sample would enhance the statistical power of our results. Statistical power analyses indicated that this sample size is enough for obtaining statistically significant results. Nevertheless, a larger database would be particularly beneficial in the case of including more recordings from patients' subtypes, such as paranoid, non-paranoid or first-episode patients. The inclusion of schizophrenia subtypes could help to confirm the performance of all the methods presented and to further characterize the cognitive dysfunctions associated to schizophrenia. In addition, the number of recorded EEG channels is another limitation. In this Doctoral Thesis, 17 and 33 electrodes have been used. A larger number of electrodes provides higher accuracy for spatially localizing the source of electrical abnormalities. Consequently, the use of high density EEG recordings could improve the findings obtained by the connectivity and LORETA analyses.

As it was highlighted in Chapter 5, the study of neural source generators is associated with several limitations. Firstly, the defined sLORETA approach using a window of interest lost time-course information. Furthermore, LORETA is a low-resolution source imaging technique. The combination between low- and high-resolution (*i.e.* shrinking sLORETA, or time-reduction region-suppression linearly constrained minimum variance, TR–LCMV) algorithms can be a useful tool for physiologist to find the neural sources of primary circuits in the brain (Sabeti et al., 2016).

In this Doctoral Thesis, all connectivity parameters are measures of functional connectivity (*i.e.* the statistical dependence between remote physiological activities). This should be compared to effective connectivity (*i.e.* the causal inference of one system over another) or/and to anatomic connectivity (*i.e.* the physical neural connections). In addition, these connectivity patterns could be used as the basis of a network analysis. The combination of the proposed two-level hierarchical analysis and a novel complex network analysis may provide valuable insights on the structural and functional organization of neural networks in the schizophrenia.

The mathematical development of time-frequency based data analyses has advanced beyond the understanding of the neurophysiological events. Thus, it might underlie the results of these analyses (Cohen and Gulbinaite, 2014). Functional connectivity between pairs of electrodes was assessed based on correlations in power series, or on phase value differences. However, it is unclear whether these connectivity measures based on power and phase reflect similar mechanisms (e.g. long-range or local-range connections) (Cohen and Gulbinaite, 2014). Likewise, it is unknown whether the same mechanism underlie connectivity in different frequency bands or in different brain regions (Cohen and Gulbinaite, 2014).

ERPAC provides a time-varying measure of CFC and solves noise sensitivity of cPAC algorithms. Nonetheless, the use of ERPAC could introduce a spurious PAC due to unspecific non-stationarities not related to neural processes (Aru et al., 2015). Therefore,

the design of a suitable surrogate procedure is required to prevent non-stationarity and non-linearity misunderstandings, as well as to assess statistical significance (Aru et al., 2015).

One of the main controversies on CFC analyses is the directionality of the CFC. Conventionally, it was established that low-frequency entrainment drives high-frequency amplitude modulation (Bonnefond and Jensen, 2015; Jensen et al., 2014; Roux et al., 2013; Voytek et al., 2010; Yanagisawa et al., 2012). However, recent researches have found a causal relationship (*i.e.* gamma amplitude is inhibited by alpha phase, as it is well known, but it could exist a feedback mechanism in which gamma drives the alpha entrainment) (Chorlian et al., 2006; Helfrich et al., 2015; Jiang et al., 2015). Further studies are necessary to obtain a representative characterization of the hierarchical organization of neural oscillations.

Chapter 9

Conclusions

9.1. Introduction

The common thread shared by all the papers included in this Doctoral Thesis is the understanding of cognitive processes altered by schizophrenia. EEG activity was acquired and analyzed while subjects performed an auditory cognitive task. In particular, time-frequency properties of EEG data were assessed using a two-level analysis including local activation, neural source generator localization, functional connectivity and cross-frequency coupling. Taken together, the signal processing techniques used in this Doctoral Thesis will promote the creation of a framework for analyzing EEG data from an auditory oddball paradigm in schizophrenia. In particular, the analysis of time-varying changes between the response to a cognitive task and the pre-stimulus baseline interval allows a dynamic characterization of the neural mechanisms associated with the schizophrenia.

In this Chapter, the original contributions of this Doctoral Thesis to the state-of-the-art are highlighted. Then, the main conclusions extracted from this compendium of publications are indicated. Finally, several questions emerged from this investigation and future research lines will be listed.

9.2. Contributions

The main original contributions provided by the compendium of publications of this Doctoral Thesis are:

- The description of a novel automatic three-step EEG artifact rejection procedure based on data statistics. It comprises the application of an independent component analysis, the segmentation of EEG data into trials and a final automatic rejection based on an adaptive thresholding method.
- The definition of a novel adaptive *WOI* approach for ERP source localization. To the best of our knowledge, this is the first time that an adaptive WOI was used for neural generators localization by means of LORETA. Previously, LORETA source imaging studies commonly used a large fixed post-stimulus WOI. However, an adaptive WOI takes into account changes in peak latency across subjects and, therefore, provides a reliable localization of ERP neural generators.
- The application of complementary time-frequency local activation measures to characterize abnormal cognitive processing during an auditory oddball task in patients

with schizophrenia. The combination of SE and MF provides useful tool for dynamically addressing the slowing and irregularity patterns of EEG data.

- The application of three complementary methods of EEG functional coupling by means of three different conceptual frameworks: connectivity, synchrony and similarity. Similarity, based on statistical distances, provides original insights to describe dynamical neural interactions. To the best of our knowledge, this is the first study that uses statistical distances to characterize auditory oddball cognitive responses in schizophrenia.

- The assessment of a time-varying measure of CFC. To the best of our knowledge, this is the first time that ERPAC methodology has been applied to EEG data from an auditory oddball paradigm in schizophrenia patients. The use of ERPAC for schizophrenia characterization provides an appropriate characterization of the complexity and the hierarchical organization of neural oscillations.

9.3. Main conclusions of the study

The analysis of the obtained results lead to the next main conclusions of this Doctoral Thesis:

1. Although several researches expressed skepticism about the usefulness of EEG recordings in understanding neural activity, event-related EEG data are considered to be indicative of the role of different cortical areas to various sensory or behavioral functions. This Doctoral Thesis contributes to support the idea that EEG data reflect not only characteristics of the brain activity itself, but they also reveal important information on the underlying associated cognitive processes.

2. Neural oscillations are a fundamental mechanism for enabling coordinated activity during normal brain functioning. Neural oscillations at different frequency ranges establish accurate temporal correlations between distributed neural responses. Therefore, impairments in these oscillations constitute a mechanism for a pervasive network impairment in schizophrenia.

3. The assessment of spectral parameters (RP, SE and MF) based on time-frequency representations is useful for the study of dynamical cognitive processing abnormalities in schizophrenia. Time-frequency analysis revealed an increasing contribution of RP at low-frequency bands as well as SE and MF decreases during the cognitive response to a target tone in healthy control group. Patients group were not able to enough modulate their neural activity as a response to an auditory task.

4. Time-frequency changes on dynamical brain activity, when subjects performed an auditory oddball task, are related to clinical severity and may be informative of the underlying altered cognitive functions in the schizophrenia. A statistically significant correlation between SE and positive symptoms was found: the higher the positive symptoms, the lower the SE changes between cognitive response and pre-stimulus baseline.

5. The cognitive response to different auditory tones involves the activation of specific brain areas. Different neural sources generate P3a and P3b: P3a generators are prominent over sensory brain regions, whereas P3b sources are observed over a large distributed network, including motor cortex. Likewise, source generators during an

auditory-oddball task are altered in schizophrenia patients. Schizophrenia is associated with a reduced response to both relevance and novelty in comparison with healthy controls. Between-group differences in P3a and P3b neural generators are mainly obtained in areas related to stimulus discrimination capacity and motor response tasks, suggesting a decreased response to relevance attribution in schizophrenia patients.

6. The selection of a post-stimulus temporal window is an important requirement for neural generators localization. Our findings suggest that the use of an adaptive *WOI* enhances LORETA performance, reducing inter-subject P300 latency variability and providing an accurately localization of the P300 brain-source generators.

7. The use of three complementary coupling measures in terms of connectivity, synchrony and similarity, which consider both amplitude and phase effects, contributes to comprehensively characterize EEG functional integration. Our findings suggest that connectivity and synchrony are appropriate for measuring both local-range and large-distance connections, whereas, similarity is better suited to focus on local-range interactions.

8. Neural connectivity patterns between different brain areas are altered in θ and β_2 frequency bands in schizophrenia patients during the performance of an auditory cognitive task. Schizophrenia patients are not able to reorganize appropriately their functional coupling patterns from the pre-stimulus baseline to the cognitive response.

9. Our CFC analyses suggest that alpha rhythms play a key role in the coordination of cognitive information processing. In particular, alpha-to-gamma modulation may reveal the significance of inhibitory processes in neural oscillatory hierarchy. It could support the hypothesis that neuropsychiatric disorders are determined by disturbances of the balance between excitation-inhibition functions.

In summary, schizophrenia patients show a failure to contextualize stimulus processing through diverse abnormalities on neuronal firing synchronization, leading to a functional disintegration or dysconnection. The decreased neural activation of schizophrenia patients as a response to both relevance and novelty stimuli contributes to support the aberrant salience hypothesis in the schizophrenia. Likewise, functional connectivity patterns between pairs of electrodes support the role of schizophrenia as a dysconnection syndrome, which is associated with a reduced capacity to integrate information among different brain regions. In conclusion, the assessment of a two-level hierarchical analysis of EEG neural signals contributes to further characterize the pathopysiology of schizophrenia.

9.4. Future research lines

There exist several questions derived from this research that can be studied in the future. They could complement our results, as well as, point out interesting topics out of the scope of this Doctoral Thesis.

One natural way to continue our research is the assessment of our methodology in a larger EEG database. The inclusion of a larger database would increase the statistical power of our results, as well as it could help to identify whether different schizophrenia subgroups could be identified. High-density EEG recordings provide a higher accuracy for both two-levels of analysis (*i.e.* local activation and EEG interactions). In this regard, LORETA analysis would improve spatial localization of the neural generators by increasing the number of electrodes.

Three different time-frequency methodologies were used in this Doctoral Thesis: Short-Time Fourier Transform, Hilbert Transform and Wavelet Transform. Further work is necessary in order to address novel time-frequency representations, as well as different mother wavelet functions that provide a more appropriate relationship between time and frequency resolution. In addition, a better understanding of the neurophysiological processes that underlie the time-frequency features observed in scalp neural data would require complementary methodological approaches, such as simultaneous invasive and non-invasive recordings, such as ECoG or fMRI data. It would allow linking the activity at the level of individual neurons and populations of neurons recorded at scalp EEG. Likewise, novel brain connectivity measures could be obtained by using autoregressive methods such as S–coherency, Granger inequality or partial DFT.

Functional brain integration can be characterized by EEG data in two ways: functional and effective connectivity. Functional connectivity describes statistical dependencies between data, whereas effective connectivity reflects the causal inference of one system over another. Future researches could address the application of complementary unidirectional functional connectivity measures and bidirectional effective connectivity to the EEG data. Furthermore, the study of the directionality of the CFC and the evaluation of pair-wise CFC patterns between electrodes could further improve the comprehension of the functional role of hierarchical neural rhythms.

On the basis of further analyses of functional, effective and pair-wise CFC connections, a complex network analysis could be addressed. In the last decade, brain networks have been brought into focus in neuroscience, allowing to use a wide array of quantitative tools and methods from complex network theory (Sporns, 2013). Network theory analysis provides an engagement between segregation and integration brain functions: functional integration measures global communication between network hubs (*i.e.* distant brain areas) and functional segregation could be formed by local network communities that are intrinsically densely connected and strongly coupled (Sporns, 2013). Preliminary analysis assessed the use of complex network theory for characterizing EEG brain networks, suggesting an abnormal organization of the brain functional network in schizophrenia (Bachiller et al., 2013). However, further analyses are required for understanding complex brain networks in this syndrome.

In summary, the analysis of the response to an auditory oddball task was used to gain further insights into the neural mechanisms underlying cognitive dysfunctions in schizophrenia. Event-related patterns based on time-frequency representations provide a more sensitive measure to describe schizophrenia alterations than resting-state EEG analysis. Our research proposal assessed time-frequency evoked and induced brain activity during an auditory cognitive task, obtaining a reliable characterization of dynamical neural patterns. Our findings supports the aberrant salience and dysconnection hypotheses: our results revealed that schizophrenia patients showed an attention-dependent modulation of spectral distribution and functional connectivity in specific frequency bands.

Appendices

Appendix A: Scientific production during this Doctoral Thesis

A.1. Papers indexed in the Journal Citation Reports

1. **Bachiller, A.**, Romero, S., Molina, V., Alonso, J. F., Mañanas, M., Poza, J. & Hornero, R (2015) Auditory P3a and P3b neural generators in schizophrenia: An adaptive sLORETA P300 localization approach. *Schizophrenia Research*, 169, 318–325. Impact Factor: 4.453. Position 25 of 140 (Q1) PSYCHIATRY

2. **Bachiller, A.**, Poza, J., Gómez, C., Suazo, V., Molina, V. & Hornero, R. (2015) A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia. *Journal of Neural Engineering*, 12, 016007. Impact Factor: 3.493. Position 10 of 76 (Q1) BIOMEDICAL ENGINEERING

3. **Bachiller, A.**, Lubeiro, A., Díez, A., Suazo, V., Domínguez, C., Blanco, J. A., Ayuso, M., Hornero, R., Poza, J., & Molina, V. (2015) Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task. *European Archives of Psychiatry and Clinical Neuroscience*, 265, 525–535. Impact Factor: 4.113. Position 36 of 193 (Q1) CLINICAL NEUROLOGY and 30 of 140 (Q1) PSYCHIATRY

4. **Bachiller, A.**, Díez, A., Suazo, V., Domínguez, C., Ayuso, M., Hornero, R., Poza, J., & Molina, V. (2014) Decreased spectral entropy modulation in patients with schizophrenia during a P300 task. *European Archives of Psychiatry and Clinical Neuroscience*, 264, 533–543. Impact Factor: 3.525. Position 47 of 192 (Q1) CLINICAL NEUROLOGY and 38 of 140 (Q2) PSYCHIATRY

5. Molina, V., **Bachiller, A.**, Gomez-Pilar, J., Lubeiro, A., Hornero, R., Cea-Cañas, B., Valcárcel, C., Haidar, MK. & Poza, J. (2017). Deficit of entropy modulation of the EEG in schizophrenia associated to cognitive performance and symptoms. A replication study. *Schizophrenia Research*, In press. Impact Factor: 3.986. Position 25 of 140 (Q1) PSYCHIATRY

6. Gómez-Pilar, J., Poza, J., **Bachiller, A.**, Gómez, C., Núñez, P., Lubeiro, A., Molina, V. & Hornero, R. (2017) Quantification of graph complexity based on the edge weight distribution balance: Application to brain networks. *International Journal of Neural Systems*, *Acepted*. Impact Factor: 6.085. Position 2 of 130 (Q1) COMPUTER SCIENCE, ARTIFICIAL INTELLIGENCE

7. Núñez, P., Poza, J., **Bachiller, A.**, Gómez-Pilar, J., Lubeiro, A., Molina, V. & Hornero, R. (2017) Exploring non-stationarity patterns in schizophrenia: neural reorganization abnormalities in the alpha band. *Journal of Neural Engineering*, 14, 046001. Impact Factor: 6.085. Position 2 of 130 (Q1) COMPUTER SCIENCE, ARTIFICIAL INTELLIGENCE

8. García, M., Poza, J., **Bachiller, A.**, Santamarta, D. & Hornero, R. (2016) Effect of infusion tests on the dynamical properties of intracranial pressure in hydrocephalus. *Computer Methods and Programs in Biomedicine*, 134, 225–235. Impact Factor: 1.862. Position 16 of 105 (Q1) of COMPUTER SCIENCE, THEORY & METHODS.

9. Khadmaoui, A., Gómez, C., Poza, J., **Bachiller, A.**, Fernández, A., Quintero, J. & Hornero, R. (2016) MEG Analysis of Neural Interactions in Attention-Deficit/Hyperactivity Disorder. *Computational Intelligence and Neuroscience*, 8450241. Impact Factor: 0.430. Position 248 of 256 (Q4) NEUROSCIENCES

10. Molina, V., **Bachiller, A.**, Suazo, V., Lubeiro, A., Poza, J. & Hornero, R. (2016) Noise power associated to decreased task-induced variability of brain electrical activity in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 266, 55–61. Impact Factor: 4.113. Position 36 of 193 (Q1) CLINICAL NEUROLOGY and 30 of 140 (Q1) PSYCHIATRY

11. Gómez-Pilar, J., Poza, J., **Bachiller, A.**, Gómez, C., Molina, V. & Hornero, R. (2015) Neural Network Reorganization Analysis during an Auditory Oddball Task in Schizophrenia using Wavelet Entropy. *Entropy*, 17, 5241–5256. Impact Factor: 1.743. Position 25 of 78 (Q2) PHYSICS, MULTIDISCIPLINARY

12. Poza, J., Gómez, C., **Bachiller, A.** & Hornero, R. (2012) Spectral and non-linear analyses of spontaneous MEG activity in Alzheimer's disease. *Journal of Healthcare Engineering*, 3, 299–322. Impact Factor: 0.662. Position 78 of 83 (Q4) HEALTH CARE SCIENCES & SERVICES

A.2. Recent papers submitted

1. **Bachiller, A.**, Poza, J., Gomez–Pilar, J., Gómez, C., Lubeiro, A., Ayuso, M., Molina, V. & Hornero, R. (2016) Investigating ERPAC patterns of brain activity: Evidence of alpha–gamma hierarchical organization elicited by an auditory oddball task. *NeuroImage: Clinical*, *Submitted*. Impact Factor: 4.348. Position 12 of 77 (Q1) COGNITIVE NEUROSCIENCE; 14 of 124 (Q1) RADIOLOGY NUCLEAR MEDICINE & MEDICAL IMAGING; 18 of 141 (Q1) NEUROLOGY AND 28 of 329 (Q1) NEUROLOGY (CLINICAL)

A.3. International conferences

1. **Bachiller, A.**, Gomez–Pilar, J., Poza, J., Núñez, P., Gómez, C., Lubeiro, A., Molina, V. & Hornero, R. Event-related phase-amplitude coupling: A comparative study. *Proceedings of the 3rd International Conference on NeuroRehabilitation*, ICNR2016, 757-761, La Granja, Segovia (Spain), 2016.

2. Núñez, P., J., Poza, **Bachiller, A.**, Gomez–Pilar, J., Gómez, C., Lubeiro, A., Molina, V. & Hornero, R. Analysis of functional connectivity during an auditory oddball task in schizophrenia. *Proceedings of the 3rd International Conference on NeuroRehabilitation*, ICNR2016, 751–755, La Granja, Segovia (Spain), 2016.

3. Núñez, P., Poza, J., Gómez-Pilar, J., **Bachiller, A.**, Gómez, C., Lubeiro, A., Molina, V., & Hornero, R. Analysis of the Non-stationarity of Neural Activity during an Auditory Oddball Task in Schizophrenia. *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Conference*, EMBC 2016, 3724-3727, August 16–20, Orlando, USA.

4. Gómez-Pilar, J., Poza, J., **Bachiller, A.**, Núñez, P., Gómez, C., Lubeiro, A., Molina, V., & Hornero, R. Novel Measure of the Weigh Distribution Balance on the Brain Network: Graph Complexity Applied to Schizophrenia. *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Conference*, EMBC 2016, 700–703, August 16-20, Orlando, USA.

5. Gómez, C., Poza, J., Gómez-Pilar, J., **Bachiller, A.**, Juan-Cruz, C., Tola, M. A., Carreres, A., Cano, M. & Hornero, R. Analysis of Spontaneous EEG Activity in Alzheimer's Disease Using Cross-Sample Entropy and Graph Theory. *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Conference*, EMBC 2016, 2830–2833, August 16-20, Orlando, USA.

6. Poza, J., Gómez, C., García, M., **Bachiller, A.**, Fernández, A. & Hornero, R. Analysis of Spontaneous MEG Activity in Mild Cognitive Impairment and AlzheimerÕs Disease using Jensen's Divergence. *Proceedings of the 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Conference*, EMBC 2014, 1501-1504, August 26–30, Chicago, USA.

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A.4. National conferences

1. Gómez-Pilar, J., Poza, J., **Bachiller, A.**, Gómez, C., Molina, V. & Hornero, R. Caracterización de la Dinámica en la Eficiencia de la Red Neuronal en Esquizofrenia en Tarea Cognitiva Auditiva. *Actas del XXXIII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2015, 167–170, November 4-6, Madrid, Spain.

2. **Bachiller, A.** Poza, J., Gómez-Pilar, J., Gómez, C., Molina, V. & Hornero, R. Análisis del acoplamiento cruzado entre frecuencias en la esquizofrenia durante la realización de una tarea cognitiva auditiva. *Actas del XXXII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2014, 1–4, November 26-28, Barcelona, Spain.

3. Gómez-Pilar, J., **Bachiller, A.**, Poza, J., Gómez, C., Molina, V., & Hornero, R. Caracterización de Potenciales Evocados del EEG en Esquizofrenia mediante Teoría de Redes Complejas. *Actas del XXXII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2014, 1–4, November 26-28, Barcelona, Spain.

4. García, M., Poza, J., Santamarta, D., **Bachiller, A.**, & Hornero, R. Caracterización de la señal de presión intracraneal empleando la transformada wavelet y la turbulencia espectral. *Actas del XXXII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2014, 1–4, November 26-28, Barcelona, Spain.

5. **Bachiller, A.**, Poza, J., Gómez, C., Carreres, A., & Hornero, R. Análisis de la conectividad en la actividad EEG de enfermos de Alzheimer mediante distancias espectrales. *Actas del XXX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2012, 1–4, November 19 - 21, San Sebastián, Spain.

6. Poza, J., García, M., **Bachiller, A.**, Carreres, A., Rodríguez, E. & Hornero, R. Aplicación de la teoría de grafos para la caracterización de la actividad electroencefalográfica en la enfermedad de Alzheimer. *Actas del XXX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2012, 1-4, November 19 - 21, San Sebastián, Spain.

7. **Bachiller, A.**, Poza, J., Carreres, A., Jimeno, N. & Hornero, R. Análisis de la irregularidad en la actividad EEG de enfermos de Alzheimer mediante distancias espectrales. *Actas del XXIX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2011, 115–118, November 16 - 18, Cáceres, Spain.

8. Poza, J., **Bachiller, A.**, García, M., Gómez, C., Fernández, A. & Hornero, R. Análisis de la actividad MEG en enfermos con Alzheimer y deterioro cognitivo leve mediante la turbulencia espectral. *Actas del XXIX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, CASEIB 2011, 119–122, November 16 - 18, Cáceres, Spain.

A.5. Invited conference presentations

1. Bachiller, A. EEG data analysis in schizophrenia. *XXX Reunión de la Asociación Castellano y Leonesa de Psiquiatría*, 2016, Oct 7-8, Palencia, Spain.

2. Bachiller, A. Cross-frequency coupling in schizophrenia. *IV Reunión Internacional de Actualización en Esquizofrenia*, 2016, May 27-28, Valladolid, Spain.

3. Bachiller, A. Entropy and small-world network in EEG patterns in schizophrenia. *III Reunión Internacional de Actualización en Esquizofrenia*, 2014, May 23-24, Valladolid, Spain.

Appendix B: Resumen en castellano

B.1. Introducción a la esquizofrenia.

La esquizofrenia es un trastorno mental crónico, caracterizado por una serie de síntomas psiquiátricos como las alteraciones en la percepción o la expresión de la realidad (alucinaciones), delirios, trastornos afectivos o de comportamiento y una deficiencia cognitiva en tareas como el lenguaje, el razonamiento o la planificación.

Los primeros signos de la esquizofrenia suelen aparecer durante la adolescencia o el comienzo de la edad adulta, aunque también se han dado casos en los que aparecen en personas mayores de 40 años. Los pacientes con esquizofrenia suelen experimentar un deterioro de su capacidad en varias destrezas importantes en el día a día, como son las relaciones interpersonales, la formación, el trabajo, la vida familiar o la comunicación. Los síntomas de la enfermedad varían de una persona a otra. Además suelen variar con el tiempo, empeorando durante los períodos con episodios psicóticos y permitiendo una actividad normal en los periodos de estabilidad.

Las causas de la esquizofrenia aún son desconocidas. Se cree que diferentes factores actúan conjuntamente en su desarrollo. Varios estudios han afirmado que los factores genéticos, ambientales o las lesiones cerebrales en el parto pueden ser importantes para el desarrollo de la enfermedad. Por otro lado, el consumo de drogas también han sido asociados con el desarrollo de la esquizofrenia y otros síntomas psicóticos.

El diagnóstico de la esquizofrenia se basa en recomendaciones oficiales conocidas como criterios DSM-V. La práctica habitual para el diagnóstico de la esquizofrenia incluye la revisión del historial médico, la realización de un examen físico y de pruebas de laboratorio para excluir otras posibles causas. Complementariamente, se recomienda realizar un examen de orina y de sangre para descartar el consumo de drogas. Una vez que se han excluido otras posibles causas, el diagnóstico médico se basa en los síntomas observados en el paciente, así como en los comentarios del paciente y de su familia. Este proceso puede ser largo y confuso, debido a que los síntomas han de estar presentes durante al menos 6 meses. Normalmente, el tratamiento de la esquizofrenia consiste en una combinación de medicación y psicoterapia. La medicación consiste en antipsicóticos (típicos y atípicos) y se utiliza generalmente para reducir los síntomas de la esquizofrenia. La psicoterapia tiene como fin ayudar al paciente a comprender la enfermedad y a sobrellevarla, con el fin de mejorar su conducta social.

Con el fin de comprender la patofisiología de la enfermedad, varias investigaciones han centrado sus esfuerzos en relacionar sus síntomas con la identificación de anormalidades en diferentes regiones corticales. Recientes estudios han establecido que la esquizofrenia provoca una deficiencia en la actividad cerebral que engloba a varias áreas corticales y la conexión entre ellas. Estos resultados han apoyado la teoría que asocia a la esquizofrenia

con un fallo en la asignación de relevancia. Asimismo, la esquizofrenia ha sido definida como un síndrome de desconexión, asociado con una disminución de la capacidad de integración de la información entre las diferentes áreas cerebrales.

La búsqueda de marcadores biológicos, que permitan caracterizar y comprender en mayor medida la esquizofrenia, ha motivado el estudio de la actividad electromagnética generada en la corteza cerebral. La esquizofrenia es un trastorno cognitivo, por lo tanto cabe esperar que las anomalías provocadas por la enfermedad puedan verse reflejadas en la actividad electromagnética cerebral. Los potenciales evocados (i.e. combinación del registro de EEG con la utilización de un paradigma de respuesta a un estímulo) reflejan la actividad post-sináptica asociada a las neuronas distribuidas por la corteza cerebral. Por lo tanto, el análisis del EEG tras la respuesta a un estímulo cognitivo es una herramienta muy útil para caracterizar la evolución temporal del funcionamiento neuronal provocado por la realización de una tarea.

B.2. Hipótesis y objetivos

En la presente Tesis Doctoral se trabaja bajo la hipótesis general de que *el análisis de las funciones de segregación e integración sobre la señal de EEG permite caracterizar los mecanismos neuronales asociados con la esquizofrenia.* Para ello, se aplican dos niveles de análisis sobre el registro de EEG: (*i*) activación local, mediante el estudio de la regularidad de las oscilaciones neuronales y el análisis de las fuentes neuronales; y (*ii*) interacciones entre ritmos cerebrales, analizando tanto la conectividad entre la señal en diferentes electrodos como la jerarquía de las oscilaciones neuronales.

De acuerdo con dicha hipótesis, el objetivo principal de la Tesis Doctoral es el *diseño y la aplicación de nuevos parámetros a los registros de EEG con el objetivo de identificar los sustratos neuronales asociados a la esquizofrenia.* Para poder llevarlo a cabo se han definido varios objetivos específicos:

I. Construir una base de datos con señales de EEG procedentes de pacientes con esquizofrenia y sujetos sanos.

II. Reducir los artefactos presentes en la señal de EEG a través de la definición de un algorítmo semi–automátivo.

III. Seleccionar e implementar aquellos métodos que son más apropiados para su utilización en la caracterización de la esquizofrenia.

IV. Explorar las alteraciones en las oscilaciones neuronales producidas como respuesta a una tarea cognitiva andítiva.

V. Localizar adecuadamente las áreas donde se genera la respuesta a una tareas cognitiva, diferenciando las fuentes para la respuesta relevante (P3b) y para la respuesta no relevante (P3a).

VI. Obtener los patrones de cambio en la conectividad funcional como respuesta a una tarea cognitiva andítiva.

VII. Evaluar la estructura jerárquica de las oscilaciones neuronales a través del estudio del acoplamiento entre frecuencias.

VIII. Realizar análisis estadísticos de los resultados obtenidos para evaluar la metodología aplicada a los registros de EEG.

IX. Comparar y discutir los resultados para extraer las conclusiones apropiadas. Este objetivo incluye la comparación con estudios previos, así como la implementación de otros métodos clásicos de análisis en nuestra base de datos.

X. Publicar los principales resultados y conclusiones obtenidos en revistas internacionales con un alto índice de impacto.

B.3. Materiales

Durante el proceso de investigación incluido en esta Tesis Doctoral se han analizado 2 bases de datos, todas ellas provenientes de sujetos adultos con esquizofrenia y sujetos de control. Los registros de EEG fueron adquiridos con la colaboración del personal clínico bajo supervisión del Dr. Vicente Molina Rodríguez, del Hospital Clínico Universitario de Valladolid. En todos los registros se empleó un paradigma auditivo para valorar los potenciales evocados asociados al procesamiento cognitivo. Este paradigma consiste en la presentación de 3 estímulos auditivos (90 dB de intensidad, 50 ms. de duración y un tiempo de subida y bajada de 5 ms.) con distinta probabilidad de aparición: estímulo *estándar* (2000 Hz.; 60 % de probabilidad), estímulo *target* (500 Hz., 20 % de probabilidad) y estímulo *distractor* (1500 Hz., 20 % de probabilidad). La tarea consistió en que el sujeto debe presionar un botón como respuesta al *target* de baja probabilidad, así como inhibir la respuesta de presionar el botón ante los estímulos estándar y distractor. La primera base de datos está formada por 69 registros de EEG adquiridos mediante un electroencefalografo (*BrainVision V-Amp de Brain Products*) de 17 canales pasivos con una frecuencia de muestreo de 250 Hz. Por otro lado, la segunda base de datos la forman 79 señales de EEG adquiridas con una frecuencia de muestreo de 500 Hz mediante un electroencefalografo de 33 canales activos (*BrainVision, Brain Products GmbH; Munich, Germany*). Las siguientes Tablas B.1 y B.2 resumen las principales características de ambas bases de datos.

B.4. Métodos

Las señales electromagnéticas cerebrales son no estacionarias, por lo tanto sus características espectrales dependen del instante de tiempo en el que se observe la señal. Asimismo, el análisis de ERP requiere conservar la información temporal de la activi-

Tabla B1: Datos demográficos y clínicos de los sujetos de la base de datos, divididos en los grupos: pacientes crónicos (CP), pacientes minimamente tratados (MTP) y controles. Los valores se expresan como: media ± desviación típica.

	CP	**MTP**	**Controles**
Sujetos (n)	20	11	38
Sexo (H:M)	12 : 8	7 : 4	23 : 15
Electrodos	17	17	17
Frecuencia de muestreo (Hz)	250	250	250
Edad (años)	40,37 ± 10,36	33,53 ± 9,91	33,65 ± 13,12
PANSS positivo	19,26 ± 5,29	21,12 ± 3,99	NA
PANSS negativo	22,00 ± 4,80	17,00 ± 4,69	NA
PANSS total	76,26 ± 15,63	76,27 ± 11,37	NA

Tabla B2: Datos demográficos y clínicos de los sujetos de la base de datos, divididos en los grupos pacientes crónicos (CP) y controles. Los valores se expresan como: media ± desviación típica.

	CP	**MTP**	**Controles**
Sujetos (n)	20	18	52
Sexo (H:M)	11 : 9	11 : 7	28 : 24
Electrodos	31	31	31
Frecuencia de muestreo (Hz)	500	500	500
Edad (años)	$35{,}95 \pm 8{,}65$	$29{,}33 \pm 8{,}27$	$31{,}60 \pm 9{,}62$
PANSS positivo	$11{,}81 \pm 4{,}52$	$10{,}06 \pm 4{,}78$	NA
PANSS negativo	$16{,}00 \pm 9{,}75$	$12{,}29 \pm 5{,}19$	NA
PANSS total	$53{,}25 \pm 23{,}67$	$41{,}18 \pm 15{,}63$	NA

dad cerebral. Por ello, en esta Tesis Doctoral se han utilizado representaciones tiempo-frecuencia que sean capaces de proporcionar simultáneamente información en tiempo y en frecuencia. En concreto, se han utilizado la transformada corta de Fourier (STFT, *Short–Time Fourier Transform*), la transformada de Hilbert (HT, *Hilbert Transform*) y la transformada *wavelet* (WT, *Wavelet Transform*). La metodología propuesta se basa en analizar el funcionamiento de la dinámica neuronal de la señal EEG basándose en las funciones cerebrales de segregación e integración. Para ello se ha realizado un análisis en dos etapas:

- La función de segregación trata de identificar cada una de las regiones cerebrales con una función específica. Por ello, en una primera etapa se realizó un análisis de la activación local en cada sensor del registro de EEG y se aplicarón técnicas de reconstrucción de fuentes con el objetivo de localizar los principales focos de generación de la actividad neuronal.
- La función de integraciń considera el cerebro como una red altamente interconectada y por lo tanto se centra en evaluar las dependencias entre regiones cerebrales. En esta Tesis Doctoral se han medido las interacciones entre la señal de EEG en los diferentes electrodos a través de un análisis de conectividad. Adenás se ha evaluado la jerarquía de las oscilaciones neuronales mediante una nueva técnica denominada acoplamiento cruzado de frecuencias (CFC, *Cross-Frequency Coupling*).

Además, en futuros estudios se abordará una tercera etapa que relaciona las funciones de segregación e integración a través de un análisis de redes complejas, tratando de extraer parámetros que permitan caracterizar las redes neuronales asociadas a la esquizofrenia.

Por último, en esta Tesis Doctoral se evalua en qué medida los parámetros calculados pueden ofrecer información complementaria, para caracterizar mejor los cambios en la red cerebral provocados por la esquizofrenia, de acuerdo con las teorías que asocian con con un fallo en la asignación de relevancia y la definen la esquizofrenia como un síndrome de desconexión.

B.5. Resultados y discusión

El análisis en dos niveles de la evolución de la señal ERP como respuesta a una tarea cognitiva auditiva ha permitido profundizar en la caracterización de las alteraciones provocadas por la esquizofrenia. Inicialmente, el estudio de la potencia relativa, la frecuencia mediana y la irregularidad de la señal mostró las diferencias entre la actividad cerebral en

reposo y tras la respuesta a una tarea cognitiva. Se observo un incremento de la potencia entre el reposo y la respuesta para frecuencias bajas, un decremento de la potencia para altas frecuencias, así como un decremento de la irregularidad de la señal. Estos cambios entre el reposo y la respuesta fueron estadísticamente más significativos en los sujetos de control que en los pacientes con esquizofrenia, respaldando la hipótesis que asocia a la esquizofrenia con un fallo en la asignación de relevancia.

La reconstrucción de las fuentes neuronales proporciona una información muy útil acerca de la localización de las funciones cerebrales. En esta Tesis Doctoral se han estudiado las áreas cerebrales activadas como respuesta al tono target (P3b) y al tono distractor (P3a). Los generadores del P3a están principalmente localizados en áreas temporales y frontales, sin embargo, el P3b está localizado sobre una red más distribuida que incluye las regiones frontal, temporal, límbica y parietal. Los análisis entre pacientes y controles revelaron una menor activación del P3a en pacientes en las regiones frontal y temporal, mientras que el P3b mostró una menor activación en pacientes en la región frontal, el cíngulo anterior y el cíngulo. Estos resultados podrían estar relacionados con un déficit en la capacidad de discriminación entre estímulos internos y externos, así como en la excitación/inhibición de las respuestas motoras.

A continuación, se ha caracterizado la función de integración mediante la medida del acoplamiento de la señal registrada en los diferentes sensores del EEG. Para ello se han aplicado tres medidas complementarias para anlizar los patrones de conectividad, sincronización y similitud. Los resultados obtenidos mostraron los cambios en los patrones de acoplamiento entre una situación de reposo y tras la respuesta a una tarea cognitiva, así como las diferencias entre los grupos de pacientes y controles. Tanto para bajas como para altas frecuencias, los resultados obtenidos muestran como los pacientes con esquizofrenia no son capaces de modular suficientemente su actividad cerebral tras la realización de una tarea cognitiva. A nivel neurofisiológico, este hecho podría reflejar un fallo a la hora de discriminar el nivel de relevancia frente a una serie de estímulos externos.

Por último, el análisis del CFC ha permitido evaluar la jerarquía de las oscilaciones neuronales. De esta manera se ha demostrado que los procesos cognitivos implican la coordinación de los ritmos cerebrales a diferentes frecuencias. Los resultados obtenidos indican que las oscilaciones neuronales presentan una organización compleja y jerarquizada. En concreto se ha observado un acoplamiento entre la fase de la señal de EEG en la banda alfa [8-13 Hz] y la amplitud en la banda gamma [17-53 Hz]. Estos resultados destacan el importante papel de la banda alfa en la organización de la red cerebral.

B.6. Conclusiones

La mejora de la comprensión de las alteraciones en la dinámica neuronal provocadas por la esquizofrenia es el hilo común de todos los artículos incluidos en esta Tesis Doctoral por compendio de publicaciones. Tras el análisis y la discusión de los resultados obtenidos se han alcanzado las siguientes conclusiones principales:

1. Las oscilaciones neuronales son el principal mecanismo que permite una actividad neuronal coordinada. La realización de diferentes tareas cognitivas puede modular estas oscilaciones en las diferentes bandas de frecuencia. Por lo tanto, alteraciones en estas oscilaciones están relacionadas con una disfunción de la actividad cerebral en la esquizofrenia.

2. Los parámetros espectrales, como la potencia relativa, la frecuencia mediana o la irregularidad, muestran alteraciones en la reconfiguración de la red cerebral mientras los sujetos realizan una tarea cognitiva auditiva. Asimismo, los cambios producidos

están relacionados con los parámetros clínicos que caracterizan la severidad de la esquizofrenia.

3. La respuesta a diferentes estímulos auditivos implica la activación de diferentes áreas cerebrales. Esta Tesis Doctoral demuestra que las fuentes de origen de la actividad electríca cerebral como respuesta a la novedad (componente P3a) y a la relevancia (componente P3b) se encuentran en diferentes regiones del cerebro.

4. La definición de una ventana de análisis adaptativa (WOI) basada en las propiedades de la componente P300 permite reducir el efecto de la variabilidad de la latencia del P300 entre sujetos. De esta manera, se consigue obtener una localización más precisa de las fuentes de la actividad eléctrica cerebral.

5. La esquizofrenia altera el acoplamiento entre diferentes regiones cerebrales. Asimismo, el uso de diferentes técnicas de medida del acoplamiento (conectividad, sincronización y similitud) permite caracterizar dicho acoplamiento desde diferentes perspectivas.

6. Las oscilaciones neuronales presentan una actividad jerárquica y compleja. De esta manera, el acoplamiento cruzado entre frecuencias puede ayudar a caracterizar el acoplamiento de los procesos neuronales en la esquizofrenia. En particular se destaca el papel principal del balance entre la función excitatoria e inhibitoria.

En resumen, en esta Tesis Doctoral se ha profundizado en la caracterización de la esquizofrenia a partir de la información extraída de la señal de EEG. Nuestra propuesta analiza los cambios a nivel neuronal producidos tras la realización de una tarea cognitiva auditiva. Los resultados obtenidos muestran que los pacientes con esquizofrenia presentan diversas anomalías en la activación local, en las fuentes neuronales, la conectividad entre diferentes electrodos y la jerarquía de las oscilaciones neuronales. La disminución de la actividad neuronal como respuesta a una tarea cognitiva en sujetos con esquizofrenia confirma la hipótesis que asocia a la esquizofrenia con un fallo en la asignación de relevancia. Asimismo, el análisis de la conectividad funcional entre pares de electrodos contribuye a apoyar el papel de la esquizofrenia como un síndrome de dexconexión.

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