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TESIS DOCTORAL

Aplicación de técnicas de resonancia magnética al estudio de los trastornos del espectro autista y los trastornos psicóticos

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Laura Pina Camacho

Directores

Mara Parellada Redondo
Joost Janssen

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APPLICATION OF MAGNETIC RESONANCE IMAGING TO THE STUDY OF AUTISM SPECTRUM DISORDERS AND PSYCHOTIC DISORDERS

Doctoral dissertation authored and presented by

LAURA PINA CAMACHO

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by Universidad Complutense de Madrid

Supervisors

Dr Mara Parellada Redondo (Universidad Complutense, IiSGM, Madrid)

Dr Joost Janssen (Instituto de Investigación Sanitaria Gregorio Marañón, IiSGM, Madrid)

Madrid, 2015

AUTORIZACIÓN DEL DIRECTOR DE TESIS PARA SU PRESENTACIÓN

Dª. MARA PARELLADA REDONDO, Lda. En Medicina, Especialista en Psiquiatría y Doctor en Medicina, Profesora Asociada de Psiquiatría del Departamento de Psiquiatría y Psicología Médica, Facultad de Medicina de la Universidad Complutense, Madrid, España

D. JOOST JANSSEN, Ldo. en Neuropsicología y Doctor en Medicina por el Departamento de Psiquiatría, UMC, Utrecht, Holanda. Investigador Postdoctoral en el Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid

INFORMAN:

Que el trabajo titulado **'Aplicación de técnicas de resonancia magnética al estudio de los trastornos del espectro autista y los trastornos psicóticos'** que presenta la licenciada Dña. Laura Pina Camacho en la Facultad de Medicina para optar al título de Doctor, ha sido desarrollado bajo nuestra dirección en el Servicio de Psiquiatría del Niño y Adolescente del Departamento de Psiquiatría del Hospital General Universitario Gregorio Marañón, Madrid.

.

Tras su revisión consideramos que está preparado para su defensa y calificación, por lo que

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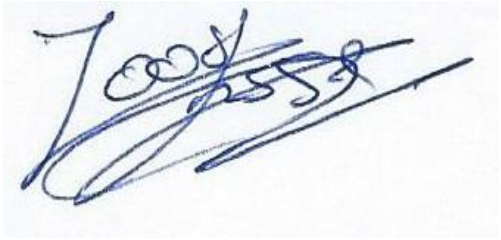

Fdo: Dra. Mara Parellada Redondo Fdo: Dr. Joost Janssen

Sólo estudiaba las partes del cuerpo que quedarían cubiertas por la mortaja.

Este hecho excluía los pies y la cabeza, una verdadera frustración (...)

Noah Gordon

El Médico

Para mi abuelo, por enseñarme a amar la Medicina

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LIST OF ABBREVIATIONS

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The following table describes the meaning of various abbreviations and acronyms used throughout the doctoral dissertation.

Abbreviation	Meaning
AD	Axial diffusivity
ADHD	Attention-deficit hyperactivity disorder
AFP	Affective psychoses
ASD	Autism spectrum disorders
CDC	Centers for Disease Control and Prevention
CNVs	Copy number variations
COS	Childhood-onset schizophrenia
CAFEPS	The Child and Adolescent First-Episode Psychosis Study
CDD	Child disintegrative disorder
CSF	Cerebrospinal fluid
CT	Computerized tomography
DMN	Default mode network
DTI	Diffusion tensor imaging
DSM	Diagnostic and statistical manual of mental disorders
EOP	Early-onset psychosis
FA	Fractional anisotropy
FASD	Fetal alcohol spectrum disorders
FEP	First-episode psychosis

fMRI	Functional magnetic resonance imaging
GM	Gray matter
HFA	High-functioning autistic disorder
ICD	International Statistical Classification of Diseases and Related Health Problems
IQ	Intelligence quotient
LFA	Low-functioning autistic disorder
MD	Mean diffusivity
MRI	Magnetic resonance imaging
NIMH	National Institute of Mental Health
NMR	Nuclear magnetic resonance
NOS	Not otherwise specified
NSS	Neurological soft signs
PANSS	Positive and negative syndrome scale
PDD	Pervasive developmental disorder
PEPs-Img	First-episode psychosis-Imaging study
RD	Radial diffusivity
RDoC	Research Domain Criteria
ROI	Region of interest
SSD	Schizophrenia spectrum disorders
SVM	Support vector machines
TBV	Total brain volume
US	United States
VBM	Voxel-based morphometry
WM	White matter

1. INTRODUCTION

1. INTRODUCTION

1.1. MAGNETIC RESONANCE IMAGING AND THE STUDY OF HUMAN BRAIN

1.1.1. Introduction to magnetic resonance imaging

Nuclear magnetic resonance (NMR) was discovered in 1946 independently by Bloch (Bloch, Hansen, & Packard, 1946) and Purcell (Purcell, Torry, & Pound, 1946), who were both awarded the Nobel Prize in 1952. The idea to apply NMR to *in vivo* studies dates back to 1968, when the first NMR signals from a live animal were produced (Jackson & Langham, 1968). Magnetic resonance imaging (MRI) in humans was subsequently developed in the late '70s to examine the anatomical and pathological macrostructure of the brain (Damadian, Minkoff, & Goldsmith, 1978; Mansfield & Maudsley, 1977). This technique provided a step forward in the study of human brain relative to computerized tomography (CT), due to its ability to display images in any plane and with an increased spatial resolution, the non-use of ionizing radiation and the lack of imaging distortion resulting from the superposition of bone material (Santa Marta, Sánchez, Pascau, & Desco, 2003).

Since then, the development of MRI techniques has offered a window through which we can look at the human brain directly and gain understanding of brain anatomy and function in health and illness (N.C. Andreasen, 2003). The two main groups of MRI techniques that can be applied to the study of human brain are

structural MRI, which is sensitive to biophysical properties of local brain tissue, and functional MRI (fMRI), which is sensitive to temporally changing neural activity.

Structural MRI (usually called 'MRI', and henceforth referred to as such), exploits the contrast in image intensity distributions between and within different tissue types, i.e. gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). These contrast differences allow for the delineation of brain structures (Fischl et al., 2002), assessment of shape variations in particular brain regions (Styner, Lieberman, Pantazis, & Gerig, 2004), and quantification of local tissue volumes. Initially, MRI studies measured global or regional tissue volumes by totaling the amount of voxels in manually predefined regions of interest (ROIs). These methods were followed up by voxel-based approaches such as voxel-based morphometry (VBM) (Ashburner & Friston, 2000), which allowed for whole brain exploration of structural differences between diagnostic groups on a voxel-by-voxel basis, and thus were not dependent on manually predefined regions. Later on, with the advent of improved image acquisition (e.g., higher field strength, higher voxel resolution, and improved GM-WM contrast), additional techniques which focused on measuring the thickness, surface area, and curvature of the cortex emerged (Fischl & Dale, 2000; Gorczowski et al., 2010), providing new information about brain morphology that could be used to detect alterations in psychiatric patients.

In parallel with the study of WM volume, **diffusion tensor imaging (DTI)** techniques emerged to provide complementary information on the study of WM

and structural connectivity within brain networks. DTI (Basser, Mattiello, & LeBihan, 1994; Basser & Pierpaoli, 1998) provides information about the fiber tracts *in vivo* by characterizing the three-dimensional diffusion of water molecules in the brain (Alexander, Lee, Lazar, & Field, 2007). Main DTI measurements include fractional anisotropy (FA), which reflects the directionality of molecular displacement by diffusion and varies between 0 (isotropic diffusion) and 1 (anisotropic diffusion); axial diffusivity (AD), which reflects diffusivity along the longitudinal axis of WM fibers (parallel diffusivity), radial diffusivity (RD), which reflects the diffusion of water perpendicular to WM fibers, and mean diffusivity (MD), which describes the rotationally invariant magnitude of water diffusion within brain tissue (Alexander et al., 2007). Furthermore, the connectivity between brain regions can be mapped more directly by following the dominant orientations of the water diffusion using DTI-based tractography (Melhem et al., 2002).

Functional MRI (fMRI) techniques emerged in the ‘90s and advanced the study of brain function by leveraging the relationship between neural activity and hemodynamics (Logothetis, 2003; Norris, 2006). Indeed, the study of activation of particular brain regions (known as functional segregation) and of the temporal co-activation of anatomically distant regions (known as functional connectivity) through fMRI has helped characterize how the brain’s responses are mediated by connections between brain areas and how these connections change with the execution of a particular task or with the presence of a particular symptom or behavioural phenotype. (Friston, 2009).

In this doctoral dissertation, we will focus on the application of MRI, DTI and fMRI, t o the study of human brain and neurodevelopmental disorders. These techniques require different analytic procedures and differ with respect to their application to the study of human brain (see Table 1). Nevertheless, the complementary information they provide is quite helpful, as the relationship between structure and function is fundamental to the understanding of brain organization (Smith et al., 2004).

Table 1. Characteristics of MRI, DTI and fMRI techniques

MRI	High spatial resolution (submillimeter to millimeter): structural information Volumetric / morphometric quantification
DTI	Moderate spatial resolution (submillimeter to millimeter): information on WM structure
fMRI	Poor spatial resolution (millimeter) High temporal resolution (seconds to minutes): assessment of function / behaviour through indirect marker (blood oxygen) Results affected by additional confounders: • Degree of cooperation, anxiety/arousal levels, and cognitive strategies used (event-related fMRI tasks) • Variation in behavioural paradigms across laboratories

Legend: DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; MRI, structural magnetic resonance imaging; WM, white matter

1.1.2. Applications of MRI techniques to the study of psychiatric disorders

MRI has proved useful in neurology and neurosurgery with a wide range of applications, from the identification of structural pathology to their application to preoperative neurosurgical planning, intraoperative functional neuronavigation or postoperative rehabilitation (Bigler, 1996; Nimsky, Ganslandt, von Keller, & Fahlbusch, 2006). However, in psychiatry, despite the significant progress in MRI techniques and the breakthroughs in technology and computational methods over the past three decades (Wise, 2013), the application of MRI to clinical practice has been limited to the identification of potentially reversible ´organic´ causes underlying psychiatric symptoms. For example, cerebral tumors are a major cause of psychiatric symptoms, especially when the tumor is in the frontal or temporal lobes (Wessling, Simosono, Escosa-Bage, & de Las Heras-Echeverria, 2006). In keeping with this, prior to the Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV), the term 'organic' mental disorder was (and still is) used by psychiatrists to define psychopathological syndromes resulting from a systemic medical or cerebral disorder, as opposed to 'functional' mental disorders, which arise from physiological abnormalities that cannot be detected by existing laboratory / imaging procedures (Fleiss, Gurland, & Roche, 1976; Hales, Polly, & Orman, 1989)

The development of the Research Diagnostic Criteria in the '70s led to the innovative DSM-III criteria for clinical use, aimed at building a long-term framework through which these - 'functional' - psychiatric disorders could be

defined and classified based on clinical observation as well as underlying physiopathology (Spitzer, Endicott, & Robins, 1978). However, diagnostic classifications to date have failed to align with this purpose (T. Insel et al., 2010). Indeed, current definitions of psychiatric disorders in classification systems such as the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or the DSM-5 are still based solely on the observation of symptoms and behaviours (American Psychiatric Association, 2013; World Health Organisation, 1992) with no laboratory / imaging marker to inform the diagnostic process. Although DSM / ICD nomenclature might help clinicians communicate about clinical pictures, and may be useful for teaching or legal and billing purposes, it seems to have a limited validity, due to the limited psychopathological rigor and understanding of the underlying pathophysiology.

In 2010, as the major federal research agency funding mental health research in the United States (US), the National Institute of Mental Health (NIMH) underscored the potential advantages of a neuroscience-based approach to psychiatric classification and tried to reach consensus as to how to achieve this goal (T. Insel et al., 2010). A new initiative, the Research Domain Criteria (RDoC) project, was launched with the aim of creating a framework for research on pathophysiology, especially for genomics and neuroscience, which ultimately will inform future classification schemes (National Institute of Mental Health, 2010). The main goal was to ensure that psychiatric diagnoses had not only reliability but also validity (T. Insel et al., 2010). Clinicians could for example supplement a clinical evaluation of what we now call an ‘anxiety disorder’ with data from functional or structural MRI or genomic sequencing to determine prognosis and

appropriate treatment for each individual patient, analogous to what is done routinely today in many other areas of medicine (T. Insel et al., 2010). The application of MRI techniques to the study of normal brain development and brain physiopathology therefore constitutes an opportunity to achieve this goal.

Among psychiatric disorders, there is a group of conditions that seem to emerge from perturbations of normal brain maturation at early stages of development, collectively known as neurodevelopmental disorders. In keeping with the RDoC initiative, MRI techniques can help advance in the understanding of their complex origins and physiopathology, through the study of both the normally developing brain and of the structural and functional brain abnormalities present in individual with these conditions.

1.2. MRI AND THE STUDY OF NEURODEVELOPMENTAL DISORDERS

1.2.1. MRI and the study of normal brain development

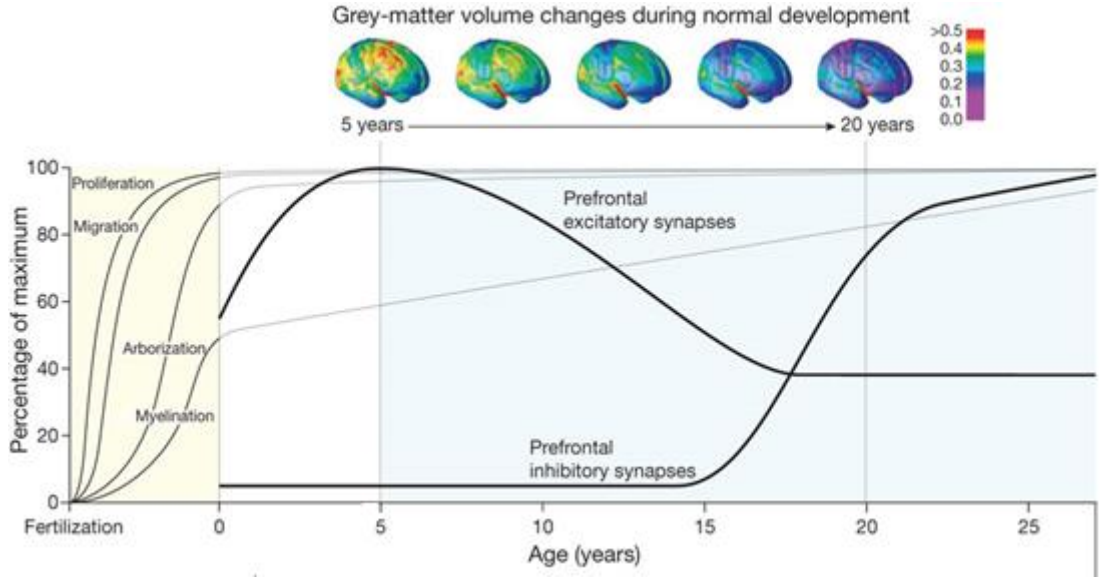
1.2.1.1. Normal brain development. Introduction

During the 20th century and the beginning of the 21st century, knowledge of the microscopic and macroscopic changes in the brain came almost exclusively from the examination of postmortem brain tissue and animal models (Kretzschmar, 2009). These tools are still quite helpful as they allow direct observation of brain morphometry changes and assessment of changes in the

distribution of cell bodies, myelin, and molecular markers within brain tissues, complementing and informing one another (Herculano-Houzel, Messeder, Fonseca-Azevedo, & Pantoja, 2015; Triarhou, 2013; Zilles, Palomero-Gallagher, & Schleicher, 2004).

The above techniques have indeed helped with describing the major events occurring at a microscopic and macroscopic level during normal brain development (see Figure 1).

Figure 1. Major events during brain development



From (T. R. Insel, 2010). Permission for reprint granted by *Nature Publishing Group* through Copyright Clearance Center ('CCC').

As shown in Figure 1, normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination (T. R. Insel, 2010) with the first two processes occurring mostly during prenatal life (e.g. the maximum number of neurons is attained around gestational week 28), and the latter two continuing through the first two postnatal decades. Circuit formation involves a

series of processes itself, such as formation and elimination of synapses, glial development and neuron-glia interaction (Sadler & Langman, 2010).

The described microscopic changes in the cerebral cortex result in changes detectable at the macroscopic level (see Figure 1). For example, in the first months after birth, there is an exponential increase in the number of neural stem cells that gives rise to the formation of multiple radial cortical columns. This results at a macroscopic level in an increase in the cortical volume through expansion of the cortical surface area, without a comparable increase in cortical thickness (Rakic, 1988, 2009). At later stages, the number of neurons increases linearly within each radial column by asymmetrical divisions of the neural progenitors, resulting in an increase in cortical thickness at a macroscopic level (Rakic, 2009). Gyrification and sulci formation occur in parallel from 14 weeks of gestation onward (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995) under the influence of physical constraints and mechanical factors (Hilgetag & Barbas, 2005; Regis et al., 2005). The increase in brain volume will continue during childhood up until the age of 6–10 years old, when the brain reaches approximately 95% of the volume of the adult brain. From this stage, volumetric increases will be small (see Figure 1). Indeed, a phase of cortical thinning and volume loss will dominate late childhood and adolescence, which might reflect the selective elimination of synapses (Huttenlocher & Dabholkar, 1997), probably accompanied by a reduction in the number of glial cells. Events occurring at the interface between WM and GM, such as the proliferation of myelin into the peripheral cortical neuropil and the changes in axonal calibers in childhood and adolescence may also influence cortical morphology (Sowell et al., 2004).

Of utmost importance in normal brain development is the concept of brain plasticity, which refers to the ability to change structure and function through experience (Knudsen, 2004). Brain development is extremely sensitive to the effect of the environment, especially during restricted temporal windows of development called 'critical or sensitive periods'. For example, an imbalance in binocular vision during childhood (a sensitive period in the development of visual networks) affects visual perception and leads to amblyopia or 'lazy eye' (Fagiolini, Jensen, & Champagne, 2009; Knudsen, 2004). Of note, adolescence is one of the most critical periods of brain development, as a transitional period for individuals to refine and attain cognitive skills necessary to become independent adults (Brenhouse & Andersen, 2011). This sensitive period encompasses vast changes within the brain in parallel with changes in the environment (e.g. increasing academic demands, changes in social relationships), environment imparting therefore long-lasting effects on shaping the adult brain (Andersen & Teicher, 2008; Chudasama & Robbins, 2006; Marsh et al., 2006).

1.2.1.2. MRI and the study of normal brain development.

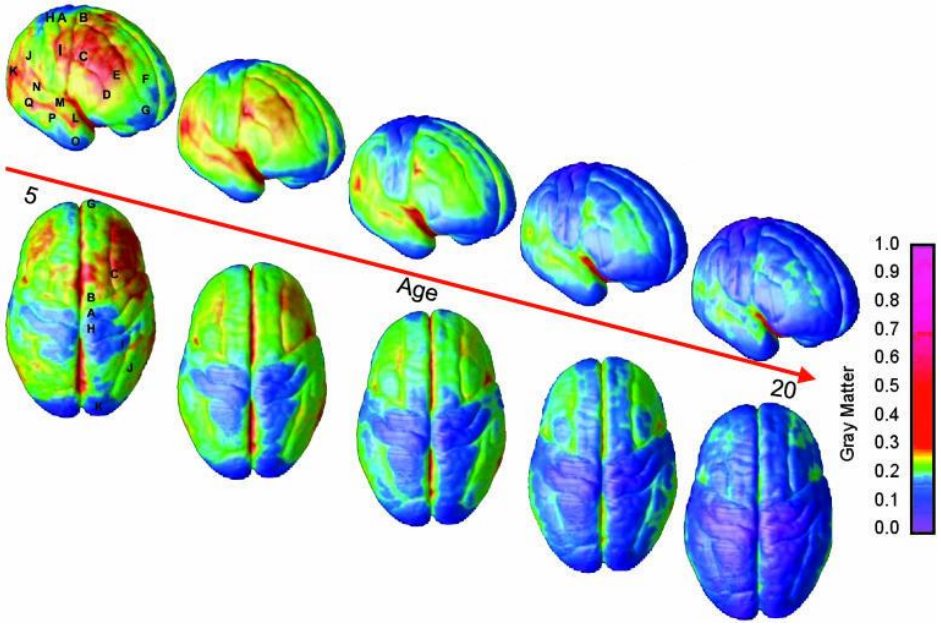
In parallel with studies of postmortem brain tissue and animals models, the advent of MRI techniques provided a new window through which we could observe *in vivo* the changes that take place in the developing human brain, including changes in brain structure, brain connectivity and brain plasticity (N.C. Andreasen, 2003).

MRI and normal brain development. Changes in brain structure

The first cross-sectional MRI studies of typical brain development measured regional (e.g. frontal, temporal, hippocampal) volumes and correlated these measurements with age (Marsh, Gerber, & Peterson, 2008). These studies described a pattern of volume reduction of cortical and subcortical GM from childhood to adulthood, after adjusting for normal variation in head size (Pfefferbaum et al., 1994), with some exceptions, such as the reported increase in amygdala and hippocampal volume with age throughout adolescence (Giedd et al., 1996). MRI longitudinal designs followed, being the first ones conducted in the Child Psychiatry Branch of the NIMH in the US. In these studies, children were scanned at different time points up until the age of 20 years old (Giedd, Blumenthal, et al., 1999). A linear increase with age of WM volume and an ‘‘inverted U-shaped’’ growth trajectory for GM volumes of frontal, parietal, and temporal lobes was reported, with GM volumes peaking 1 to 2 years earlier in girls than in boys (Giedd, Blumenthal, et al., 1999). Subsequent studies conducted mainly (but not only) by the same group consistently showed how GM volumes follow heterochronous trajectories, with different brain regions maturing at different ages and rates, in a typical ‘back-to front and top-to bottom’, non-linear and sex-specific pattern with age (see Figure 2) (Brain Development Cooperative, 2012; Courchesne et al., 2000; Giedd et al., 2015; Gogtay, Giedd, et al., 2004; Lenroot et al., 2007; Raznahan et al., 2011; Raznahan et al., 2014; Sowell et al., 2004). For example, the parietal cortex reached peak maturity in late childhood (around 7.5 years in girls and 9 in boys), whereas the frontal and temporal cortices matured later during adolescence (around 10-11 years, earlier

in girls than in boys) (Giedd et al., 2015). Expansion of subcortical structures such as basal ganglia or of the hippocampus occurred later – i.e. around late adolescence and early adulthood (Raznahan et al., 2014).

Figure 2. Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface



From (Gogtay, Giedd, et al., 2004). Permission for reprint granted by *National Academy of Sciences, U.S.A*, *Copyright (2004).* Legend: The sidebar shows a color representation in units of GM volume. Letters depict regions of interest in the cortex that were selected for analyses in each hemisphere. GM: gray matter.

Studies have also assessed trajectories of cortical thickness, reporting a progressive thickening of the cortex from birth to age 6-7 years (Nie, Li, & Shen, 2013; Nie et al., 2014); thickening of language regions of the frontal (i.e., Broca's area) and left temporo-parietal cortices (Wernicke's area) in parallel with a widespread thinning in the right frontal and bilateral parietal and occipital association cortices (Sowell et al., 2004) from age 5 to 11 years; and a pattern of widespread cortical thinning during adolescence (Aleman-Gomez et al., 2013;

Mutlu et al., 2013), which is reportedly more prominent in girls in frontal and temporal regions (Mutlu et al., 2013). With regard to cortical gyrification, studies show that primary and secondary folding is well-developed before birth, tertiary folding structures undergo rapid development after birth (Nie et al., 2014), and most cortical regions show either constant (i.e. no change) or linearly decreasing trajectories from childhood to adulthood (Mutlu et al., 2013).

The NIMH group has also reported that cortical growth trajectories differ in terms of complexity across cortical regions, with those with laminar architecture (e.g. allocortex, including most limbic areas) showing linear growth trajectories, and polysensory and high-order association areas (e.g. isocortex in the prefrontal cortex) show more complex (e.g. cubic) developmental trajectories. The latter are areas thought to support more complex psychological functions (e.g. working memory, cognitive flexibility) (Gogtay et al., 2006; Shaw et al., 2008). This description may in fact be much more complicated, as brain systems may have multiple critical developmental periods and thus follow more complex developmental trajectories (Knudsen, 2004). Recent studies have indeed shown how these trajectories may be divergent and vary by topological location (Mutlu et al., 2013), for example, within the gyral and sulcal cortex (Vandekar et al., 2015). Other recent studies have reported a simple linear decline in most cortical areas by age 5 years, and all areas by age 8 years, with no cortical thickness peak at early adolescence (Ducharme et al., 2015), so the debate about how the cortex changes is still very much alive. Regarding the progressive cortical thinning during adolescence, a recent study by our group showed that in typically developing adolescents cortical geometric features such as thickness, surface

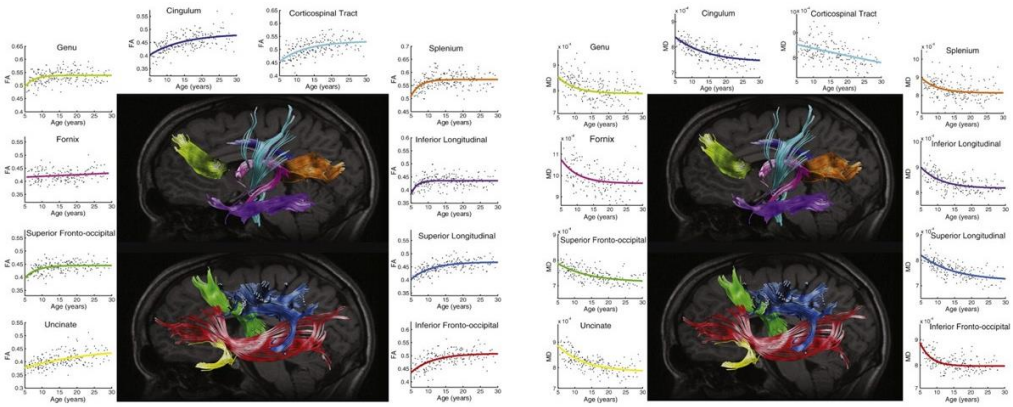
area, sulcal width and depth are related and conjointly contribute to this flattening of the cortex (Aleman-Gomez et al., 2013). This suggests that cortical thinning involves both changes in GM and effects of the maturation of WM (Aleman-Gomez et al., 2013).

MRI and normal brain development. Changes in brain function and brain connectivity

In parallel with MRI studies exploring the structural changes of brain systems throughout development, fMRI studies (most of them cross-sectional) have investigated the changes in the activity and functional connectivity during the development of various brain regions reportedly supporting particular cognitive functions. For example, normal acquisition of reading and phonological skills throughout childhood and adolescence has been associated with age-related increases in activation of left frontal and temporal cortices in parallel with a protracted anatomical thinning of these regions (Sakai, 2005). Normal acquisition of 'inhibitory control' skills during childhood has been associated with age-related increases in the activation of the prefrontal cortex, along with that of anatomically connected subcortical brain regions (Rubia et al., 2000). The development of emotional control during adolescence (associated in turn with the ability to understand social and emotional cues) has been associated with age-related increases in the ability to modulate the activation of the amygdala in response to emotionally evocative stimuli (e.g. fearful faces) through activation of the prefrontal cortex in response to non-emotional salient stimuli (Monk et al., 2003).

DTI and DTI-tractography studies have also been helpful in determining WM changes with age in different brain regions, as well as the development of network connectivity patterns between brain regions. As such, studies (most of them cross-sectional) have shown age-dependent increases in FA (Paus, Keshavan, & Giedd, 2008) in frontostriatal regions from childhood to adulthood (Marsh et al., 2008). This age-related increase in FA has also been described in fronto-temporal regions, the maturation of which seems to be protracted and extends well into adulthood (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008) (see Figure 3).

Figure 3. Age-related fractional anisotropy increases (left) and mean diffusivity decreases (right) by region-of-interest measured by tractography in 202 typically developing subjects



From (Lebel et al., 2008). Permission for reprint granted by *Elsevier* through Copyright Clearance Center ('CCC'). Legend: FA increases (left) and mean diffusivity decreases (right) by ROI measured by tractography in 202 typically developing subjects. ROI: region of interest.

MRI and normal brain development. Brain plasticity and the effect of experience

MRI has also allowed for the study of brain plasticity and assessment of how experience can shape neurodevelopment. Among numerous examples, one longitudinal VBM study showed that medical students who were scanned before studying for an exam, while studying, and 3 months after taking the exam, showed an increase in posterior and lateral parietal GM volumes during the 'learning' period that stabilized thereafter, while hippocampal GM volume increased continuously during the observation period (Draganski et al., 2006).

1.2.2. Abnormal brain development. The neurodevelopmental disorders

1.2.2.1. Introduction. The neurodevelopmental disorders

All processes of brain development that we have described above (neuronal maturation, migration, synaptic pruning, etc.) are the result of a heterochronous, tightly-regulated, and genetically-encoded program with clear influence from experience / environment. This suggests that any deviation from this program early in life may result in the development of aberrant neurodevelopmental trajectories and could lead to the emergence of pathology later in life (Meyer, Feldon, & Dammann, 2011; Owen, O'Donovan, Thapar, & Craddock, 2011).

For example, chemical distortions during early development can cause significant developmental problems, not only in the brain but at a multi-system level. A well-known example is fetal alcohol spectrum disorder (FASD), a group of conditions children are born with if the mother drinks heavily during pregnancy (Mukherjee, Hollins, & Turk, 2006). These children show varying degrees of mental retardation, attention deficit and hyperactivity symptoms, motor problems, heart defects and facial abnormalities. Exposure to other environmental risk factors (e.g. higher parental age, intrauterine infections, maternal stress, childhood maltreatment, deprivation) has also been associated with the emergence of aberrant neurodevelopmental trajectories either through a direct 'toxic' effect on brain tissue or through epigenetic mechanisms (i.e. the environmental factor altering gene expression in the brain through chromatin modifications [Fagiolini et al., 2009]).

Similarly, common genetic variations can confer increased disease vulnerability independently or through moderation of the individual's vulnerability to early environmental stressors (Caspi et al., 2003). For example, cortical thickness and surface area are known to show different neurodevelopmental trajectories which are reportedly 'programmed' by different sets of genes (C. H. Chen et al., 2013; Panizzon et al., 2009). Variation in these genes in conjunction with early environmental insults during 'critical' developmental periods can lead to abnormal developmental trajectories of these cortical components. Abnormal maturation of the cortex and constitution of brain networks may, in turn, lead to the emergence of abnormal behavioural phenotypes, including different

psychopathological manifestations or cognitive deficits (Ecker et al., 2013; Raznahan et al., 2012).

Different combinations of these varied symptoms and cognitive deficits are present in a group of conditions conceptualised as the 'neurodevelopmental disorders'. In these disorders, the development of the central nervous system is disturbed from early stages in life and typically (but not always) manifests in childhood or adolescence, leading to major impairments of personal, social, academic, and/or occupational functioning (American Psychiatric Association, 2013). The new DSM-5 classification system has indeed replaced the DSM-IV section of 'Disorders usually first diagnosed in infancy, childhood, or adolescence' with a new chapter entitled 'Neurodevelopmental Disorders'. This chapter includes intellectual disabilities, communication disorders (the latest including the new social communication disorder), autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), specific learning disorders (reading, writing and mathematics), motor (including tic) disorders, and other specified or unspecified neurodevelopmental disorders (American Psychiatric Association, 2013).

The above being said, it is well known that most psychiatric disorders, including schizophrenia and other psychotic disorders which do not fall into this chapter of 'neurodevelopmental disorders', show their first manifestations during childhood and adolescence (Kessler et al., 2005; Paus et al., 2008). For example, 11-18% of individuals with schizophrenia and other psychotic disorders experience their first episode before the age of 18 years (Amminger et al., 2011;

M. Cannon et al., 1999). This would be congruent with the idea of childhood and adolescence being an early window of vulnerability (a sensitive period) in brain development and with the idea that these conditions share an abnormal neurodevelopmental origin. Studies have indeed shown that patients show delays in signs of early neurodevelopment during childhood and adolescence before the emergence of the first psychotic episode (McGorry et al., 2006), and that there is an 'exaggeration' of typical adolescent changes in the brain occurring in these patients (J. L. Rapoport & Gogtay, 2008). As such, a neurodevelopmental pathophysiology of schizophrenia has been proposed (Murray & Lewis, 1987; Weinberger, 1986).

In keeping with this, this doctoral dissertation will focus on two neurodevelopmental conditions, ASD and psychotic disorders, and on the application of MRI (i) to the study of their complex origins and physiopathology, and (ii) as a tool to aid in their identification and management in clinical practice.

1.2.2.2. Schizophrenia and other psychotic disorders

Introduction, epidemiology, clinical features and illness outcome

In the early 19th century, Wilhelm Griesinger and many others believed in the idea of a unified psychosis (*Einheitspsychose*), with distinct disease varieties deriving from this single universal madness' (Berrios & Beer, 1995). However, by the early 1850s two French psychiatrists Falret and Morel made the distinction between '*folie circulaire*' (i.e. what we now think of as type I bipolar disorder) and '*demence precoce*', a progressive disorder characterized by the presence of

social withdrawal, self-neglect and bizarre behaviour (Falret, 1878; Morel, 1860). In 1893, the German psychiatrist Emil Kraepelin translated Morel's term '*demence precoce'* to '*dementia precox',* a term that emphasized a particular cognitive process (dementia) with an early onset (precox), and distinguished these patients from those with '*manic-depressive insanity'*, equivalent to Falret's and Morel's '*folie circulaire'*. Kraepelin described '*dementia precox'* as a 'peculiar simple condition *of* mental weakness of subacute development, characterized by delusions and hallucinations, disordered thought, loss of interest in the outside world and loss of emotional reactions, and a long-term deteriorating course occurring at a youthful age' (Kraepelin, 1893).

Later on, in 1911, the Swiss psychiatrist Eugen Bleuler coined the term 'schizophrenia' to replace Kraepelin's term of '*dementia praecox'*, and suggested that the primary and main symptoms of this condition would be ambivalence, autism (loss of interest in the outside world), affective blunting (loss of emotional responses) and altered associations (thought fragmentation), while delusions and hallucinations would be secondary symptoms often present but not specific to the illness (Bleuler, 1911). In 1950, Kurt Schneider adjusted Bleuler's definition of this condition, as he regarded certain symptoms as particularly indicative of the disorder, for example particular types of auditory hallucinations, which were labelled as 'first rank symptoms' (Schneider, 1959). The Schneiderian concept of schizophrenia remained dominant up until the early 21st century diagnostic thinking. Indeed, until recently, classifications in psychiatry have used the term 'psychotic disorders' to describe a broad spectrum of conditions - the most common of these being schizophrenia - in which individuals present with the

hallmark symptoms of abnormal thinking and/or hallucinations. In the DSM-IV-TR there was a chapter on 'Schizophrenia and Other Psychotic Disorders' (American Psychiatric Association, 2000), which included brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, and shared psychotic disorder. The new DSM-5 classification system has (i) renamed this chapter 'schizophrenia spectrum disorders – SSD - and other psychotic disorders' (American Psychiatric Association, 2013), thus adding the word 'spectrum' to the title, (ii) retained the same basic diagnoses, and (iii) eliminated the special treatment of bizarre delusions and special hallucinations included in previous DSM editions, as the diagnostic specificity of Schneiderian first-rank symptoms for schizophrenia has long been questioned (Tandon et al., 2013)

Other psychiatric disorders that do not fall into the category of SSD and other psychotic disorders, e.g. brief and transient psychotic disorders, type I bipolar disorder (Carlson & Goodwin, 1973) or major depressive episode (Ohayon & Schatzberg, 2002) can also present with symptoms of psychosis (especially positive psychotic symptoms). This is particularly relevant in young people with mood disorders, who frequently present with psychotic symptoms, in particular auditory hallucinations (Ulloa et al., 2000).

A broader concept of 'psychotic disorders' would therefore include a large and heterogeneous group of conditions with varied epidemiology, clinical presentation, prognosis and potential outcome. Prevalence figures for psychotic

disorders in the general population are variable, with one-year prevalence rates of about 0.7% (Widerlov, Lindstrom, & von Knorring, 1997), and lifetime prevalence rates up to 3% (Perala et al., 2007). Furthermore, most available data are restricted to schizophrenia, with a prevalence of about seven individuals per 1,000 (McGrath, Saha, Chant, & Welham, 2008). This prevalence is reportedly higher in male subjects - male: female ratio of approximately 1.4 (Aleman, Kahn, & Selten, 2003; McGrath et al., 2008), in urban as compared to rural settings, (McGrath et al., 2008) and in migrants (McGrath et al., 2008), although this may be related to ethnicity or to a lower socioeconomic status rather than to the effect of migration per se (McGrath et al., 2008). Prevalence rates for bipolar disorder vary between 1.5 - 3.9% (in the US) and 1.7% - 3.5% (in Europe) in studies including patients with bipolar I and II disorders (Faravelli, Guerrini Degl'Innocenti, Aiazzi, Incerpi, & Pallanti, 1990; Grant et al., 2005; Narrow, Rae, Robins, & Regier, 2002; Wittchen, Nelson, & Lachner, 1998), with most studies reporting an almost equal male to female ratio.

With regard to clinical manifestations, there is significant heterogeneity across psychotic disorder categories, with patients presenting with varying sets of symptoms, including positive symptoms (hallucinations, delusions and disorganized speech and/or behaviour), negative symptoms (such as flat affect, poverty of speech, and loss of interests and drive), cognitive symptoms (such as deficits in working memory and attention), psychomotor deficits (such as motor retardation), and mood symptoms (such as depressed mood) (Tandon, Nasrallah, & Keshavan, 2009), in addition to the presence of social or occupational dysfunction (American Psychiatric Association, 2013). Within each

psychotic disorder category, there is further heterogeneity in terms of clinical manifestations, course and treatment response. For example, although almost 40% of patients with schizophrenia will achieve social or functional recovery (Zipursky, Reilly, & Murray, 2013), and some will have a relatively good outcome even if medication is discontinued (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013), there is still a large group of patients at risk of poor outcome, such as those presenting with what is called 'deficit syndrome' (i.e. prominent primary negative symptoms) (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001).

Etiology and physiopathology

The idea of schizophrenia (as the most prevalent psychotic disorder) being part of the larger group of neurodevelopmental disorders was proposed in the late '80s (Murray & Lewis, 1987; Weinberger, 1986). In this disorder, the interaction between genetic variation and exposure to early environmental insults would increase the risk of the disease (van Os & Murray, 2008). With regard to genetic risk, the familial nature of schizophrenia has been well-established, as it is known that relatives of individuals with schizophrenia have a higher risk for the disease than the general population, the greatest risk being among first-degree relatives. Indeed, risk in the general population is below 1%, compared to 6.5% in first-degree relatives of patients (Kendler et al., 1993), and rising to over 40% in monozygotic twins of affected patients (Cardno et al., 1999). Overall, it seems there are more contributing genetic factors than previously thought in both schizophrenia and bipolar disorder, and while the effects of most of these factors

are small, together they are quite meaningful (International Schizophrenia Consortium et al., 2009).

The fact that concordance rates in monozygotic twins is not 100% implies the influence of environmental factors. The discovery of numerous environmental risk factors in the prenatal and perinatal periods (prenatal exposure to infection or obstetric complications) and in the intermediate childhood period (e.g. urbanicity, early traumatic events) has been important to the understanding of the neurodevelopmental model in schizophrenia (Dean & Murray, 2005). Overall, we could postulate that patients probably inherit several risk genes which interact with each other and the environment to produce abnormal developmental trajectories (Howes et al., 2004; Tandon, Keshavan, & Nasrallah, 2008; van Os, Rutten, & Poulton, 2008).

As mentioned previously, from a developmental perspective, adolescence may be a critical period in the epigenesis of psychotic disorders (Walker & Bollini, 2002). According to the 'two-hit' hypothesis, genetic vulnerabilities (first 'hit') lead to an aberrant trajectory (e.g. GM loss or WM growth deficits) early in development, followed by a second 'hit' around adolescence (typical age of onset of psychosis), due to the emergence of new environmental risk factors (e.g. drug misuse). Together, the confluence of genetic and environmental factors may be critical in determining the onset of a psychotic break during this developmental stage (Rapoport et al., 2012). The two-hit hypothesis is supported by prospective neuroimaging studies of non-psychotic full siblings of childhood-onset schizophrenia (COS) patients. These individuals show a pattern of GM and WM

growth deficits in childhood (possibly due to genetic vulnerabilities, the first hit), that 'normalize' by the time the subjects reach late adolescence, which would mean that the second hit is absent or overcome by a response of 'normalization' of the early GM abnormalities, thus representing a 'resilient phenotype' (Gogtay et al., 2012; J. L. Rapoport & Gogtay, 2011).

With regard to the observed neuropathological changes in schizophrenia, an 'exaggeration' of progressive GM loss seen in typically developing individuals throughout adolescence and young adulthood has been reported, which may reflect glial and vascular rather than purely neuronal changes (J. L. Rapoport & Gogtay, 2008), excessive and aberrant synaptic pruning with a reduction of neuropil rather than a deficit in the total number of neurons (T. D. Cannon et al., 2014; Whitford et al., 2007), aberrant neurogenesis, axonal growth or myelination (Mauney et al., 2013; van Os, Kenis, & Rutten, 2010). Oxidative damage (Fraguas et al., 2012) and a rise in pro-inflammatory status (Garcia-Bueno et al., 2014) has also been reported in patients with first episodes of psychosis.

MRI and the study of psychotic disorders: what questions have been answered?

Do patients with psychotic disorders show differences in brain structure relative to typically developing individuals? Since the first MRI studies showing an increased volume of the ventricular system in patients with schizophrenia relative to controls (Chua & McKenna, 1995; Raz & Raz, 1990), studies have consistently reported structural and functional abnormalities in the brains of these patients relative to healthy people of the same age (Arango &

Kahn, 2008; Arango et al., 2008). Many MRI studies have scanned patients during the first psychotic episode (FEP) and have included samples representing different stages of brain development (e.g. childhood to early adulthood). These studies are indeed of the utmost importance to gain understanding of the physiopathological processes underlying schizophrenia and other psychotic disorders. The study of FEP patients avoids the effect of potential confounding factors such as duration / chronicity of the illness, years of education and the effects of treatment on brain structure and function (N. C. Andreasen, Liu, Ziebell, Vora, & Ho, 2013; Navari & Dazzan, 2009; Tomelleri et al., 2009). Most of these studies have used cross-sectional designs. Studies in first-episode SSD patients have reported focal parietal deficits when the first episode occurs in childhood or early-adolescence (Burke, Androutsos, Jogia, Byrne, & Frangou, 2008; Greenstein et al., 2006; Thompson et al., 2001) and more widespread GM cortical (e.g., frontal, temporal) and subcortical volume and/or thickness deficits when onset is in late adolescence or early adulthood (Adriano, Spoletini, Caltagirone, & Spalletta, 2010; Giedd, Jeffries, et al., 1999; Jacobsen et al., 1996; Janssen et al., 2012; Janssen et al., 2014; Janssen et al., 2008; Narr et al., 2005; Olabi, Ellison-Wright, Bullmore, & Lawrie, 2012; Radua et al., 2012; Rimol et al., 2010; Rimol et al., 2012; Voets et al., 2008). This pattern has also been reported in patients with first-episode affective psychoses (AFP), with alterations being larger and more widespread in the SSD group (Arango, Fraguas, & Parellada, 2014; El-Sayed et al., 2010; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Janssen et al., 2014; Janssen et al., 2008). Furthermore, our group has shown that there is gyral and sulcal cortical thinning in prefrontal and temporal regions in adolescents with first episode early-onset psychosis (EOP), which underlies

cortical volume deficits (Janssen et al., 2009). A further study by our group also showed that increased prefrontal sulcal width was a mediator between the decreased prefrontal thickness and gyrification found in these patients (Janssen et al., 2014).

Are structural brain abnormalities in these patients associated with symptoms and cognitive deficits? Cross-sectional MRI studies have also explored the association between morphometric measurements and the presence and severity of the core clinical symptoms and cognitive deficits in psychosis. For example, one recent study in adult patients with schizophrenia, schizoaffective and bipolar disorder showed that the positive and negative syndrome scale (PANSS) - positive subscore was inversely correlated with GM volume and thickness of frontal and temporal regions, the PANSS negative subscore was inversely correlated with frontal cortical volume and surface area, and overall, cortical thickness measurements appeared more strongly associated with psychopathology (Padmanabhan et al., 2015), although the reported correlations were weak in magnitude. Morphometric abnormalities in the insular cortex (a key region for high-order cognitive functions such as the distinction between self/non-self) have also been proposed as key to the pathophysiology and emergence of symptoms of psychosis (Moran et al., 2014; Palaniyappan & Liddle, 2012). Indeed, in schizophrenia patients, an association has been reported between insular deficits and severity of negative symptoms (Virupaksha et al., 2012). Additionally, insular volume deficits (in cross-sectional studies) and increased insular GM loss over time (in longitudinal studies) have been

associated with presence and severity of positive symptoms (Moran et al., 2014; Takahashi, Wood, Soulsby, McGorry, et al., 2009; Wylie & Tregellas, 2010).

Are brain structural changes in these patients progressive over the first stages of the illness? MRI studies using longitudinal designs have proved helpful in answering this question. Recent meta-analyses assessing longitudinal brain changes over a 2 to 10-year follow-up period have shown progressive decreases over time in cortical GM volume especially in frontal and temporal regions in subjects with adult-onset schizophrenia compared to healthy controls (Fusar-Poli et al., 2013; Haijma et al., 2013; Olabi et al., 2011; Vita, De Peri, Deste, & Sacchetti, 2012). However, fewer studies have investigated the longitudinal changes in brain structure occurring in patients with EOP, besides for those conducted in the US by the NIMH (Gogtay, Sporn, et al., 2004; Sporn et al., 2003), in the United Kingdom (James, James, Smith, & Javaloyes, 2004) and in Spain by our research group (Arango et al., 2012; Reig, Moreno, et al., 2009). Table 2 shows a description of the main characteristics of these EOP samples and study designs. Our group recently conducted a meta-analysis of the data derived from these studies, and found there was a greater progressive frontal GM loss in patients relative to controls over the first few years after illness onset (Fraguas, Diaz-Caneja, Pina-Camacho, Janssen, & Arango, 2014). This loss was not observed in total brain volume (TBV), parietal, temporal or occipital GM volumes, however. Furthermore, age at baseline (the younger the patient, the greater the loss of temporal GM volume at follow-up with respect to the control group) and schizophrenia diagnosis (greater loss of occipital GM volume at follow-up as compared with other psychotic disorders) were reported to be

significant moderators of these progressive volume changes in EOP (Fraguas et al., 2014). All these MRI findings are particularly relevant insofar as they inform the neurodevelopmental vs neurodegenerative hypotheses / models in schizophrenia and other psychotic disorders (Arango et al., 2014). Of note, the progressive brain changes observed in first episode patients (especially in EOP) seem to be more prominent during the first 2 years after the first psychotic episode (probably related to secondary variables – e.g. effects of substances or medication [Zipursky et al., 2013]), and are related to worse outcomes (Arango et al., 2012; van Haren et al., 2007). These findings might be of utmost importance to inform research involving agents that prevent these progressive brain changes (e.g. agents that regulate the oxidative imbalance) (Fraguas et al., 2012).

Table 2. Summary of MRI longitudinal studies in EOP patients

Author, year	EOP Patients								Controls				MRI[a]		Follow-up (y)[b]
	n	% M	Age[c]	% RH	Diagnostic criteria	% SCZ	CPZ Equiv.	Duration until MRI (y)	n	% M	Age[c]	% RH			
James, 2004	16	56.3	16.6	94.1	DSM-III-R	100	281.3	1.55	16	56.3	16.0	58.8	1.5, 3		2.11
Sporn, 2003[d]	39	6.,5	15.0	NA	DSM-III-R or DSM-IV	100	NA	4.60	43	62.8	14.8	NA	1.5, 1.5		3.40
Gogtay, 2004a (COS)[e]	23	82.6	13.9	78.3	DSM-III-R or DSM-IV	100	NA	3.77	38	84.2	13.3	94.7	1.5, 1.5		2.51
Gogtay, 2004b (psychosis NOS)[e]	19	84.2	13.3	89.5	DSM-III-R or DSM-IV	0	NA	5.50	38	84.2	13.3	94.7	1.5, 1.5		2.60
Reig, 2009	21	76.2	15.7	90.5	DSM-IV	38.10	NA	0.27	34	61.2	15.2	85.3	1.5, 1.5		2.02
Arango, 2012	61	65.6	15.3	91.7	DSM-IV	40.98	217.2	0.28	70	32.9	15.3	87.1	1.5, 1.5		2.13

Adapted from (Fraguas et al., 2014). Permission for reprint granted by Elsevier through Copyright Clearance Center ('CCC'). COS, childhood-onset schizophrenia; CPZ equiv., chlorpromazine equivalents (mean daily dose of antipsychotic during follow-up); EOP, early-onset psychosis; M, males; MRI, magnetic resonance imaging; NA, not available; NOS, not otherwise specified; RH, right-handed; SCZ, schizophrenia. [a] MRI: Tesla, slice thickness (mm); [b] Duration of follow-up (years); [c] Mean age at initial MRI (years); [d] Patients evaluated in Sporn et al. (2003) were also evaluated in Gogtay et al. (2004a) (COS). Here, they were used to conduct different meta-analyses: Sporn et al. (2003) for TBV, total GM volume, frontal GM volume, parietal GM volume, and temporal GM volume, and Gogtay et al. (2004a) (COS) for occipital GM volume; [e] Healthy controls included in Gogtay et al. (2004a) (COS) and Gogtay et al. (2004b) (psychosis NOS) were also included in Sporn et al. (2003).

Do patients with psychotic disorders show differences in brain connectivity measures relative to typically developing individuals? In 1908, Bleuler coined the term schizophrenia (Bleuler, 1908), understanding the disease to be the result of the 'division' of mental functions. This could amount to the idea of abnormal connectivity between different brain regions of patients with schizophrenia. The introduction of fMRI and DTI techniques has rescued this 'dysconnectivity' hypothesis, with studies reporting anomalies in the functional and structural connectivity of certain brain networks in patients with schizophrenia and other psychotic disorders (Stephan, Baldeweg, & Friston, 2006). Although results so far have been somewhat inconsistent, data suggest that schizophrenia is associated with a widespread connectivity deficit, affecting key network nodes known as the rich hub (van den Heuvel et al., 2013), which is the backbone of communication between different brain areas, including regions of the default mode network (DMN), or fronto-parietal and fronto–striatal-temporal circuits. Over this widespread deficit, there would be superimposed functional abnormalities at a local / regional level (Baker et al., 2013; Fornito, Zalesky, Pantelis, & Bullmore, 2012). DTI studies have shown a parallel alteration in the structural connectivity of the described networks (Ellison-Wright & Bullmore, 2009). These functional and structural connectivity deficits have been reported across different psychotic disorders (Baker et al., 2013; Skudlarski et al., 2013), and also in relatives of affected individuals, (MacDonald, Thermenos, Barch, & Seidman, 2009; Skudlarski et al., 2013), therefore making interesting endophenotypes for the study of these neurodevelopmental conditions.

1.2.2.3. Autism spectrum disorders

Introduction, epidemiology, clinical features and illness outcomes

As stated in the Introduction to Schizophrenia and psychotic disorders (see section 1.2.2.2), Kraepelin´s description of '*dementia precox'* included a group of individuals who presented with a very early-onset form of the disorder. From there proceeded a steady rise of individual case reports of juvenile schizophrenia or psychosis, including De Sanctis' children with '*demencia precocissima*' (Sanctis, 1909) or Heller's '*dementia infantilis*' (Heller, 1908). Of note, when in 1911, Eugen Bleuler (Bleuler, 1911) coined the term 'schizophrenia' to replace Kraepelin's term of '*dementia praecox*', he described in these patients a 'turning inward into the own world' and a denial of contact, a symptom that he named 'autism'. For a long time 'autism' was therefore considered a symptom of schizophrenia, and children with early forms of 'demencia precox' were reclassified as patients with 'childhood schizophrenia' (Lutz, 1937/38).

It was not until 1943 that Leo Kanner described a particular group of children within those with psychosis who had difficulties in establishing relationships since the beginning of their lives (Kanner, 1943) and presented with 'extreme autistic isolation' (hence he called it 'infantile autism'). Independently from him and almost in parallel (in 1944) an Austrian psychiatrist, Hans Asperger, described a group of children with similar characteristics and coined the term 'autistic psychopathy'. His work remained unknown until it was cited in a publication by Lorna Wing in 1981 (Wing, 1981).

During the ‘50s and ‘60s, and despite Kanner’s delineation of ‘infantile autism’ as a separate entity, the terms ‘autism’, ‘childhood schizophrenia’ and ‘childhood psychosis’ were used to describe the same children, depending on the tradition of the institution where the diagnosis was established. Furthermore, European and American diagnostic classification systems such as DSM-I (1952), DSM-II (1968), ICD-7 (1955), and ICD-8 (1967) still conceptualised autism as a form of child psychosis. It was not until 1972 that, based on Kolvin´s studies (Kolvin, Ounsted, Humphrey, & McNay, 1971), the differential value of Kanner’s autism was recognized by Michael Rutter (Rutter, 1972). Autism and child schizophrenia were acknowledged as separate entities, and as a result, in the DSM-III classification system (1980) (i) the category of autism was included but, to avoid confusion between the schizophrenia symptom ‘autism’ and the disorder described by Kanner, the term ‘Pervasive developmental disorder’ (PDD) was also initiated; (ii) ‘schizophrenia childhood-type’ disorder was removed and lumped together with the adult forms of schizophrenia. The ICD- 9 (1978) also recognised autism and childhood schizophrenia as separate diagnostic entities**,** but kept the term ‘psychoses with origin specific to childhood’ to refer to infantile autism, childhood disintegrative disorder, and other atypical or unspecified childhood psychosis. The autism / schizophrenia distinction was maintained in subsequent editions of the DSM and ICD.

After DSM-III and through DSM-III-R (1987), ICD-10 (1992), and DSM-IV (1994) classification systems, there was a further refinement of increasingly complex criteria for autistic disorder / PDD which resulted in a broadening of the

concept of autism. Indeed, in 1979, Lorna Wing had launched the concept of the 'autistic continuum or spectrum' (Wing & Gould, 1979) and, nine years later, Allen coined the term 'autism spectrum disorder' (Allen, 1988), which took precedence over PDD in many grounds and was subsequently used in the DSM-5 (American Psychiatric Association, 2013). Indeed, the current DSM-5 classification system uses the term ASD to describe a group of neurodevelopmental disorders in which affected individuals show early-onset reciprocal interaction and communication impairments as the sine qua non symptoms. This group encompasses previous DSM-IV-TR groups such as Kanner autism, Asperger syndrome, atypical autism and a group of non-specified PDD.

With regard to the clinical presentation of ASD, both ICD-10 (World Health Organisation, 1992) and DSM-IV-TR (American Psychiatric Association, 2000) classifications include a core triad of impairments in individuals with PDD, i.e. impairments in the areas of social interaction (the core / most common deficit in ASD) and communication (including impairments in semantic-syntactic language comprehension, in the pragmatic use of language, and in prosody of speech [Rapin & Dunn, 2003]), and the presence of restricted and repetitive behaviours. The DSM-5 revision, however, includes two instead of three main symptoms domains: social/communication deficits and fixed interests and repetitive behaviours (American Psychiatric Association, 2013). This diagnostic construct is supported by numerous factor analytic studies of autism symptoms, in which the social and communication domains reportedly emerge as a single factor, and the repetitive behaviour domain (including repetitive language) is consistently separate from the social and communication domains, see Shuster, Perry,

Bebko, & Toplak, 2014 for a review. Other aspects, such as the presence of low intelligence quotient or delayed speech are also common but not essential for a diagnosis of ASD, and can be applied to individual cases as clinical specifiers. ASD is understood as a 'spectrum' and therefore includes children with a broad range of severities, the degree of severity being one of the clinical specifiers of ASD in the DSM-5.

The onset of ASD manifestations can occur in different ways. Some individuals show an early onset pattern, i.e. abnormalities in social-communicative development in the first 12 months or so of life, some present with a regressive pattern, in which children develop typically for some period and then lose previously developed skills over the first two years of life, and finally, a 'plateau' group displays typical levels of social-communication in the first year, but fails to make expected developmental progress over time (Ozonoff et al., 2011). With regard to ASD outcomes, these are generally regarded as lifelong conditions. Children with ASD exhibit varied outcomes and studies have found that a combination of intellectual ability and communicative speech at early ages are the best predictors of outcome in these individuals (Billstedt, Gillberg, & Gillberg, 2005; Eaves & Ho, 2008).

Prevalence rates of ASD have increased dramatically in the last few decades, with reported rates increasing from 1/2,500 around 1980 (when autism was delineated as a separate entity in DSM-III) to the figure currently used by the US Centers for Disease Control and Prevention (CDC), in which 1 in every 110 children is affected (Baxter et al., 2014; Weintraub, 2011). This is in spite of the

dearth of data beyond childhood and adolescence in ASD epidemiological studies (Baxter et al., 2014) and the difficulties in detecting / diagnosing this condition in very young children. Since this last figure by the CDC, there has been ongoing debate over whether the prevalence of this disorder is indeed increasing. This debate is out of the scope of this doctoral dissertation and is therefore presented as supplemental information in Annex I. As for schizophrenia, there is a higher rate of ASD in males as compared to females (Halladay et al., 2015). The association of a higher socioeconomic status with ASD has been explained by other factors such as the association between living in poorer areas, lower access to healthcare, and older age at diagnosis, which could result in lower prevalence in this population group (Mandell et al., 2009).

Etiology and physiopathology of ASD

As for schizophrenia and other psychotic disorders, data is progressively and robustly accumulating regarding the biological basis of ASD within the framework of abnormal neurodevelopment (Parellada et al., 2014). Genetic studies indicate a large influence of genetic factors in autism, although the condition is not always heritable. For example, complex autism with dysmorphic features is more frequently associated with an identifiable genetic abnormality than essential autism, but is less heritable (Miles, 2011). Many different genetic variants confer risk for autism, with common variants of the genome explaining a small part of the variance in autism risk, and rare variants such as copy number variations (CNVs) explaining a greater amount of genetic liability, particularly in

the case of dysmorphic or intellectually disabled individuals (Parellada et al., 2014).

With regard to environmental factors and their possible association with autism, plenty of potential effectors have been studied (Parellada et al., 2014). Some of these (e.g. early exposure to toxic agents – e.g. the insecticide chlorpyrifos, rubella infection during pregnancy) account for a very limited number of ASD cases but are illustrative as examples of how they can initiate, through interplay with genetic vulnerabilities, a pathophysiological cascade starting very early in prenatal life and resulting in an autistic phenotype in the first years of life. As in schizophrenia, some data support a pro-inflammatory molecular landscape in ASD, with an uncertain role for these immune factors initiating or maintaining brain disease (Pardo, Vargas, & Zimmerman, 2005). In any case, in vulnerable periods of brain development (gestational periods and first years of life), all these factors could trigger the pathophysiological pathways leading to abnormal developmental trajectories and the emergence of the various autistic phenotypes (Parellada et al., 2014).

MRI and the study of ASD: what questions have been answered?

Do patients with ASD show differences in brain structure relative to typically developing individuals? Over the past 15 years, there has been a steady rise in the number of MRI studies examining the brain anatomy in patients with ASD, although – as in schizophrenia and other psychotic disorders - findings have been inconsistent (Brambilla et al., 2003; Pina-Camacho et al., 2013).

Initially cross-sectional and then longitudinal MRI studies on volumetric abnormalities comparing samples of different types of PDD and healthy controls were the most prevalent type of design. The finding of an early brain overgrowth (in early childhood) in ASD is the most consistently replicated volumetric finding to date (Courchesne, Campbell, & Solso, 2011; Stanfield et al., 2008) together with the increase in volume of cerebellar hemispheres and caudate nucleus and the reduction of the corpus callosum volume after initial overgrowth (Frazier & Hardan, 2009; Stanfield et al., 2008). More recently, studies have reported increased cortical thickness (R. Chen, Jiao, & Herskovits, 2011) and folding (Kates, Ikuta, & Burnette, 2009) of the parietal lobe in children with ASD relative to healthy controls, whereas reported abnormalities in other brain regions have been more inconsistent (R. Chen et al., 2011).

Recent studies have also used longitudinal designs to examine brain development in infants with ASD, at high familial risk for ASD, and healthy controls, scanning them at 6, 12 and 24 months of age, and incorporating MRI and DTI techniques together (Wolff et al., 2012). Promising findings suggest that the aberrant development of WM pathways may precede the manifestation of autistic symptoms in the first year of life (Wolff et al., 2012). Among other examples, corpus callosum overgrowth could be among the earliest neural signatures of autism. Indeed, there is an increased thickness of this structure in babies who develop ASD relative to children who do not, particularly at 6 months of age. Furthermore, differences between unaffected high-risk siblings and controls in corpus callosum thickness at 12 months of age point to the presence of a subpopulation who may later meet criteria for a neurodevelopmental disorder

or to the low-level expression of a shared but developmentally variant phenotypic feature (Wolff et al., 2015).

Are structural brain abnormalities in these patients associated with symptoms and cognitive deficits? MRI studies in ASD have also assessed the association between the described volumetric and morphometric abnormalities and the core clinical features of this disorder. Among other examples, larger volume of the caudate (Hollander et al., 2005) or thickening of frontal regions (Ecker et al., 2013) have been associated with higher severity of repetitive behaviours; thickening of frontal regions (Ecker et al., 2013) with higher severity of communication difficulties; and smaller amygdala volumes with higher level of impairment in social reciprocity (Nacewicz et al., 2006) However, data are still variable and inconsistent and the reported correlations are frequently weak in magnitude (Ecker et al., 2013). This may be due to methodological and design limitations inherent to MRI studies, but also to the fact that structural brain changes do not always encompass changes in behaviour (Brambilla et al., 2003; Pina-Camacho et al., 2013).

Do patients with ASD show differences in brain connectivity measures relative to typically developing individuals? Functional MRI studies in ASD have reported abnormal activation patterns in regions related to social cognition tasks (Philip et al., 2012), an overall pattern of long-distance 'under connectivity' (e.g. from frontal to posterior regions) and a pattern of local and short-range 'over connectivity' (e.g. in visual areas), mainly in adult patients (Schipul, Keller, & Just, 2011; Wass, 2011). In parallel, DTI studies have reported

abnormal structural connectivity between long-distance WM tracts, such as the superior longitudinal fasciculus, corpus callosum and the uncinated fasciculus (Aoki, Abe, Nippashi, & Yamasue, 2013; Gozzi et al., 2012). These functional and structural connectivity deficits could lead to a lack of effective integration between brain regions, and therefore to an ineffective complex information processing (Philip et al., 2012). This in turn might lead to the emergence of the varied clinical manifestations of ASD (Pina-Camacho et al., 2012).

1.2.3. MRI and the neurodevelopmental disorders: what questions have not been answered?

1.2.3.1. Introduction

Despite the amount of data provided by MRI studies in relation to the structural and functional changes in brains of patients with neurodevelopmental disorders, findings have been quite inconsistent, and, to date, there are still unanswered questions with regard to the pathophysiology of these conditions. In keeping with this, no imaging finding has emerged to date as a sensitive and specific marker to inform diagnosis, prognosis or prediction of therapeutic response in ASD or psychotic disorders in clinical practice.

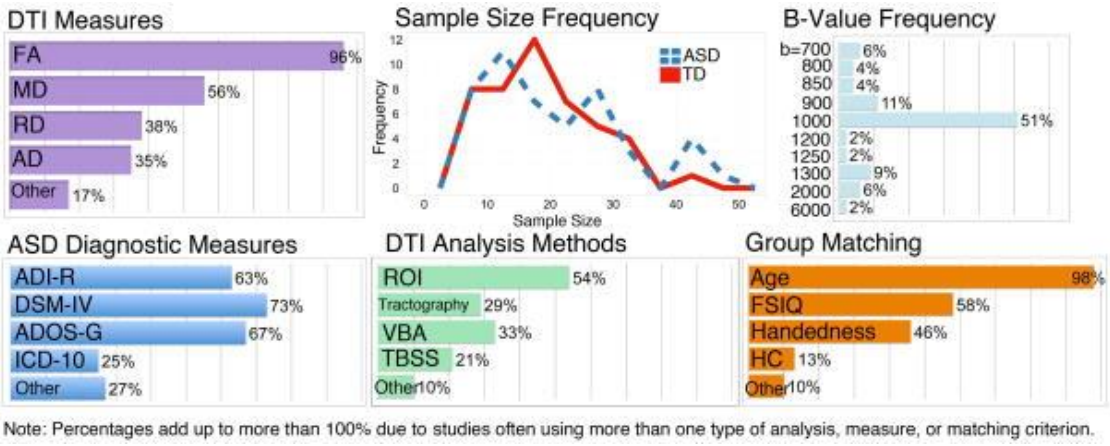
The **reliability** of MRI, DTI and fMRI measurements and the lack of replication are the main problems when interpreting data from imaging studies in ASD and psychosis. Firstly, differences between groups in brain structure and

function reported in these studies are based on averages over groups of individuals, which might not reflect the variability among different individuals with these conditions. Moreover, study designs often rely on small and sometimes quite heterogeneous samples (Button et al., 2013). The study of patients in the early stages of the illness (e.g. FEP patients or even those at risk of developing psychosis) helps make samples more homogenous. The use of cross-sectional instead of longitudinal designs or of different image acquisition protocols, imaging processing techniques and statistical analyses also has an impact on the reliability of the findings. The problem of small sample sizes may be overcome, to some extent, by relying on findings from meta-analysis (Ellison-Wright & Bullmore, 2010; Fraguas et al., 2014; Vita et al., 2012). Multicenter designs have also become a powerful tool in overcoming this problem and therefore in improving the reliability of the findings. However, reported data in multicenter studies are affected by the between-scanner variation in the morphometric measurements under study (Bartlett & Frost, 2008). For this reason, MRI reproducibility studies are recommended in any multicenter study in order to determine whether the effect of the site obscures the group differences detected (Schnack et al., 2010).

The indirect measure of brain activation (oxygen-dependent changes) provided by fMRI, and a number of potential confounders (see Table 1) might preclude accurate interpretation of the findings and limit reliability. Generalizability of fMRI-derived findings may also be limited by the fact that most fMRI task-related studies in ASD and psychosis rely on samples of high-functioning individuals (i.e. with no mental retardation) (Philip et al., 2012). With

regard to DTI or DTI-tractography studies, reliability is also affected by a high degree of methodological variability. This is related to the sample selection procedure itself, but also to the varied types of measures used to assess WM and the different acquisition and processing protocols in these studies. Figure 4 exemplifies the methodological variability observed in a review of DTI studies in ASD (Button et al., 2013; Philip et al., 2012).

Figure 4. Methodological variability described in a review of DTI studies in ASD



From (Travers et al., 2012). Permission for reprint granted by *John Wiley and Sons* through Copyright Clearance Center ('CCC'). Legend: Key features of the 48 empirical studies reviewed in this paper, including sample size, how participants were diagnosed with ASD, how participant groups were matched, the types DTI measures reported in the studies, the DTI methods, and the b-values used for data acquisition. AD, axial diffusivity; ADI-R, Autism Diagnostic Interview-Revised; ADOS-G, Autism Diagnostic Observation Scale-General; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FA, fractional anisotropy; FSIQ, full-scale intelligence quotient; HC, head circumference; ICD-10, International Classification of Diseases, 10th Revision; MD, mean diffusivity; RD, radial diffusivity; ROI, region of interest; TBSS, tract-based spatial statistics; TD, typically developing; VBA, voxel-based analysis.

Aside from the limitations described above, it could be posited that the reason why there are a number of unanswered questions in relation to the pathophysiology of neurodevelopmental disorders is that **we are probably not**

asking the right questions. If we want neuroimaging to help unravel the relationship between 'mind and brain', we must know what questions we are asking and just how far we can go in answering them with these techniques. In 1999, the neuroscientist Stephen Kosslyn argued that to do this, 'we must devise theories, test them, revise, and test again (…), just as in any other branch of science', and that 'facts about neuroanatomy, particularly about connectivity between areas, should have a crucial role in this theory development' (Kosslyn, 1999).

This doctoral dissertation will focus on the application of MRI techniques to help answer three unanswered questions in the research field of ASD and psychotic disorders, and will assess how far we can go in answering these questions through the use of these techniques.

1.2.3.2. Question 1: How does age at onset influence the structural abnormalities found in patients with first episodes of psychosis?

Interpretation of results from previous MRI studies assessing the effect of age at first episode on brain structure may be hampered by (i) using age as a linear variable and therefore disregarding the non-linear relationship between age and brain development (Takahashi, Wood, Soulsby, Kawasaki, et al., 2009; Velakoulis et al., 1999); (ii) stratifying cases into adolescent vs adult groups instead of treating age as a continuous variable (Kyriakopoulos et al., 2009; Tordesillas-Gutierrez et al., 2015), or (iii) using narrow age-range samples of patients that do not encompass important stages of brain development (Burke et

al., 2008). All in all, when assessing the effect of age at first episode of psychosis on the diagnostic-related brain structural deficits, a sample comprising the various stages of brain maturation and the use of non-parametric procedures is preferred. We do not know of a study assessing the non-linear effect of age on brain deficits in FEP patients whose first episode onset ranges from early adolescence through adulthood.

1.2.3.3. Question 2: Do MRI findings support symptom grouping within diagnostic categories in current classification systems?

We have described in the Introduction section how diagnostic classification systems in psychiatry, such as the DSM and ICD, have failed to align with findings emerging from clinical neuroscience and genetics (T. Insel et al., 2010) and how diagnostic categories are described on the basis of clinical / behavioural criteria with limited validity, as they are not based on the etiological / physiopathological underpinnings to these conditions. As such, the DSM-5 classification system proposes that ASD be described on the basis of (i) presence of social and communication deficits, as a single set of symptoms and (ii) presence of repetitive behaviours / restricted interests, as a different symptom domain.

To further the understanding of the physiopathology of psychiatric disorders, the primary focus of the RDoC initiative is on neural circuitry, with levels of analysis progressing upwards from measures of circuitry function to clinically relevant variation, or downwards to the genetic and molecular/ cellular factors that ultimately influence such function (T. Insel et al., 2010). In keeping

with this approach, fMRI and DTI techniques can prove helpful in assessing whether there is a neuroanatomical substrate that supports the different clusters of behavioural / symptom domains comprising the current ASD category.

1.2.3.4. Question 3: Can MRI help in the prediction of psychosis outcomes (e.g. diagnostic outcomes) and therefore be applied in clinical settings as a tool to inform prediction statements?

The overlap and lack of specificity of symptoms during a FEP, and the fact that current diagnostic classifications require a temporal criterion for the diagnosis of psychotic disorders (which makes initial diagnoses for these patients relatively unstable) (Bromet, Naz, Fochtmann, Carlson, & Tanenberg-Karant, 2005; Castro-Fornieles et al., 2011; Menezes & Milovan, 2000; Schwartz et al., 2000) makes the early distinction between SSD and other psychotic disorders very difficult in clinical practice (Craddock & Owen, 2010). For this reason, studies that help to identify predictors of diagnostic outcomes at a very early stage of the illness should be a priority, as an early and accurate diagnosis enables early optimization of treatment and accurate use of prognostic statements for patients.

Other fields of medicine have demonstrated that clinical prediction, especially in complex disorders, often requires a combination of multiple measurements from different sources (Sperling & Johnson, 2013). To this end, prediction methodologies based on high-dimensional multivariate statistical approaches and including a combination of multiple clinical and biological (e.g.

MRI data) seem promising, as they can potentially improve prediction accuracy at the early stages of the illness (Johnston, Mwangi, Matthews, Coghill, & Steele, 2013). The identification of these predictors may (i) help refine current diagnostic classification systems through sensitive and specific imaging markers in line with the RDoC initiative, (ii) guide clinicians in their practice to inform differential diagnosis, choice of appropriate treatment, and prediction of functional outcomes at early stages of the illness. We do not know of a study using support vector machines (SVMs) - a high-dimensional multivariate statistical tool - to identify particular variables from different sources to predict a diagnostic outcome of SSD in the early stages of an early-onset FEP.

2. OBJECTIVES

2. OBJECTIVES

General Objective

To advance in the study of the physiopathology and illness outcomes of two of the hallmark neurodevelopmental disorders, schizophrenia / psychotic disorders, and ASD, through the use of MRI techniques.

Specific Objectives

- To determine whether age at first episode has a non-linear effect on the diagnosis-related structural abnormalities detected in FEP.

- To assess whether results from fMRI and DTI studies support the symptom grouping / clustering proposed by the DSM-5 for the new ASD diagnostic category.

- To predict a SSD diagnostic outcome in FEP patients using volumetric MRI data, alone or in combination with various sets of clinical, neuropsychological, and biochemical data.

3. HYPOTHESES

3. HYPOTHESES

- Diagnosis-related volume and thickness abnormalities are dependent on the age at first episode of psychosis.

- The dependency of structural abnormalities on age at first episode follows a non-linear curve.

- In patients with ASD, social and communication deficits are associated with shared abnormalities in functional and structural connectivity in the same brain regions/ networks, so they can be collapsed into a single symptom domain. The affected networks are different than those associated with the presence of repetitive behaviours and restricted interests.

- Combined clinical, cognitive and volumetric MRI data can accurately predict a diagnostic outcome of SSD in patients with early-onset FEP.

4. METHODS

4. METHODS

This doctoral dissertation consists of three published articles authored by the doctoral student, including one systematic review and two original articles (please refer to Section 5. Publications).

5. PUBLICATIONS

5. PUBLICATIONS

5.1. PUBLICATION # 1

***Pina-Camacho L.**, Del Rey-Mejias A., Janssen J., Bioque M., González-Pinto A., Arango C., Lobo A., Sarró S., Desco M., Sanjuan J., Lacalle-Aurioles M., Cuesta MJ., Saiz-Ruiz J., Bernardo M., Parellada M., and the PEPs group. Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophrenia Bulletin (in press), doi:10.1093/schbul/sbv128.*

5.2. PUBLICATION # 2

***Pina-Camacho L.**, Villero S., Fraguas D., Boada L., Janssen J., Navas-Sánchez FJ., Mayoral M., Llorente C., Arango C., Parellada M. Autism Spectrum Disorder: Does neuroimaging support the DSM-5 proposal for a symptom dyad? A systematic review of functional magnetic resonance imaging and diffusion tensor imaging studies. Journal of Autism and Developmental Disorders 42(7):1326-41, 2012.*

5.3. PUBLICATION # 3

***Pina-Camacho L.**, García-Prieto J., Parellada M., Castro-Fornieles J., Gonzalez-Pinto AM., Bombin I., Graell M., Paya B., Rapado-Castro M., Janssen J., Baeza I., Del Pozo F., Desco M., Arango C. Predictors of Schizophrenia Spectrum Disorders in Early-onset First Episodes of Psychosis: A Support Vector Machine Model. European Child and Adolescent Psychiatry 24:427–440, 2015.*

6. DISCUSSION

6. DISCUSSION

The studies that are part of this doctoral dissertation present an advance in the study of the physiopathology of two of the hallmark neurodevelopmental disorders, schizophrenia / psychotic disorders, and ASD, through the use of MRI techniques. The main findings of these studies can be summarized as follows:

1. Diagnosis-related volume / thickness abnormalities in patients with FEP are mainly present in brain regions undergoing maturation at each particular developmental stage. Age at first episode modulates these abnormalities in a nonlinear manner.

2. Results from fMRI and DTI studies partially support the new ASD symptom dyad proposed by the DSM-5. Data support the presence of separate neuroanatomical substrates for the 'social communication' and 'repetitive behaviour/restricted interest' symptom domains that comprise the dyad. There are also separate neuroanatomical substrates for syntactic and pragmatic language impairments, which is congruent with the DSM-5 inclusion of syntactic language impairment as an independent clinical specifier. However, there is a shared neuroanatomical substrate for social and pragmatic language deficits, which suggests that an explicit mention of pragmatic language deficits should be included within this 'social communication' cluster.

3. An SVM model containing a combination of clinical and neuropsychological variables has the highest predictive value for a diagnostic

outcome of SSD in patients with early-onset FEP. MRI volumetric data do not add to the predictive value. SVMs could prove helpful in predicting diagnostic outcomes in patients with FEP.

Findings derived from the first MRI study (PEPs-Img study) are in keeping with the **neurodevelopmental model of schizophrenia / psychotic disorders**, as they show an interaction between brain maturation events and the morphometric abnormalities detected in FEP. As such, when SSD starts after early adolescence (around 15‑18 years), no volume / thickness abnormalities are found in cases relative to controls in the parietal lobe (a brain region that reaches peak maturity in late childhood) (Giedd et al., 2015) but do exist in frontal and temporal lobes (volume / thickness deficits) and in ventricular system and basal ganglia (volume enlargements). Similarly, first-episode AFP patients showed smaller cingulate cortex volumes and thicker temporal cortex only at early ages. Findings derived from the third study also reinforce the neurodevelopmental hypothesis of psychotic disorders, specifically in SSD. Indeed, in this study we found that prevalence of obstetric complications was one of the first-ranked predictors amongst the 243 variables demonstrating high predictive value for an SSD diagnostic outcome. Among other authors, Mary Cannon and colleagues have shown that obstetric complications are one of the best-replicated 'environmental' risk factors for schizophrenia (M. Cannon, Jones, & Murray, 2002; Clarke, Harley, & Cannon, 2006). Moreover, among the selected 243 variables not shown in Table 4 of the third article, we also found that an arrest of certain early developmental milestones (e.g. motor development impairment, history of enuresis, learning or reading difficulties) and a previous diagnosis of other

neurodevelopmental disorders such as ADHD were also good predictors of SSD, which is in keeping with the neurodevelopmental hypothesis as well as with the 'staging model' in schizophrenia (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006), which posits that during the pre-morbid phase preceding the prodrome and the psychotic episode it is possible to identify such delays in signs of early neurodevelopment in these patients.

With regard to **structural brain abnormalities in FEP patients**, the PEPs-Img study (publication # 1) presents an advance in that it shows divergent brain abnormalities in early- and late-onset FEP patients relative to healthy controls. Except for the increased volume of the ventricular system and the - less consistently reported - decreased volume of prefrontal lobe in patients with first-episode schizophrenia relative to controls (El-Sayed et al., 2010; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Janssen et al., 2012; Janssen et al., 2014; Narr et al., 2005; Radua et al., 2012; Voets et al., 2008), results have been inconsistent among previous MRI studies. Many of these were using age at first episode as a categorical discrimination factor for comparing FEP patients (e.g. adolescent vs adult groups) and healthy controls, were including patients with first episode onset under and over 20 years, or were simply relying on narrow age-range samples that do not encompass important stages of brain development. The PEPs-Img study demonstrates that in order to further the understanding of the physiopathology of schizophrenia and other psychotic disorders, a sample comprising the various stages of brain maturation at the first stages of the illness is preferred. Moreover, our study may inform future MRI study designs as it indicates that disregarding the non-linear relationship of age

with brain development may lead to finding no or significantly less marked differences among diagnostic groups.

In this first publication, we discussed how the onset of positive psychotic symptoms may not be reflective of the actual onset of psychosis itself, and furthermore, how the reported brain abnormalities in this study could be representing to some extent the effect of both **the emergence and progression of psychosis** over the initial stages of the psychotic break (Pantelis et al., 2005). Studies should explore whether brain deficits that are already present at first positive psychotic break predate the emergence of psychosis - and thus represent a risk marker for illness onset - or if they represent a cause or effect of the emergence of psychosis, as this remains unclear. This issue highlights the need for longitudinal studies in FEP patients as well as in subjects at high-risk for developing psychosis, in order to assess in detail abnormal brain developmental trajectories in these individuals. The publication presented here was based on cross-sectional data obtained at the baseline visit for the PEPs-Img study, but patients and controls have since been re-scanned at the 2-year follow-up visit, which will provide further insights into the progressive brain changes present in these patients during the first stages of the illness. In addition, this longitudinal design will help advance in the understanding on how these brain deficits present at first episode affect the clinical phenotype and the course of illness (Arango et al., 2008).

With regard to the **diagnosis-related differences within psychosis subgroups**, results have been contradictory to date and the studies within this doctoral dissertation do not help resolve these inconsistencies. In the first publication of this dissertation, contrary to our expectations, brain morphometric measurements in AFP were not positioned in between healthy individuals and SSD. Furthermore, our third study showed that neither an SVM model including only volumetric MRI data - nor the MRI variables included within the classifier that considered all the baseline variables together - demonstrated good accuracy in classifying SSD vs non-SSD individuals. Some studies have not found any differences between first-episode SSD and AFP patients, and many others do not include diagnostic subgroup comparisons (Arango et al., 2014). Other studies have however reported distinctive GM volume deficits at first episode in SSD vs other non-SSD GM compared to healthy controls (e.g. deficits in left medial frontal and left middle frontal cortex in SSD vs in left medial frontal only in bipolar disorder type I vs in the insula and right occipital cortex in other psychotic disorders [Janssen et al., 2008]). The fact that in both studies we used an **ROI-based approach** might have precluded finding differences between psychosis diagnostic subgroups, as structural abnormalities in these disorders might actually be more distributed / widespread (Yu et al., 2010).

In addition, a series of obstacles inherent to MRI studies have probably precluded drawing consistent conclusions in this regard. Firstly, both the first and third study **included children** with psychotic disorders and there are inherent methodological limitations to the image acquisition or processing procedures in youth (e.g. movement artifacts are more common) (Johnston et al., 2013).

Secondly, both studies used a **multicenter design**. With regard to the PEPs-Img study (publication #1), 11 of the 16 recruiting sites participated in the neuroimaging module, and 196 patients and 157 controls were scanned at six different MRI scanner platforms, which were different in terms of manufacturer and field strength. For this reason, and to avoid the effects of site on the associations reported, a reproducibility study was conducted beforehand (see supplementary material 2 to publication # 1). Based on results obtained in this reproducibility study, all diagnostic comparative analyses (parametric and non-parametric ones) included *site* as a covariate. Furthermore, results were presented only for those ROIs that showed reasonable reproducibility among the six scanners ($ICC_{all\ sites} \geq 0.7$). For those ROIs with poor reproducibility among the six scanners ($ICC_{all\ sites} < 0.7$) but with reasonable reproducibility between sites 1 and 2 ($ICC_{sites\ 1\text{-}2} \geq 0.7$), results referred only to the subsample of patients (n=131) and controls (n=111) scanned at these sites, as described in the Methods section. In the Child and Adolescent First-Episode Psychosis Study - CAFEPS (publication # 3), FEP patients were scanned at five different MRI scanner platforms, which were different in terms of manufacturer and field strength. Here again, a compatibility study was conducted beforehand (Reig, Sanchez-Gonzalez, et al., 2009), showing that the inter-site coefficient of variation ranged from 1.8% to 5.2%, respectively, for GM and CSF volumes, whereas estimations of WM volume and occipital lobe volumes were more prone to site-related errors. In this particular study, the SVM models we developed all considered the effect of site (i.e. sites 1 to 5 were included as variables of interest within the high-dimensional database) in combination with all the imaging variables while removing or retaining the relevant ones. All in all, we can conclude that one

strength of the PEPs-Img and the CAFEPS study is that the difficulties arising from their multicenter design were addressed. Not only we conducted a reproducibility study beforehand for each study, and concluded that we needed to include site as a covariate, but also used the results of these reproducibility studies to disregard some comparisons between groups in specific regions where the reproducibility was poor. However, even with the analyses controlling for site and despite the reproducibility studies conducted beforehand, it is difficult to argue that the effect of site was fully controlled for, meaning that in both cases results need to be interpreted with caution.

Differences in brain structure in patients with SSD and AFP could also be partially accounted for by **differential clinical profiles** in terms of symptom presentation and severity (DeLisi, Sakuma, Ge, & Kushner, 1998; Nery et al., 2009; Padmanabhan et al., 2015; Strakowski et al., 2002). In the PEPs-Img study (publication # 1), SSD patients and younger patients had greater symptom severity at baseline, which warrants caution when interpreting the results. That said, no significant correlations were found between symptom presentation/severity measures at baseline and any of the morphometric measurements under study, except for a negative correlation between both PANSS total and positive scores, and caudal middle frontal gyrus GM volume. This was acknowledged as a limitation to the manuscript. Similarly, both antipsychotics – more prescribed in the SSD group (Lesh et al., 2015; Radua et al., 2012) and lithium – more prescribed in the AFP / non-SSD group (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012; Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011) have been reported to be potential confounders of the brain

abnormalities reported for FEP patients. However, both the PEPs-Img (publication # 1) and the CAFEPS (publication # 3) study included patients in the early stages of the illness (i.e. FEP patients), which made samples more homogenous and reduced the effect of factors such as chronicity or the effect of pharmacological treatments (N. C. Andreasen et al., 2013; Navari & Dazzan, 2009; Tomelleri et al., 2009). Treatment duration was indeed relatively short in these samples so we deem it unlikely that medication intake biased our results. The careful patient-control matching strategy in both the CAFEPS and the PEPs-Img study, the inclusion of sex and intelligence quotient (IQ) as covariates in the analyses of the PEPs-Img study, and the use of an SVM model in the CAFEPS study also helped in the handling of other relevant confounders.

The above being said, both the first and third study present an advance in the study of the physiopathology of schizophrenia / psychotic disorders, as they are **in keeping with the RDoC initiative**. Indeed, both studies included samples of patients with different DSM-IV-TR diagnostic labels within the 'psychotic disorder' group. Of note, the main aim of the first study was to determine whether age at first episode has an effect on the diagnosis-related structural abnormalities detected in FEP. Similarly, the main aim of the third study was not to use MRI as a diagnostic tool at FEP but as a tool to inform prediction of particular diagnostic outcomes within the psychosis umbrella. Findings derived from this third study reinforce the idea that clinical prediction in psychiatry (including prediction of diagnosis) requires a combination of multiple measurements from different sources, especially in complex disorders (Sperling & Johnson, 2013). Although we were studying predictors of diagnostic outcomes in quite a heterogeneous

sample of psychosis patients, following the RDoC initiative, one of the main limitations of this study was that the clinical variables that were included in the classifier (i) conformed to a DSM-IV-TR diagnosis, and (ii) outnumbered the other types of variables, so it is not that striking that clinical variables were the most predictive within the classifier. It would have been interesting to use other classification methods different from SVM and coming from the machine learning perspective to ascertain the predictive value of all variables in general, and of MRI volumetric variables in particular. Along these lines, 'non-supervised' classification methods (e.g. cluster analysis or non-supervised neural networks) that automatically discovers regularities in the data and classifies individual into different but not predefined – i.e. unknown – diagnostic categories (Vapnik, 1998) could be of special interest. As opposed to 'supervised' classification methods (e.g. SVMs), where outputs are a priori known categories (as was the case in our study - SSD vs non-SSD individuals), 'non-supervised' classification techniques do not use any a priori information regarding the existence of classes between objects (Cochocki & Unbehauen, 1993).

Another interesting approach would have been to group FEP patients by a range of other relevant outcomes (transdiagnostically), including functional outcomes, response to antipsychotic treatment or illness course (relapsing, number of admissions, etc.), among others. The identification of children and adolescents with early-onset psychosis who go on to develop poor outcomes should be a research priority (Díaz-Caneja et al., 2015; Parellada et al., 2015). Models that stratify patients according to their risk of poor outcome could help determine whether more intensive interventions (e.g. earlier initiation of clozapine

treatment or more intensive psychosocial support) are justified for a defined subset of these patients, which would in turn improve quality of life in this group and reduce the burden of disease and cost to national health systems (Díaz-Caneja et al., 2015). For example, it might be the case that a poorer outcome is associated with the presence of premorbid impairments, the presence of comorbid developmental conditions, higher severity of negative symptoms, or brain volumetric deficits transdiagnostically rather than with a categorical diagnosis of SSD or non-SSD (Díaz-Caneja et al., 2015; Parellada et al., 2015). Along these lines, SVMs could prove promising in the search for sensitive and specific biomarkers across psychotic disorders, and from there, they might (i) assist clinicians in the process of differential diagnosis, treatment choice or in supporting prognostic statements at early stages of psychosis, and (ii) help refine current diagnostic classification systems in keeping with the RDoC initiative. Until then, it seems that current psychosis classification systems should continue to be based on traditional nosology for the purpose of clinical work, while the research on the underlying biological mechanisms should explore the use of this transdiagnostic approach (e.g. across psychotic disorders).

Results from the systematic **review of fMRI and DTI studies on ASD** (publication # 2) are in keeping with the latest idea and do also provide evidence of blurred boundaries among different neurodevelopmental disorders. The main changes in the DSM-5 relative to the DSM-IV-TR in regard to ASD are (i) the term PDD has been changed to ASD and this category is now included in a general chapter of ‘neurodevelopmental disorders’, (ii) the classic symptom triad of DSM-IV-TR (impaired social interaction, impaired communication, and presence of

restricted interests and activities) is now changed to the dyad 'social communication' (which lumps together 'social interaction' and 'communication difficulties') and 'restricted interest / repetitive behaviour' domains; (iii) in relation to the second change, there is also a new 'social communication disorder' category in which the social-communication element of the dyad is present but the restricted interest / repetitive behaviour is not; (iv) there is an inclusion of various clinical specifiers; (v) the previous categories for autism, PDD - not otherwise specified (PDD-NOS), child disintegrative disorder (CDD), and Asperger's Syndrome are subsumed within this new ASD category (American Psychiatric Association, 2013).

The DSM-5 was supposed to be a more 'research-based' / physiopathology-based classification. But do neuroimaging findings to date support all these changes? With regard to the first change, we can argue that the finding of early brain overgrowth (i.e. in early childhood) (Courchesne et al., 2011; Stanfield et al., 2008), increased local gyrification in adolescence (Wallace et al., 2013), abnormal patterns of structural and functional connectivity from an early age (Pina-Camacho et al., 2012), or a combination of both abnormal patterns of gyrification and connectivity (Bos et al., 2015) support the inclusion of the new ASD category in the general chapter of neurodevelopmental disorders.

With regard to the 'symptom dyad' change (i.e. second change), publication # 2 of this doctoral dissertation showed that fMRI and DTI studies provided support for separate neuroanatomical substrates for the social

communication and the behavioural symptom domains, the former being more related to abnormal functional and structural connectivity within fronto-temporal and limbic networks, whereas the latter was related to fronto-striato-cerebellar network deficits. These findings would be also in keeping with the third DSM-5 change regarding the creation of a new social communication disorder. However, we also found that the available neuroimaging data only partially support the collapse of the classical social and language symptom domains into a single 'social communication' domain (both for the ASD and social-communication category). In the DSM-IV-TR, syntactic and pragmatic language impairments were mixed up in the second set of criteria within the triad ('qualitative impairments in communication'). Data from our review support the idea that syntactic language impairment and pragmatic language impairment should be considered separately, with the former being associated with temporo-parieto-occipital network deficits and the latter being associated with the same abnormal connectivity patterns that underlie social cognition deficits (i.e. deficits in fronto-temporal and limbic networks). Therefore, our data are congruent with the DSM-5 inclusion of syntactic language impairment as an independent clinical specifier (i.e. fourth change), but they also support semantic-pragmatic language impairments being merged with social communication deficits. Therefore, we suggested at the time that it would be reasonable to include an explicit mention of pragmatic language deficits within the DSM-5 'social communication' cluster.

Findings derived from this second study are of particular relevance given that if different behaviours / deficits that are currently lumped together have different neurobiological underpinnings, or behaviours / deficits that are currently

not merged together have shared neurobiological underpinnings, this would have substantial implications for clinical management and treatment development. Indeed, exploring the biological underpinnings to the different symptom clusters / domains may help refine current diagnostic classification systems and inform future research on specific and effective treatments for these patients.

To answer the question of whether neuroimaging data support the idea of subsuming previous DSM-IV-TR categories under the new ASD category (i.e. the fifth proposed change), we conducted an additional systematic review of 285 structural MRI studies published between January 1990 and February 2012 and including patients with the different DSM-IV-TR diagnosis of PDD and healthy controls to assess whether they were distinguishable in terms of volumetric abnormalities (Pina-Camacho et al., 2013). This review concluded that there were not enough arguments from MRI data for or against subsuming DSM-IV-TR categories under a single ASD category. This was due to the fact that one group of studies posited that Asperger's syndrome, high-functioning and low-functioning autistic disorder (HFA and LFA) were 'quantitatively different' diagnostic categories and that volumetric abnormalities should be positioned within a spectrum of abnormality from LFA to HFA to Asperger´s syndrome to healthy control brains; conversely, another group of studies supported the claim that all DSM-IV-TR categories were 'qualitatively different' diagnostic entities with specific brain structural abnormalities (Pina-Camacho et al., 2013). In 2000, Fred Volkmar argued that the inclusion of a specific diagnosis within a diagnostic classification system, such as Asperger´s syndrome, should be made 'only if the use of the concept could be supported on the basis of some external validating

factor'' (Volkmar, Klin, Schultz, Rubin, & Bronen, 2000). Before the DSM-5 release, some authors argued that Asperger´s syndrome should be maintained in this classification system as a distinct entity on the basis of its distinctive clinical features as compared to other types of ASD (Ghaziuddin, 2010). For example, patients with Asperger´s syndrome usually present with an ego-dystonic lack of reciprocal social interaction which may in turn increase the risk for emotional comorbidities such as depression (Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 1998; Strang et al., 2012), which has a higher prevalence in patients with this syndrome. Authors were claiming that this ego-dystonia at least be considered a clinical specifier, as it could be relevant for prognosis and for treatment plan designing. However, if we rely on structural MRI findings, the available data do not help resolve the controversy about whether or not DSM-IV-TR categories should be subsumed under the ASD definition.

There might be several reasons why we cannot resolve this controversy. Firstly, due to the scarcity, inconsistency, and aforementioned methodological limitations of MRI and fMRI studies. Secondly, because the relationship between structural findings and brain function is far from clear and partially complete at the most, and the meaning of the volume or thickness deficits at a neuropathological level remains unclear. Further levels of analysis progressing from measures of brain function to structure and downwards to the cellular, molecular and genetic factors that ultimately influence such function are warranted. Along these lines, studies integrating multiple research modalities (e.g. imaging genetics, the combination of MRI and magnetoencephalography or neuropathology designs, etc.) may help address these unanswered questions and controversies.

Finally, we should note that neurodevelopmental conditions such as schizophrenia and ASD share symptomatic / psychopathological manifestations and neurocognitive deficits in a 'transdiagnostic' manner, making it difficult in many cases to differentiate thereof, especially in those cases with an earlier onset form of the disease. The main commonalities / overlaps in clinical features, social cognition and neuropsychological deficits are described in Annex IIa. These overlaps present a challenge in clinical practice to the distinction between schizophrenia / psychotic disorders and ASD in a significant number of cases. This may, to some extent, explain the main controversies surrounding the categorization of these disorders throughout the history of psychiatry. Even though both categories were separated in 1980 on the basis of the two disorders showing unique characteristics with different symptom profiles and course of illness (Rutter, 1972), the 'broadening' in the diagnostic criteria for autism in the last three decades has led to further discussions of the boundaries of both conditions. In parallel, the idea of psychosis / schizophrenia being part of the larger group of neurodevelopmental disorders (Murray & Lewis, 1987; Weinberger, 1986) has once again brought forth the discussion of schizophrenia and autism having a variety of overlapping features and of the possibility of these disorders representing final pathways for common causal factors and pathophysiological processes (Watkins, Asarnow, & Tanguay, 1988).

Findings on schizophrenia and autism genetic and neuroimaging research fields reinforced this idea of shared pathophysiological underpinnings in both disorders (see Annex IIb). However, the clinical heterogeneity of ASD and

psychotic disorders, and the scarcity of studies to date assessing transdiagnostic aspects in people with such diseases has precluded progress in the understanding of their possible pathophysiological and etiological overlap. This has resulted, in turn, in the absence of objective criteria for the diagnosis of these disorders. In keeping with the RDoC initiative, it would therefore make sense to study whether complex psychiatric disorders of neurodevelopmental origin with common clinical / cognitive deficits in behavioural domains, show common and / or distinct underlying physiopathological processes and thus biological underpinnings. The joint study of both conditions may help revisit and improve the understanding of relationship and inform more effective management strategies. Indeed, emerging evidence points towards some promising psychological and pharmacological interventions which may be useful in both ASD and psychotic disorders, since they aim at tackling symptoms which are present transdiagnostically, such as social and communication impairments or negative symptoms.

In keeping with this approach, our group our group has been interested in studying the overlap between ASD and psychosis in the last 10 years and is participating now in a multi-center European project which uses an integrative approach to schizophrenia / psychotic disorders and ASD, entitled ‘From autism to schizophrenia’ which aims at studying the genetic mechanisms underlying common and distinct brain functional and structural phenotypes in both disorders, funded by the ERA-NET NEURON (Call for transnational research projects 2010). As part of the study of the overlap, we were particularly interested in the fact that both groups of patients present, as previously mentioned, with difficulties

in social cognition, in integrating information from the external and internal world and in the perception / understanding of self (e.g. self-awareness) and others, resulting in a limited ability to interpret (or understand) reality and themselves, and to generate appropriate responses to external demands (Addington & Rapoport, 2009; Bolte & Poustka, 2003; Couture et al., 2010; Crespi, Stead, & Elliot, 2010; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008; J. Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Roberts & Penn, 2013; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011).

It is unclear whether this shared clinical phenotype is related to a common neuroanatomical substrate but recent evidence suggests the insular cortex is a key region for these social cognitive functions (Craig, 2009; Moran et al., 2014; Nieuwenhuys, 2012). Indeed, a recent meta-analysis of VBM studies showed that a reduction of (largely anterior) insular volume was associated with different psychotic and non-psychotic psychiatric diagnoses (Goodkind et al., 2015). This meta-analysis did not include ASD, disorders in which social cognition difficulties are not only core but defining. Convincing evidence for a shared structural abnormality in the insular cortex in ASD and psychotic disorders can be obtained through a direct comparison of patients with these conditions (Cheung et al., 2010; Pinkham et al., 2008; Radeloff et al., 2014; Sugranyes et al., 2011; Toal et al., 2009), but these studies have a great deal of limitations. We therefore set up a study to test whether individuals with ASD and psychotic disorders (the hallmark group of disorders with deficits in interpreting and understanding oneself and reality) shared this common neural substrate - i.e. insular pathology.

In this ongoing study we are using an VBM approach to analyze whole and regional (i.e. anterior and posterior) insular volume and thickness in a sample of 30 children and adolescents with ASD and no mental retardation per DSM-IV-TR criteria (American Psychiatric Association, 2000), 29 with FEP and 26 healthy controls, matched for age, handedness and socioeconomic status. We want to evaluate, firstly, whether both patient groups show insular volume and thickness abnormalities (globally, and in the anterior and posterior sub-regions) with respect to healthy controls, and secondly, whether both patient groups share an insular volumetric / thickness deficit at the voxel-level areas. Our hypothesis is that both patient groups will show overlapping insular deficits and that these deficits will be associated with the severity of symptoms (e.g. socio-communication deficits, insight deficits).

Findings derived from this study seem promising and support the idea that a transdiagnostic approach is key to capturing fundamental underlying mechanisms of brain dysfunction, an approach that is central to the RDoC project (T. Insel et al., 2010). Further studies lumping together different psychiatric conditions are needed in order to understand their overlapping / distinct brain pathology. These might help gain new fundamental insights into the pathophysiology of these complex conditions but also impact disease management as they raise the possibility that interventions that target the commonly affected brain regions/networks may prove helpful across psychopathology.

This doctoral dissertation is fully engaged with the 'science of the brain' (Bullmore, Fletcher, & Jones, 2009) and demonstrates that MRI techniques can help psychiatrists advance in the understanding of the physiopathology of two of the hallmark 'disorders of the mind', ASD and schizophrenia / psychotic disorders. The main conclusions drawn from this doctoral dissertation can be found in the following section (see section 7. Conclusions).

7. CONCLUSIONS

7. CONCLUSIONS

1. Diagnosis-related volume and thickness abnormalities in patients with psychotic disorders are dependent on age at FEP, and are present in brain regions undergoing maturation at each particular developmental stage.

2. Age at first episode has a non-linear effect on the diagnosis-related structural abnormalities detected in FEP.

3. The DSM-5 proposal of a symptom dyad in ASD is only partially supported by fMRI and DTI data. A shared neuroanatomical substrate for social and pragmatic language deficits suggests that it would be reasonable to include an explicit mention of pragmatic language deficits within the 'social communication' cluster.

4. Combined clinical and cognitive data but not volumetric MRI data can accurately predict a diagnostic outcome of SSD in patients with early-onset FEP.

5. MRI techniques are helpful tools for gaining insight into the physiopathology of ASD and psychotic disorders.

6. Although it is reasonable that diagnostic classification systems in psychiatry continue to be based on traditional nosology for the purpose of clinical work, research on the underlying biological mechanisms may

require the use of transdiagnostic or even phenomenon-based approaches, in line with the RDoC initiative.

8. SUMMARY

8. SUMMARY

"APPLICATION OF MAGNETIC RESONANCE IMAGING TO THE STUDY OF AUTISM SPECTRUM DISORDERS AND PSYCHOTIC DISORDERS"

8.1. INTRODUCTION

Among psychiatric disorders, there is a group of conditions that seem to emerge from perturbations of normal brain maturation at early stages of development, collectively known as neurodevelopmental disorders. Indeed, the new Diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) classification system includes a new chapter entitled 'Neurodevelopmental Disorders', which includes – among others - the autism spectrum disorders (ASD) (American Psychiatric Association, 2013). Although schizophrenia and other psychotic disorders do not fall into this chapter, a neurodevelopmental pathophysiology of these conditions has been proposed (Murray & Lewis, 1987; Weinberger, 1986), as patients show delays in signs of early neurodevelopment during childhood and adolescence before the emergence of the first psychotic episode (McGorry et al., 2006), which usually occurs around late adolescence / young adulthood (Kessler et al., 2005; Paus et al., 2008).

With the advances in neuroscience and particularly in neuroimaging, psychiatrists can further the understanding of the complex origins and physiopathology of these two highly prevalent and debilitating neurodevelopmental conditions. Specifically, magnetic resonance imaging (MRI)

techniques can help achieve this goal through the study of both the normally developing brain and of the structural and functional brain abnormalities present in the affected individuals. Indeed, despite the scarcity and numerous methodological limitations of MRI studies, and although the relationship between structural findings / brain function / symptoms is far from clear, the advent of MRI techniques has shed some light on the pathogenesis / physiopathology of these neurodevelopmental conditions. For example, there are some consistent disease-specific findings derived from MRI studies, including (i) the increased volume of the ventricular system or the - less consistently reported - decreased volume of prefrontal lobe in brains of patients with first-episode schizophrenia relative to controls (El-Sayed et al., 2010; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Janssen et al., 2012; Janssen et al., 2014; Narr et al., 2005; Radua et al., 2012; Voets et al., 2008); (ii) the progression of these brain structural changes over the first years of the illness in these patients (Fusar-Poli et al., 2013; Haijma et al., 2013; Olabi et al., 2011; Vita, De Peri, Deste, & Sacchetti, 2012; Gogtay, Sporn, et al., 2004; James, James, Smith, & Javaloyes, 2004; Arango et al., 2012; Reig, Moreno, et al., 2009; Fraguas, Diaz-Caneja, Pina-Camacho, Janssen, & Arango, 2014); or (iii) the early brain overgrowth observed in early childhood in patients with ASD (Courchesne, Campbell, & Solso, 2011; Stanfield et al., 2008).

However, there is still a number of unanswered questions in relation to the pathophysiology of these conditions**.** For example, it is unclear if and how age at onset influences the structural abnormalities found in patients with first episodes of psychosis (FEP). It is also unclear whether MRI findings support symptom

grouping within diagnostic categories in current classification systems such as the DSM-5. Finally, the value of MRI data as a tool to inform prediction / prognostic statements in clinical settings is largely unexplored.

By gaining further insight into the pathophysiology of ASD and psychotic disorders, diagnostic classification systems in psychiatry could be refined, as diagnostic categories are still based solely on the observation of symptoms and behaviours with a limited psychopathological rigor and understanding of the underlying pathophysiology (American Psychiatric Association, 2013; World Health Organisation, 1992), In 2010, the National Institute of Mental Health (NIMH) of the United States underscored the potential advantages of a neuroscience-based approach to psychiatric classification (T. Insel et al., 2010). The Research Domain Criteria (RDoC) initiative was then launched with the main goal of ensuring that psychiatric diagnoses had not only reliability but also validity. The NIMH suggested that this could be achieved by creating a framework for research on pathophysiology, especially for genomics and neuroimaging, which ultimately will inform future classification schemes (T. Insel et al., 2010). In keeping with this initiative, this doctoral dissertation will focus on two neurodevelopmental conditions, ASD and psychotic disorders, and on the application of MRI (i) to the study of their complex origins and physiopathology, and (ii) as a tool be applied in clinical settings to inform prediction statements and clinical management.

8.2. OBJECTIVES

This thesis investigates how structural MRI, functional MRI (fMRI) and diffusion tensor imaging (DTI) techniques may be used to advance in the understanding of the physiopathology of two of the hallmark neurodevelopmental disorders, ASD and psychotic disorders. Specifically, it addresses three unanswered questions in this regard: (i) Does age at first psychotic episode have a non-linear effect on the diagnosis-related structural abnormalities detected in patients experiencing a first episode of psychosis (FEP)? (ii) Do results from fMRI and DTI studies support the ASD symptom grouping / clustering proposed by the new DSM-5 classification system? and (iii) Do volumetric MRI data help predict a diagnostic outcome of SSD in early-onset FEP patients?

8.3. HYPOTHESES

We hypothesized that (i) in patients with psychosis, diagnostic-related volume and thickness abnormalities are dependent on the age at first episode, (ii) the dependency of structural abnormalities on age at first episode follows a non-linear curve, (iii) in patients with ASD, social and communication deficits are associated with shared abnormalities in functional and structural connectivity in the same brain regions / networks, so they can be collapsed into a single symptom domain, (iv) the affected networks are different to those associated with the presence of repetitive behaviours and restricted interests, and (v) combined clinical, cognitive and volumetric MRI data can accurately predict a diagnostic

outcome of schizophrenia spectrum disorder (SSD) in patients with early-onset FEP.

8.4. METHODS

Two original articles and one systematic review authored by the doctoral student are included in this thesis dissertation.

***Pina-Camacho L.**, Del Rey-Mejias A., Janssen J., Bioque M., González-Pinto A., Arango C., Lobo A., Sarró S., Desco M., Sanjuan J., Lacalle-Aurioles M., Cuesta MJ., Saiz-Ruiz J., Bernardo M., Parellada M., and the PEPs group. Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophrenia Bulletin (in press), doi:10.1093/schbul/sbv128. Original study.*

This was a multicenter cross-sectional case-controlled brain MRI study. Patients with FEP (n = 196), 65.3% males, with a wide age range at FEP onset (12-35 years), and healthy controls (n = 157), matched for age, sex, and handedness, were scanned at six sites. Gray matter (GM) volume and thickness measurements were generated for several brain regions using FreeSurfer software. The non-linear relationship between age at scan (a proxy for age at FEP in patients) and volume and thickness measurements was explored in patients with SSD, affective psychoses (AFP), and healthy controls.

***Pina-Camacho L.**, Villero S., Fraguas D., Boada L., Janssen J., Navas-Sánchez FJ., Mayoral M., Llorente C., Arango C., Parellada M. Autism Spectrum Disorder: Does neuroimaging support the DSM-5 proposal for a symptom dyad? A systematic review of functional magnetic resonance imaging and diffusion tensor imaging studies. Journal of Autism and Developmental Disorders 42(7):1326-41, 2012. Systematic review.*

A systematic Medline/Pubmed review of 208 studies published in English between January 1990 and April 2011 and comprising fMRI and DTI imaging data in patients with ASD was conducted. Studies were classified according to the neuroimaging technique used as follows: (a) fMRI studies using tasks related to social cognition and interaction, (b) fMRI studies using language-related tasks, (c) fMRI studies using tasks related to repetitive behaviours or restricted interests, (d) studies using 'fMRI at resting state,' and (e) studies using a DTI technique. Within each fMRI study, we extracted the information about the affected regions in patients with ASD compared with healthy controls, in terms of abnormal activation of particular brain regions or abnormal functional connectivity. For DTI studies, we looked at affected regions and networks in patients with ASD compared with controls in terms of abnormal structural integrity of white matter (WM) tracts.

***Pina-Camacho L.**, García-Prieto J., Parellada M., Castro-Fornieles J., Gonzalez-Pinto AM., Bombin I., Graell M., Paya B., Rapado-Castro M., Janssen J., Baeza I., Del Pozo F., Desco M., Arango C. Predictors of Schizophrenia Spectrum Disorders in Early-onset First Episodes of Psychosis: A Support Vector Machine*

Model. European Child and Adolescent Psychiatry 24:427–440, 2015. Original study.

Data were gathered from a 2-year, prospective, longitudinal study of 81 patients (age 9–17 years) with early-onset FEP and a stable diagnosis during follow-up and 42 age- and sex-matched healthy controls. The input was different combinations of baseline clinical, neuropsychological, MRI brain volumetric and biochemical data, and the output was the diagnosis at follow-up (SSD vs. non-SSD, SSD vs. control, and non-SSD vs. control). Several support vector machine (SVM) classifiers were developed and enhanced recursive feature elimination was performed to select and rank the input variables with the highest predictive value for a diagnostic outcome of SSD. Classifiers were validated using leave one out cross-validation, jackknifing, and an independent test set.

8.5. RESULTS

Results from the first study indicate that (i) diagnosis-related volume / thickness abnormalities in patients with FEP are mainly present in brain regions undergoing maturation at each particular developmental stage, and (ii) age at first episode modulates these abnormalities in a nonlinear manner.

The second study supports (i) the presence of separate neuroanatomical substrates for the ‘social communication’ and ‘repetitive behavior / restricted interest’ symptom domains that comprise the DSM-5 diagnostic dyad for ASD, (ii)

the presence of separate neuroanatomical substrates for syntactic and pragmatic language impairments, and (iii) the presence of a shared neuroanatomical substrate for social and pragmatic language deficits.

In the third study we show that (i) an SVM model containing a combination of clinical and neuropsychological variables has the highest predictive value for a diagnostic outcome of SSD in patients with early-onset FEP, and (ii) that MRI volumetric data do not add to the predictive value.

8.6. DISCUSSION

The studies that are part of this doctoral dissertation present an advance in the study of the physiopathology of two of the hallmark neurodevelopmental disorders, schizophrenia / psychotic disorders and ASD, through the use of MRI techniques.

Results from the first study are in keeping with the neurodevelopmental model of schizophrenia / psychotic disorders, as they show an interaction between brain maturation events and the morphometric abnormalities detected in FEP. They also indicate that MRI studies in FEP should take into account the nonlinear effect of age on brain structure when interpreting samples with different age at FEP and diagnosis.

Findings derived from the second study are of particular relevance given that if different behaviours / deficits that are currently lumped together have different neurobiological underpinnings, or behaviours / deficits that are currently not merged together have shared neurobiological underpinnings, this would have substantial implications for clinical management and treatment development. Along these lines, this second study supports the creation of the new ASD dyad and the creation of the new social communication disorder. Similarly, the presence of separate neuroanatomical substrates for syntactic and pragmatic language impairments, is congruent with the DSM-5 inclusion of syntactic language impairment as an independent clinical specifier. However, the presence of a shared neuroanatomical substrate for social and pragmatic language deficits suggests that it would be reasonable to include an explicit mention of pragmatic language deficits within the 'social communication' cluster. This shows how exploring the biological underpinnings to the different symptom clusters / domains through the use of MRI techniques may help refine current diagnostic classification systems and inform future research on specific and effective treatments for these patients.

Findings derived from the third study reinforce the idea that clinical prediction in psychiatry (including prediction of diagnosis) requires a combination of multiple measurements from different sources, and support that SVMs could prove promising in the search for sensitive and specific biomarkers across psychotic disorders. From there, these tools might (i) assist clinicians in the process of differential diagnosis, treatment choice or in supporting prognostic statements at early stages of psychosis, and (ii) help refine current diagnostic

classification systems in keeping with the RDoC initiative. Until then, it seems that current psychosis classification systems should continue to be based on traditional nosology for the purpose of clinical work, while the research on the underlying biological mechanisms should explore the use of this transdiagnostic approach (e.g. across psychotic disorders, or even across neurodevelopmental conditions such as ASD and psychotic disorders).

In summary, the studies that are part of this doctoral dissertation demonstrate that we can advance in the understanding of the physiopathology of 'disorders of the mind' (such as ASD and psychotic disorders) through the use of 'the science of the brain' (e.g. the use of MRI techniques) (Bullmore et al., 2009). The main conclusions drawn from this doctoral dissertation can be found in the following section.

8.7. CONCLUSIONS

1. Diagnosis-related volume and thickness abnormalities in patients with psychotic disorders are dependent on age at FEP, and are present in brain regions undergoing maturation at each particular developmental stage.

2. Age at first episode has a non-linear effect on the diagnosis-related structural abnormalities detected in FEP.

3. The DSM-5 proposal of a symptom dyad in ASD is only partially supported by fMRI and DTI data. A shared neuroanatomical substrate for social and pragmatic language deficits suggests that it would be reasonable to include an explicit mention of pragmatic language deficits within the 'social communication' cluster.

4. Combined clinical and cognitive data but not volumetric MRI data can accurately predict a diagnostic outcome of SSD in patients with early-onset FEP.

5. MRI techniques are helpful tools for gaining insight into the physiopathology of ASD and psychotic disorders.

6. Although it is reasonable that diagnostic classification systems in psychiatry continue to be based on traditional nosology for the purpose of clinical work, research on the underlying biological mechanisms may require the use of transdiagnostic or even phenomenon-based approaches, in line with the RDoC initiative.

9. RESUMEN

9. RESUMEN

‘‘APLICACIÓN DE TÉCNICAS DE RESONANCIA MAGNÉTICA AL ESTUDIO DE LOS TRASTORNOS DEL ESPECTRO AUTISTA Y LOS TRASTORNOS PSICÓTICOS”

9.1. INTRODUCCIÓN

Entre los trastornos psiquiátricos, existe un grupo determinado de trastornos cuyo origen parece estar relacionado con la aparición de alteraciones en el proceso de maduración normal del cerebro en las primeras etapas del desarrollo, conocido como el grupo de los ‘trastornos del neurodesarrollo’. De hecho, el nuevo sistema de clasificación DSM-5 incluye un nuevo capítulo titulado ‘Trastornos del neurodesarrollo’, que incluye - entre otros - los trastornos del espectro autista (TEA) (American Psychiatric Association, 2013). Aunque la esquizofrenia y otros trastornos psicóticos no forman parte de este capítulo, podrán ser entendidos como trastornos que también emergen de una alteración en el neurodesarrollo (Murray & Lewis, 1987; Weinberger, 1986), dado que estos pacientes muestran signos de retraso en el desarrollo temprano, los cuales son observables durante la infancia y la adolescencia previo a la aparición del primer episodio psicótico (McGorry et al., 2006), episodio que suele ocurrir en la adolescencia o etapa adulta temprana (Kessler et al., 2005; Paus et al., 2008).

Gracias a los avances en el ámbito de la neurociencia y en particular en el de la neuroimagen, los psiquiatras podemos hoy día avanzar en el conocimiento de

los orígenes y la fisiopatología de ambos trastornos del neurodesarrollo, altamente prevalentes en la población y de elevado impacto socio-sanitario. En concreto, las técnicas de resonancia magnética (RM) parecen ser herramientas muy valiosas de cara a la consecución de dicho objetivo, a través del estudio tanto del cerebro normal en desarrollo como de las anomalías cerebrales estructurales y funcionales presentes en los individuos afectados.

A pesar de la escasez de resultados consistentes y de las numerosas limitaciones metodológicas de los estudios de RM, y a pesar de que la relación entre los hallazgos de estructura, función cerebral y síntomas no está completamente establecida, el advenimiento de las técnicas de RM ha permitido arrojar algo de luz sobre la patogénesis / fisiopatología de estas enfermedades del neurodesarrollo. Por ejemplo, determinados hallazgos relativamente específicos de trastorno han sido bien replicados por estudios de RM, lo cual ha permitido avanzar en el conocimiento de las bases neurobiológicas de estos trastornos. Entre dichos hallazgos se incluyen el aumento de volumen del sistema ventricular o la disminución de volumen del lóbulo prefrontal (este último quizá menos replicado) observado en cerebros de pacientes con un primer episodio de esquizofrenia en comparación con controles sanos (El-Sayed et al., 2010; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Janssen et al., 2012; Janssen et al., 2014; Narr et al., 2005; Radua et al., 2012; Voets et al., 2008), la progresión de dichos cambios estructurales cerebrales en estos pacientes durante los primeros años de la enfermedad (Fusar-Poli et al., 2013; Haijma et al., 2013; Olabi et al., 2011; Vita, De Peri, Deste, & Sacchetti, 2012; Gogtay, Sporn, et al., 2004; James, James, Smith, & Javaloyes, 2004; Arango et al., 2012;

Reig, Moreno, et al., 2009; Fraguas, Diaz-Caneja, Pina-Camacho, Janssen, & Arango, 2014), o el crecimiento excesivo del cerebro descrito en pacientes con TEA en la infancia temprana (Courchesne, Campbell, & Solso, 2011; Stanfield et al., 2008). Sin embargo, siguen existiendo numerosas preguntas sin respuesta en torno a las bases neurobiológicas y la fisiopatología de estas condiciones. Por ejemplo, no está claro si la edad de inicio influye en las anomalías cerebrales estructurales detectadas en pacientes con un primer episodio de psicosis (PEP), y de qué manera lo hace. Tampoco está claro si los hallazgos de la RM apoyan las diferentes agrupaciones sintomáticas presentes en los sistemas de clasificación diagnóstica actuales, tales como el DSM-5. Por último, existen pocos datos acerca del valor de las variables obtenidas por RM como herramienta de ayuda en la predicción de pronóstico y manejo de los pacientes con trastornos del neurodesarrollo en la práctica clínica.

Mediante el avance en el conocimiento de la fisiopatología de los TEA y los trastornos psicóticos, los sistemas actuales de clasificación diagnóstica en psiquiatría podrían ser perfeccionados. De hecho, las categorías diagnósticas actuales están únicamente basadas en la observación de síntomas y comportamientos, con un rigor psicopatológico limitado y una escasa comprensión de la fisiopatología subyacente a estas condiciones psiquiátricas (American Psychiatric Association, 2013; World Health Organisation, 1992). En 2010, el Instituto Nacional de Salud Mental (NIMH) de los Estados Unidos rescató la idea del DSM-III según la cual existirían numerosas ventajas en la creación de un enfoque de clasificación psiquiátrica basado en la neurociencia (T. Insel et al., 2010). En este sentido, el NIMH trató de llegar a un consenso

sobre la manera de lograr este objetivo y puso en marcha la iniciativa *Research Domain Criteria (RDoC)*, cuyo objetivo principal era asegurar que los diagnósticos psiquiátricos fueran no sólo fiables, sino también válidos. El NIMH sugirió que dicho objetivo podría lograrse mediante la creación de un marco de investigación de la fisiopatología de las enfermedades mentales, especialmente en el área de la genómica y la neuroimagen, que en última instancia ayudaría a diseñar los futuros esquemas de clasificación (T. Insel et al., 2010). En consonancia con esta iniciativa, esta tesis doctoral se centra en dos grupos de trastornos del neurodesarrollo, los TEA y los trastornos psicóticos, y en la aplicación de las técnicas de RM (i) como herramienta de estudio de sus orígenes complejos y fisiopatología subyacente, y (ii) como herramienta de ayuda en la predicción de pronóstico y manejo de los pacientes con estos trastornos en la práctica clínica.

9.2. OBJETIVOS

Esta tesis investiga cómo las técnicas de RM estructural (RM), RM funcional (fMRI) y la imagen por tensor de difusión (DTI) pueden ayudar a avanzar en la comprensión de la fisiopatología de dos de los trastornos claves del neurodesarrollo, los TEA y los trastornos psicóticos. En concreto, se abordan tres preguntas no contestadas hasta la fecha en relación con ambos trastornos: (i) en pacientes con un primer episodio de psicosis (PEP), ¿tiene la edad del primer episodio psicótico un efecto no lineal en las anomalías estructurales relacionadas con el diagnóstico? (ii) ¿Apoyan los resultados derivados de

estudios de fMRI y DTI en TEA la propuesta de agrupación de síntomas en una diada realizada por el nuevo sistema de clasificación DSM-5? (iii) En pacientes con un PEP de inicio temprano, ¿los datos de volumetría cerebral obtenidos por RM ayudan en la predicción de un diagnóstico futuro de trastorno del espectro de la esquizofrenia (TESZ)?

9.3. HIPÓTESIS

Las principales hipótesis de esta tesis doctoral son las siguientes: (i) en pacientes con trastornos psicóticos, las alteraciones detectadas en volumen y grosor de corteza y relacionadas con el diagnóstico dependen de la edad del primer episodio psicótico, (ii) la asociación entre dichas anomalías cerebrales y la edad del primer episodio sigue un patrón no lineal, (iii) en pacientes con TEA, los déficits sociales y de comunicación están asociados con anomalías comunes de conectividad funcional y estructural que afectan a las mismas regiones / redes cerebrales, por lo que se pueden agrupar en un mismo dominio sintomático, (iv) dichas redes afectadas son distintas a las asociadas con la presencia de conductas repetitivas e intereses restringidos, y (v) una combinación de datos clínicos, cognitivos y volumétricos obtenidos por RM ayuda a predecir con exactitud un diagnóstico futuro de TESZ en pacientes con un PEP de inicio temprano.

9.4. MÉTODOS

Esta tesis está compuesta por tres publicaciones: dos artículos originales y una revisión sistemática, todas ellas lideradas por el doctorando.

***Pina-Camacho L.**, Del Rey-Mejias A., Janssen J., Bioque M., González-Pinto A., Arango C., Lobo A., Sarró S., Desco M., Sanjuan J., Lacalle-Aurioles M., Cuesta MJ., Saiz-Ruiz J., Bernardo M., Parellada M., and the PEPs group. Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophrenia Bulletin (in press), doi:10.1093/schbul/sbv128.* Artículo original.

Estudio trasversal y multicéntrico de RM cerebral de casos y controles. Una muestra de pacientes con PEP (n = 196), 65.3% varones, con una amplio rango de edad de inicio del PEP (12-35 años), y de controles sanos (n = 157), emparejados por edad, sexo y lateralidad manual fue reclutada y escaneada en seis centros. Se realizaron mediciones de volumen y grosor de sustancia gris (SG) cortical para varias regiones del cerebro empleando el software FreeSurfer. La relación no lineal entre la edad en el momento del escáner (un proxy de la edad del PEP en pacientes) y las medidas de volumen y grosor cortical fue analizada en pacientes con TESZ, trastornos afectivos psicóticos (TAFP) y controles sanos.

***Pina-Camacho L.**, Villero S., Fraguas D., Boada L., Janssen J., Navas-Sánchez FJ., Mayoral M., Llorente C., Arango C., Parellada M. Autism Spectrum Disorder:*

Does neuroimaging support the DSM-5 proposal for a symptom dyad? A systematic review of functional magnetic resonance imaging and diffusion tensor imaging studies. Journal of Autism and Developmental Disorders 42(7):1326-41, 2012. Revisión sistemática.

Se realizó una revisión sistemática en Medline / Pubmed de 208 estudios publicados en Inglés entre enero de 1990 y abril de 2011 que contuviesen datos de fMRI y DTI de pacientes con TEA. Los estudios fueron clasificados de la siguiente manera, de acuerdo con la técnica de neuroimagen empleada: (a) estudios de fMRI que emplean tareas relacionadas con cognición social e interacción social, (b) estudios de fMRI que emplean tareas relacionadas con lenguaje, (c) estudios de fMRI que emplean tareas relacionadas con comportamientos repetitivos o intereses restringidos, (d) estudios de fMRI en 'estado de reposo' (*resting state*), y (e) estudios que emplean técnicas de DTI. Para cada estudio de fMRI, se extrajo la información sobre las regiones afectadas en pacientes con TEA en comparación con controles sanos, en términos de activación anormal de regiones particulares del cerebro o de conectividad funcional alterada. Para los estudios de DTI, se extrajo la información sobre las regiones y redes afectadas en relación con la integridad estructural de la sustancia blanca (SB) en pacientes con TEA en comparación con controles.

***Pina-Camacho L.**, García-Prieto J., Parellada M., Castro-Fornieles J., Gonzalez-Pinto AM., Bombin I., Graell M., Paya B., Rapado-Castro M., Janssen J., Baeza I., Del Pozo F., Desco M., Arango C. Predictors of Schizophrenia Spectrum*

Disorders in Early-onset First Episodes of Psychosis: A Support Vector Machine Model. European Child and Adolescent Psychiatry 24:427–440, 2015. Artículo original.

Los datos provienen de un estudio longitudinal, prospectivo, de 2 años de seguimiento de 81 pacientes (edad 9-17 años) con un PEP de inicio temprano y un diagnóstico estable durante el seguimiento y 42 controles sanos emparejados por edad y sexo. Las variables predictoras estudiadas incluían diferentes combinaciones de datos clínicos, neuropsicológicos, de volumétrica cerebral por RM y bioquímicos, y la variable a predecir era el diagnóstico en el seguimiento longitudinal (TESZ frente a no-TESZ, TESZ frente a control, y no-TESZ frente a control). Varios clasificadores tipo máquina de vectores de soporte (*support vector machine - SVM*) fueron desarrollados y una función recursiva de eliminación fue aplicada a cada modelo para seleccionar y clasificar las variables de entrada según su valor predictivo para el diagnóstico de TESZ. Los distintos clasificadores fueron validados mediante validación cruzada tipo *leave one out cross-validation*, *jackknifing*, y una submuestra de individuos independiente.

9.5. RESULTADOS

El primer estudio de esta tesis doctoral encuentra que (i) las anomalías de volumen / grosor cortical relacionadas con el diagnóstico en pacientes con PEP están presentes principalmente en aquellas regiones del cerebro que presentan un proceso de maduración activa en cada momento particular del desarrollo, y

(ii) que la edad de inicio del primer episodio modula dichas anomalías de forma no lineal.

El segundo estudio apoya (i) la existencia de un sustrato neuroanatómico diferente para los dos dominios sintomáticos que conforman la diada diagnóstica de los TEA incluida en el DSM-5: 'déficits sociales y de comunicación' y 'comportamientos repetitivos / intereses restringidos, (ii) la existencia de un sustrato neuroanatómico diferente para los déficits sintácticos vs pragmáticos del lenguaje y (iii) la presencia de un sustrato neuroanatómico común para el subdominio sintomático 'déficits en interacción / cognición social' y los déficits pragmáticos del lenguaje, lo que sugiere que sería razonable incluir una mención explícita a este déficit pragmático del lenguaje dentro del dominio de 'déficits sociales y de comunicación'.

En el tercer estudio se muestra (i) que el modelo SVM que contiene una combinación de variables clínicas y neuropsicológicas tiene el mayor valor predictivo para el diagnóstico de TESZ en pacientes con un PEP inicio temprano, y (ii) que los datos de volumetría cerebral de RM no poseen valor predictivo por sí mismo ni añaden valor predictivo al mejor modelo.

9.6. DISCUSIÓN

Los estudios que forman parte de esta tesis doctoral representan un avance en el estudio de la fisiopatología de dos de los trastornos clave del

neurodesarrollo, la esquizofrenia / trastornos psicóticos y los TEA, a través del uso de técnicas de RM.

Los resultados del primer estudio están en consonancia con la hipótesis del neurodesarrollo de los trastornos psicóticos / esquizofrenia, ya que muestran que existe una interacción entre los eventos de maduración del cerebro en desarrollo y las anomalías morfométricas detectadas durante el PEP. Estos resultados también indican que los estudios de RM en PEP deberían siempre tener en cuenta el efecto no lineal de la edad en la estructura del cerebro, en especial si incluyen muestras con diferentes edades de inicio del PEP y diagnóstico.

Los resultados derivados del segundo estudio son de especial relevancia dado que si diferentes síntomas / déficits que se agrupan actualmente bajo un mismo dominio tienen diferentes bases neurobiológicas, o, del otro modo, síntomas / déficits que actualmente no se consideran juntos comparten bases neurobiológicas, esto tendría implicaciones muy importantes en cuanto a manejo clínico de los pacientes y desarrollo de nuevos tratamientos. En este sentido, este segundo estudio apoya la creación de la nueva diada diagnóstica y de la nueva categoría trastorno de ‘déficits sociales y de comunicación’ Asimismo, la existencia de un sustrato neuroanatómico diferente para los déficits sintácticos vs pragmáticos del lenguaje es congruente con la inclusión en el DSM-5 de los déficits sintácticos del lenguaje como especificador clínico independiente. Sin embargo, la presencia de un sustrato neuroanatómico común para el subdominio sintomático ‘déficits en interacción / cognición social’ y los déficits pragmáticos

del lenguaje sugiere que sería razonable incluir una mención explícita a este déficit pragmático del lenguaje dentro del dominio de ‘déficits sociales y de comunicación’. Este segundo estudio muestra por tanto cómo el conocimiento de las bases biológicas de los diferentes grupos de síntomas / dominios a través de técnicas de RM puede ayudar en el perfeccionamiento y mejora de los sistemas de clasificación diagnóstica actuales y servir de base para futuras investigaciones en líneas de tratamientos específicas y eficaces para estos pacientes.

Los resultados derivados del tercer estudio refuerzan la idea de que la predicción clínica en psiquiatría (incluyendo la predicción del diagnóstico) requiere una combinación de múltiples datos / medidas provenientes de múltiples fuentes, y apoyan la teoría de que las SVMs podrían ser herramienta prometedoras para la búsqueda de biomarcadores sensibles y específicos en los diferentes trastornos psicóticos. Partiendo de esa base, estas herramientas permitirían (i) ayudar a los clínicos en el proceso de diagnóstico diferencial, elección del tratamiento o información a pacientes y familiares sobre el pronóstico en las primeras etapas de la psicosis, y (ii) ayudar a perfeccionar los sistemas de clasificación de diagnóstico actuales de acuerdo con la iniciativa RDoC. Hasta entonces, parece que los sistemas de clasificación actuales tendrán que seguir basándose en la nosología tradicional con fines clínicos y de manejo. Sin embargo, la investigación sobre los mecanismos biológicos subyacentes a los trastornos psiquiátricos debería emplear un enfoque transdiagnóstico (por ejemplo estudiando muestras de pacientes con diferentes trastornos psicóticos, o incluso pacientes con diferentes trastornos del

neurodesarrollo, tales como los TEA y los trastornos psicóticos de forma conjunta) de cara a ayudar al diseño de sistemas de clasificación no sólo fiables sino también válidos.

En resumen, los estudios que forman parte de esta tesis doctoral demuestran que las técnicas de RM pueden ayudar a avanzar en el conocimiento de la fisiopatología de dos 'trastornos de la mente' por excelencia (los TEA y los trastornos psicóticos), a través del uso de la 'ciencia del cerebro' o neurociencia (ej. a través del uso de técnicas de RM) (Bullmore et al., 2009). Las conclusiones de esta tesis doctoral se resumen en la siguiente sección.

9.7. CONCLUSIONES

1. En pacientes con un PEP, las alteraciones de volumen y grosor de corteza relacionadas con el diagnóstico dependen de la edad de inicio de dicho primer episodio, y están presentes en aquellas regiones del cerebro que presentan un proceso de maduración activa en cada momento particular del desarrollo.

2. En pacientes con un PEP, la edad del primer episodio tiene un efecto no lineal en las anomalías cerebrales estructurales relacionadas con el diagnóstico.

3. La nueva propuesta de diada sintomática de los TEA realizada por el DSM-5 es sustentada por datos de estudios de fMRI y DTI, pero sólo de manera parcial. La presencia de un sustrato neuroanatómico común para el subdominio sintomático 'déficits en interacción / cognición social' y los déficits pragmáticos del lenguaje sugiere que sería razonable incluir una mención explícita a este déficit pragmático del lenguaje dentro del nuevo dominio de 'déficits sociales y de comunicación'.

4. En pacientes con un PEP de inicio temprano, una combinación de datos clínicos, cognitivos, pero no de volumetría cerebral por RM predice con exactitud un diagnóstico futuro de TESZ.

5. Las técnicas de RM son herramientas prometedoras para avanzar en el conocimiento de la fisiopatología de los TEA y los trastornos psicóticos.

6. Aunque parece razonable que los sistemas de clasificación diagnóstica en psiquiatría sigan basándose en la nosología tradicional para su uso en la práctica clínica, la investigación sobre los mecanismos biológicos subyacentes a los trastornos psiquiátricos debería emplear un enfoque transdiagnóstico, en la línea del proyecto RDoC. Esto ayudaría a diseñar en el futuro sistemas de clasificación no sólo fiables, sino también válidos.

10. REFERENCES

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11. ANNEXES

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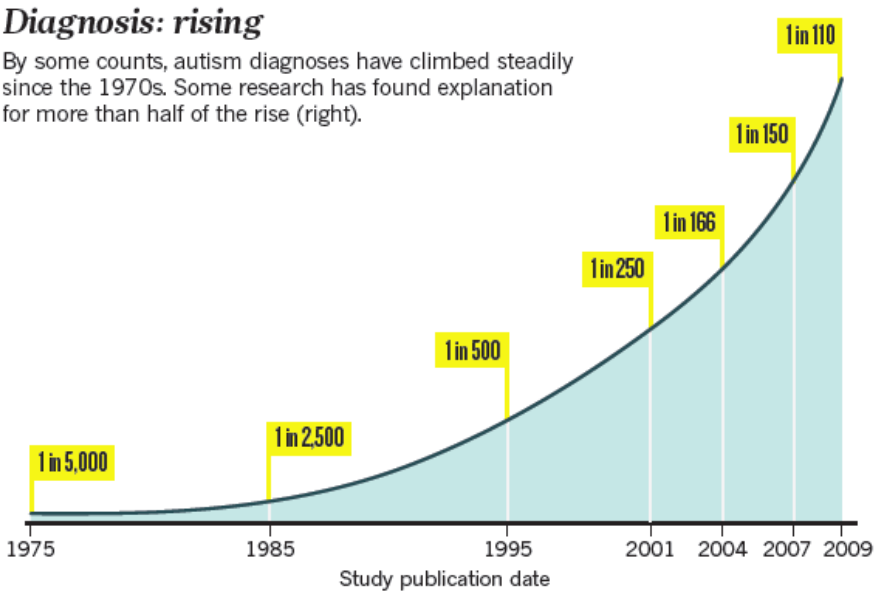
Annex I. Is prevalence of ASD increasing?

Since the release of last figure by the US Centers for Disease Control and Prevention (CDC), in which 1 in every 110 children is affected of ASD (Baxter et al., 2014; Weintraub, 2011), there has been ongoing debate over whether the prevalence of this disorder is indeed increasing (see Annex 1 – Figure 1).

Annex 1 – Figure 1. Raise in autism diagnoses since the 1970s



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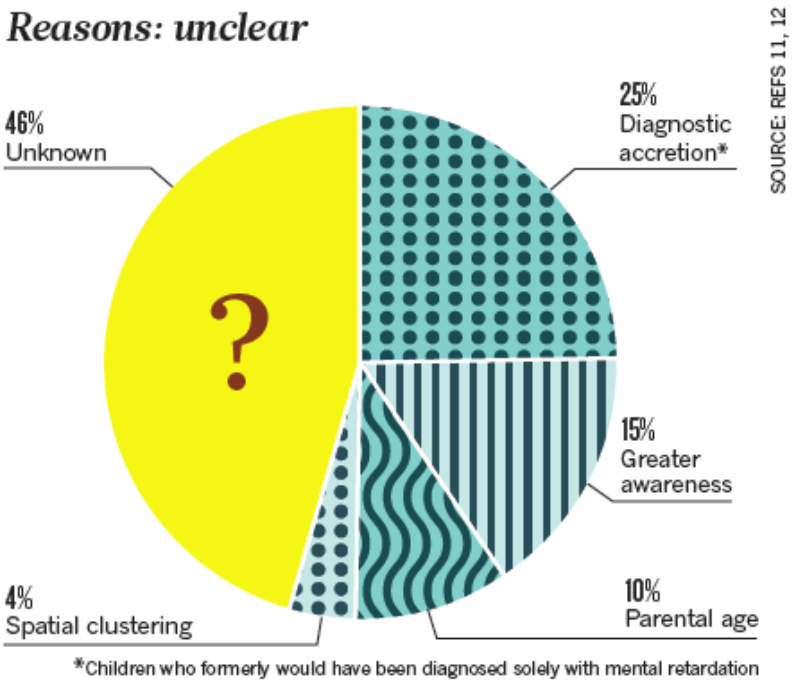
This phenomenon is probably due to a combination of different factors, such as increased recognition, increased early detection by pediatricians / teachers, and broadening of the concept from the classic childhood autism

described by Kanner to the more extended phenotypes (i.e. autism spectrum disorders [Wing, 1996]) (see Annex 1 – Figure 2). For example, subjects who would have been diagnosed with mental retardation according to earlier criteria would be now additionally diagnosed with autism, a phenomenon which is called 'diagnostic accretion' (Baxter et al., 2014; Parellada et al., 2014; Weintraub, 2011).

Annex 1 – Figure 2. Potential reasons underlying the raise in autism diagnoses since the 1970s



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The increase in prevalence due to the potential effect of increasingly common environmental factors, such as the increased rates due to advanced paternal or maternal age (King, Fountain, Dakhlallah, & Bearman, 2009; Kong et

al., 2012) or the effect of new environmental toxins (Landrigan, 2010; Rossignol & Frye, 2012) is also under study - please refer to section 1.2.2.3. ASD, Etiology and physiopathology).

Annex IIa. ASD and psychotic disorders: overlaps in clinical features, social cognition and neuropsychological deficits

Autistic characteristics can be present both before and after the diagnosis of psychotic disorders (Mouridsen, Rich, Isager, & Nedergaard, 2008; Sporn et al., 2004; Tsakanikos, Sturmey, Costello, Holt, & Bouras, 2007) while a proportion of children with ASD may present with psychotic-like symptoms (Kyriakopoulos et al., 2015). Moreover, these neurodevelopmental disorders frequently co-occur (J. Rapoport et al., 2009), with numerous studies showing how a significant proportion of youth with psychotic experiences or schizophrenia fulfill criteria for ASD or present with marked developmental abnormalities during childhood (Alaghband-Rad et al., 1995; Bevan Jones, Thapar, Lewis, & Zammit, 2012; Eggers, Bunk, & Krause, 2000; J. Rapoport et al., 2009; Sporn et al., 2004; Sprong et al., 2008). Of note, pre-existing ASD is as frequent as 30-50% in childhood-onset schizophrenia (COS) cases and may appear many years before schizophrenia is diagnosed (J. Rapoport et al., 2009). The same applies to individuals with adult onset schizophrenia (Mouridsen et al., 2008; Selten, Lundberg, Rai, & Magnusson, 2015; Unenge Hallerback, Lugnegard, & Gillberg, 2012).

Furthermore, although autism and schizophrenia, as traditionally described, are quite distinct clinically (e.g. different age at illness onset, different symptom profiles [Konstantareas & Hewitt, 2001; Rumsey, Andreasen, & Rapoport, 1986; Spek & Wouters, 2010]), both disorders show a range of common / overlapping clinical features. For example, premorbid and early negative symptoms of

schizophrenia (e.g. early social withdrawal, flat affect, poor eye contact) are sometimes indistinguishable from symptoms present in individuals with autism. The language difficulties in ASD and schizophrenia (e.g. restricted dialogue or poverty of speech or even neologisms) can also easily be confused. Besides, not only patients with ASD but also those with schizophrenia can present with odd mannerisms and stereotyped behaviours and with rigid, inflexible pattern of thinking and behaving (Delahunty, Morice, & Frost, 1993; Leung & Zakzanis, 2014; Ridley, 1994). Catatonia has also been described as a common phenotype for both ASD and schizophrenia patients and indeed there are descriptions of children presenting with mixed forms of catatonia, autistic and psychotic symptoms (Shorter & Wachtel, 2013).

Deficits in higher order social cognition, including deficits in social reciprocity and theory of mind are hallmarks of ASD (Baron-Cohen, 1989) but can also be present in schizophrenia (Frith, 1992). Indeed, both patient groups present with difficulties in integrating information from the external and internal world and in the perception / understanding of self (e.g. self-awareness) and others (e.g. identifying emotions or intentions in other people), resulting in a limited ability to interpret (or understand) reality and themselves, and to generate appropriate responses to external demands (Addington & Rapoport, 2009; Bolte & Poustka, 2003; Couture et al., 2010; Crespi et al., 2010; Pinkham et al., 2008; J. Rapoport et al., 2009; Roberts & Penn, 2013; Sugranyes et al., 2011). ASD and schizophrenia (and other psychotic disorders) also share numerous neuropsychological deficits, including impairments in executive function and cognitive flexibility, abstract reasoning, and goal-directed problem solving

behaviours, as well as impaired general functioning as measured with the intellectual quotient (Mayes & Calhoun, 2008; Pennington & Ozonoff, 1996; Tiihonen et al., 2005). Neurological soft signs (NSS) are also a vulnerability marker in schizophrenia, reflecting abnormal brain maturation (Bombin, Arango, & Buchanan, 2005), but patients with ASD have also been noted to display sensorimotor impairments (Halayem et al., 2009). One study compared the prevalence of NSS in a sample of patients with Asperger's syndrome, EOP and healthy controls and did not find significant differences between the groups of patients in their NSS profile (Mayoral et al., 2010).

Annex IIb. ASD and psychotic disorders: shared genetic, environmental factors and neurobiological underpinnings

Although several lines of genetic evidence supporting the distinction between COS and autism emerged initially (Sporn et al., 2004), further evaluation of all studies suggested some common genetic abnormalities associated with both disorders (J. Rapoport et al., 2009). Furthermore, both disorders share environmental risk factors (e.g. higher parental age, intrauterine infections, maternal stress or immune disorders) which, in the interplay with genetics, might lead to similar (although probably distinct in time-sensitivity) changes in neuronal maturation, migration, synaptic integrity, and neurotransmitter functions (Meyer et al., 2011)

Neuroimaging studies have also reported abnormal structure and function of brain regions associated with social cognition both in subjects with ASD (Pelphrey, Adolphs, & Morris, 2004) and psychosis (Bertrand et al., 2008). For example, volumetric GM deficits (Giedd et al., 2015), microstructural WM changes (Dwork, Mancevski, & Rosoklija, 2007; Ke et al., 2009) and abnormal brain gyrification (Kates et al., 2009; Palaniyappan & Liddle, 2012) have been reported as early vulnerability markers for both disorders. However, few neuroimaging studies have directly compared brain structure or function between these patient groups (Pinkham et al., 2008; Radeloff et al., 2014; Toal et al., 2009). Indeed, the main available information on the neurological overlaps and differences between ASD and schizophrenia comes from reviews and meta-analyses that put together findings from studies comparing each group separately

with healthy controls. (Abdi & Sharma, 2004; Cheung et al., 2010; Sugranyes et al., 2011). For example, fMRI studies show that ASD and schizophrenia patients both share activation deficits in similar brain regions within the 'social brain network' (e.g. hypoactivation within the superior temporal sulcus while performing a theory of mind task), and also demonstrate deficits unique to each condition (e.g. hypoactivation of thalamus unique to schizophrenia) (Sugranyes et al., 2011).