UNIVERSIDAD DE CANTABRIA

FACULTAD DE MEDICINA

DEPARTAMENTO DE MEDICINA Y PSIQUIATRÍA

TESIS DOCTORAL

"Diferencias en volumen de materia gris en pacientes con un primer episodio psicótico y efectos de edad de inicio utilizando morfometría basada en vóxeles"

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Santander 2016

A Pablo, Pau y Teo

A Merche

Agradecimientos

Quiero empezar agradeciendo al Prof. Benedicto Crespo Facorro por haber depositado su confianza en mí para echar a andar el laboratorio de neuroimagen cuando yo era una recién licenciada con todo por aprender. Por introducirme al campo de la neuroimagen y al equipo del programa PAFIP. Gracias por insistir en la importancia de este trabajo y ser un ejemplo de constancia.

Así mismo quiero agradecer a todos los miembros del equipo PAFIP, actuales y pasados, su valiosa labor, sin la que este trabajo no hubiera sido posible. Y sobre todo, su compañerismo y buen hacer.

A los pacientes del programa PAFIP y a los voluntarios que han colaborado con el programa y han permitido la realización de esta tesis doctoral. Espero que la continua investigación favorezca el avance en el conocimiento de la psicosis y mejore la calidad de vida de los enfermos.

Al equipo de neuroradiología del HUMV, radiólogos y técnicos, por su colaboración y apoyo en la toma de datos.

Gracias a Rosa, por apoyarme fuertemente en la realización de esta tesis y sus mensajes de ánimo en el sprint final.

Mi más sincero agradecimiento a mi madre, Merche, por ser un ejemplo de superación y persistencia. Por su apoyo y amor incondicional.

A todas las buenas personas, familia y amigos, que, cuidando de mis hijos o con una llamada telefónica, me han permitido llegar hasta aquí.

En último lugar a Pablo, por su amor, cariño, comprensión y apoyo durante estos 15 años. Por hacerme feliz y ser el padre de Pau y Teo, la alegría de mis días. A mis niños, a quienes quiero con locura y a los que esta tesis ha robado muchas horas que espero sepan entender algún día.

Financiación y apoyo institucional

La realización de los estudios de investigación que componen esta tesis doctoral se han realizado en el contexto del Programa de Atención de las Fases Iniciales de Psicosis de Cantabria (PAFIP), el cual está integrado en el Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM, Grupo 26), así como en el Instituto de Investigación Sanitaria Valdecilla (IDIVAL).

Mi contratación ha sido a cargo de dos programas de contratación competitiva como técnico de apoyo del Instituto de Salud Carlos III (CA12/00312 y CA08/00181)

Estos estudios de investigación han sido posibles gracias al apoyo de financiación externa procedente de procesos competitivos del CIBERSAM, el Instituto de Salud Carlos III (PI020499, PI050427, PI060507), la SENY Fundació Research Grant 2005-0308007 y la Fundación Marqués de Valdecilla (API07/011).

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Abbreviations

DARTEL	Diffeomorphic Anatomical Registration Through Exponential Lie Algebra
3D	Three-Dimensional
BPRS	Brief Psychiatric Rating Scale
CASH	Comprehensive Assessment Of Symptoms And History
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DICOM	Digital Imaging And Communications In Medicine
DPP	Duration Of Prodromal Period
DSM	Diagnostic And Statistical Manual Of Mental Disorders
DUI	Duration Of The Untreated Disorder
DUP	Duration Of The Untreated Psychotic Episode
FEP	First Episode Psychosis
FOV	Field Of View
FWHM	Full Width At Half Maximum
GDP	Gross Domestic Product
GLM	General Linear Model
GM	Grey Matter
GMV	Grey Matter Volume
HC	Healthy Controls
HMRF	Hidden Markov Random Field
HUMV	University Hospital Marques Of Valdecilla
MAP	Maximum A Posterior
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NEX	Number Of Excitations
NIFTI	Neuroimaging Informatics Technology Initiative
NSNA	Non-Specified Non-Affective Psychosis
PAFIP	Programa De Atención A Las Fases Iniciales De Psicosis
PVE	Partial Volume Estimation
ROI	Region Of Interest
SANS	Scale For The Assessment Of Negative Symptoms
SAPS	Scale For The Assessment Of Positive Symptoms
SCID-I	Structured Clinical Interview For DSM-IV Axis I Disorders
SPGR	Spoiled Gradient Recalled Acquisition In The Steady State
SPM	Statistical Parametric Mapping
SPSS	Statistical Package For The Social Science
SZ	Schizophrenia Disorder
SZF	Schizophreniform Disorder
TE	Echo Time
VBM	Voxel-Based Morphometry
WHO	World Health Organization
WM	White Matter

1.INTRODUCTION

The use of neuroimaging in schizophrenia spectrum research emerged in the mid-70s, when the enlargement of the lateral ventricles measured on CT (Computed Tomography) images was published (Johnstone et al., 1976). Since then, and especially in the 80s and 90s, the advance of neuroimaging techniques and the introduction of Magnetic Resonance Imaging (MRI) in hospitals made the neuroimaging research on mental disorders grow. The first study using magnetic resonance imaging in schizophrenia was published in 1984 (Smith et al., 1984) with negative results.

Most studies have been performed with chronic schizophrenia patients. However, in patients with several years of illness different variables take place that complicate the interpretation of the neurobiological findings. Antipsychotic long-term treatments have profound effects on the neurochemistry and perhaps in brain morphology. Other factors that may confound interpretation of studies conducted with patients include chronic stress secondary to live with the disease and characteristics of the lifestyle in patients with this disease (poor diet, high intake of nicotine, poor physical condition). Given these confounders in the population of patients with long evolution, a growing number of studies are being carried out in the early stages of the disease. Patients in the early stages of schizophrenia have clear advantages over chronic patients. It has been shown that the time between the onset of psychotic symptoms and diagnosis and treatment of schizophrenia is one year or even longer (Beiser et al., 1993; Johnstone et al., 1986), suggesting that in patients with first episode psychosis may have been an insidious onset and slowly progressive course of the disease even years before enrolling the studies. Therefore, research on early episodes of non-affective psychosis offers great potential for future neurobiological studies will better understand the pathological basis of the disease and long-term forecasts.

This work is aimed to the quantification of the physical markings associated to schizophrenia and the tool used to achieve this goal is magnetic resonance imaging. This technique has been chosen, as it is one of the few

methods that allow producing great detail images of in vivo soft-tissue in a non-invasive way. This has made MRI the choice tool for daily qualitative diagnostic in radiology departments around the world. However, quantitative techniques are optimal for research and measuring population differences, as they allow looking for anatomical variations that occur, for instance due to age, gender or pathology.

In this introduction we will present a brief history of magnetic resonance, accompanied with a necessarily reduced description of its physical principles. This will be followed by an overview of the quantitative methods used in the field of structural MRI, mainly Voxel Based Morphometry (VBM), key to the developments in this work. Finally we will introduce non-affective psychosis and the search of biomarkers and different aspects of schizophrenia.

1.1. History of magnetic resonance imaging

In 1945 Felix Bloch and Edgard Purcell independently demonstrated that some nuclei absorb electromagnetic radiation whose energy, in the radio-frequency range (also known as microwaves), strongly depends on the magnetic field applied to the sample. This absorption is produced when the incident light has the exact energy (the so-called resonance) to invert the state associated to the intrinsic magnetic moment of the nucleus (up to down or viceversa). Recording the signal associated to this absorption allowed a detailed characterization of the nuclei and matter in the sample, reason for which Bloch and Purcell were awarded with the Nobel Prize in 1952.

In 1971 the first medical application of nuclear magnetic resonance was produced. Raymond Damadian discovered that the variation of the magnetic resonance signal with time, the so-called relaxation time, of certain mouse tumors was different to that of normal tissue. This breakthrough enabled the discovery of a new method for in vivo imaging of the human body where the potential contrast between tissues and disease was many times greater than that offered by X-rays or ultrasound devices. In 1974 Damadian patented an "Apparatus and method for detecting cancer in tissue" (see Fig. 1).

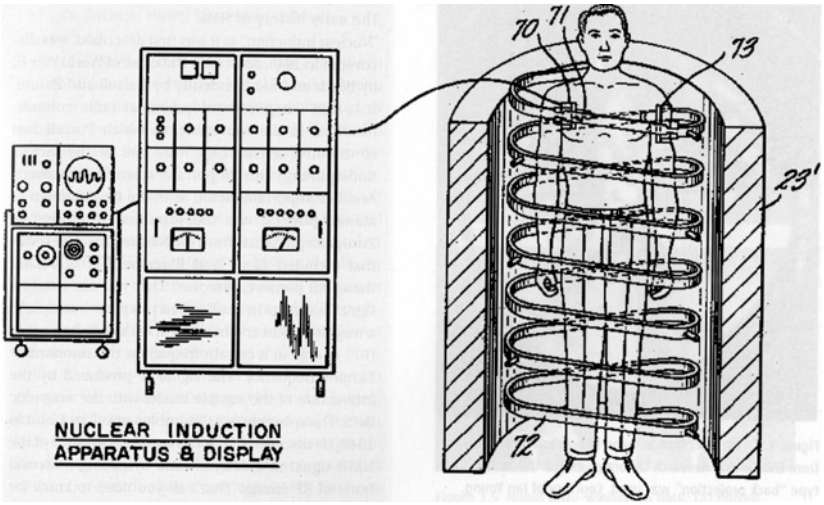

Figure 1. *Raymond Damadian's "Apparatus and method for detecting cancer in tissue".*

In 1973 Paul Lauterbur published an article in Nature in which he proposed using magnetic field gradients to differentiate nuclear magnetic resonance signals originating from different locations. This discovery was quickly followed in 1974 by that of Peter Mansfield and his group who discovered that the nuclei could be selectively excited with radio signals and the result mathematically analyzed making possible their interpretation into images. This achievement, in the form of frequency encoding, is the basis for modern magnetic resonance imaging and the reason why Lauterbur and Mansfield were awarded the Nobel Prize in 2003. In 1975 the technique was further developed by Richard Ernst who invented two-dimensional Fourier transform imaging.

The first image of a human body part was produced by Peter Mansfield in 1976, of a cross-section of the finger of his research student Andrew Maudsley, but the first MRI body scan took place on the 3rd of July of 1977 by Damadian's group. Since then, and based on the early ground breaking steps described above, there has been a continuous advance in the MRI field leading to the modern apparatuses that have typical resolutions below the milimeter.

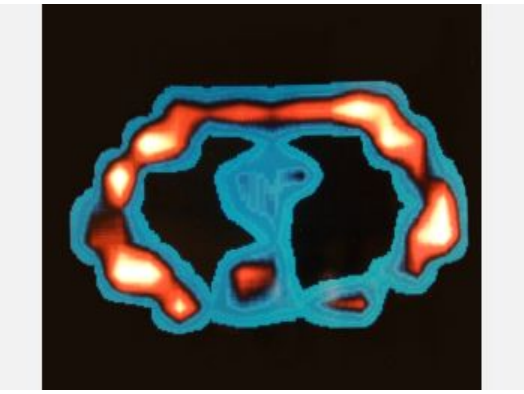

Figure2. *First MRI of the human body. Cross section of a chest. Damadian Lab.*

1.2. Principles of magnetic resonance

This section is based on general references on MRI mainly the book "MRI: From Picture to Proton" (McRobbie and et al., 2006).

Magnetic resonance imaging is derived from nuclear magnetic resonance, a physical phenomenon in which the electrons or the atom's nucleus can selectively absorb radiofrequency energy when placed under a strong magnetic field. As indicated above this energy is used in altering the spin of the particle. This process, controlled by quantum mechanics, involves an exchange of angular momentum between matter and the radiation field. Given that the angular momentum must be conserved through the whole process and that radiation carries a single angular momentum quantum (an aspect of the so-called photon) only a few of the many possible changes of spin can be observed experimentally. This makes that, of all the nuclei, those that can usually be observed by nuclear resonance are those that have an odd number of neutrons (N) or protons (Z) given that the flip of the unpaired particle corresponds, exactly, with a change in angular momentum of one quantum (as transported by the radiation). As we will see below, an special case is that of the hydrogen nucleus (1H) that contains a single proton and displays the strongest magnetic resonance signal for a nucleus of the whole periodic table. This is particularly important for imaging in biological tissues due to the large concentration of this particular isotope.

The absorbed radiofrequency energy (resonance) is not accumulated indefinitely in the sample (as this would raise, for example, the temperature of

the sample) but released, after a characteristic time, in the form of radio waves (the so-called relaxation process). This energy release can be captured as an electric signal in a receiving antenna and later used to form an (MRI) image.

In the present section we will discuss in a more quantitative way the different elements involved in the process, like the role of the magnetic field and its interaction with the nuclei.

As it is well known that electric charges interact depending on their position, as stated by Coulomb's law, the interaction also depends on the relative movement of the charges. In this way, it is well known that charges in movement (an electric current) can alter space around them in a number of ways like e.g. changing the orientation of iron particles in the vicinity of the cable carrying the current. These changes in the surrounding space are associated to the presence of a magnetic field. This property is usually denoted by the letter B and is a vector quantity, i.e. the magnitude is defined by its intensity (the modulus of the vector), its spatial direction and sense.

The value of B (called intensity or magnitude of the magnetic field) is expressed in units of magnetic induction. The units more usually employed in MR are the Tesla (T) and the Gauss and their relationship is:

1 T = 10,000 Gauss .....(1)

To provide an estimation of their magnitude we could mention that the value of the Earth's magnetic field is around 0.5 Gauss (varying according to geographical and temporal factors). Usually MRI scanners vary from 0.5 to 3T in clinical settings, going up to 9.4 T in research sites (meaning that artificial fields are between 4 to 5 orders of magnitude larger than Earth's magnetic field).

One of the main conditions to be considered in assessing the magnetic field in MRI is its uniformity and stability. These concepts refer, respectively, to the relative variations of the magnetic field in space and time. In order to obtain a homogeneous magnetic field, i.e. the magnetic field has a constant value in space, the shape of the conductor generating the field must be

carefully controlled. The most used design is that of the helix-shaped conductor (solenoid) that produces a very homogeneous magnetic field around its center point (isocenter). In this way the patients are introduced in cylindrical cavities that contain the conductive helix.

The atomic nucleus is formed by nucleons, i.e. the neutrons and the protons. Particularly important for MRI are the protons which are particles having an elementary positive electric charge (+e) and a magnetic moment μP=2.72μN, where μN is the nuclear magneton, that can only be in an up or down state. This magnetic moment is very small compared to that of the electrons, largely due to the mass ratio between both particles, but its interaction with electromagnetic fields is the basis for the nuclear magnetic resonance, the phenomenon behind the MRI technique. The reason is that the most common isotope of the nucleus of hydrogen (with a 99.9885% abundance), 1H, is formed by a single proton and this nucleus is present in all biological molecules and water, that is the main constituent of the soft tissue in living organisms.

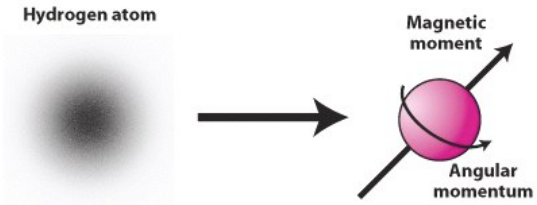

Figure 3. *Hidrogen atom.*

Our bodies have a large quantity of Hydrogen atoms: from the water within us, in cells and in extracellular fluid, (and to a lesser extent to the adipose tissue (fat)). These charge-carrying 'unpaired' protons (Hydrogen nuclei) rotate around their axes, but since all are spinning in a random fashion; their net spin is zero, or in other words, their net magnetic moment is zero.

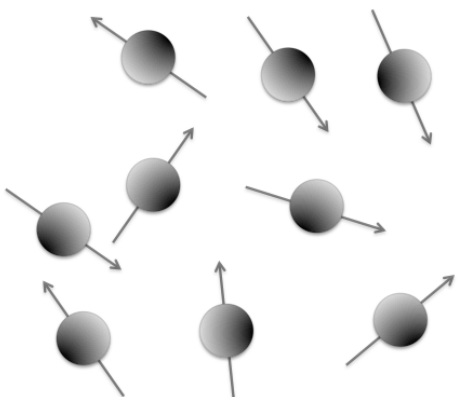

Figure 4. *Random nuclei.*

In the absence of magnetic field both directions of the proton's magnetic moment are equally probable in nature. However, when a strong magnetic field, B, is applied the level corresponding to the direction that is parallel to the field will have a lower energy. As a consequence, when a magnetic field is applied the magnetic moment of all hydrogen atoms aligns with the magnetic field.

The energy necessary to flip a spin under typical magnetic fields (B~1T) is in the radiofrequency range. For that reason, the proton can absorb this kind of radiation.

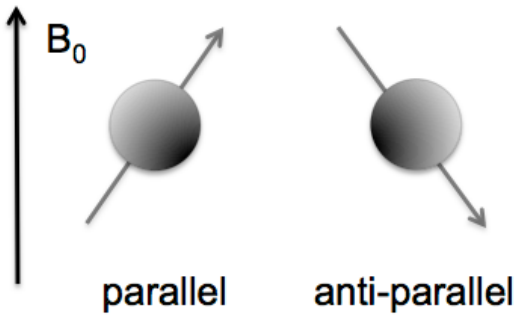

Figure 5. *Possible orientations for the proton in an external magnetic field.*

Thus, when nuclei are subjected to a pulse of radiofrequency radiation some nuclei flip from parallel to antiparallel orientation. This promotes the nuclei from a low energy state (spin parallel to the field) to high energy spin (spin antiparallel to the field), a process that requires absorbing energy and that sends the system into an excited state. The frequency required to make this happen is specific to the difference in energy between the parallel and anti-parallel (the so-called Larmor frequency). The excited nuclei will, at some later point in time, drop back to its low energy state (parallel) emitting the same amount of energy received to go to the excited state (that is specific for those nuclei).

The magnetic moment of the nuclei can also undergo precession, a movement in which the orientation of the magnetic moment oscillates around the direction of the magnetic field (see Fig.6).

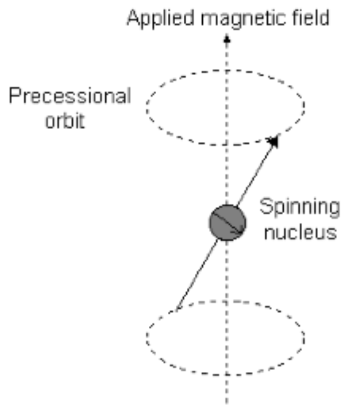

Figure 6. *Proton precessing around a magnetic field.*

The precession occurs naturally to any ^{1}H nucleus under a magnetic field and involves no radio frequency emission. The frequency associated to the oscillation of the precession is called precession frequency or resonance that is proportional to the magnetic field sensed by the nucleus. This is quantified by the fundamental law of magnetic resonance or Larmor law.

$$fp = \gamma B_0 / 2 \Pi \ (Hz) \qquad (2)$$

Where fp is the linear precession frequency expressed in cycles / second or Hz, Bo is the static magnetic field and γ is the nuclear gyromagnetic ratio, a nuclear constant characteristic of every isotope. Its value for 1H it is 42.5 MHz/T.

The main importance of precession in MRI is related to the relaxation processes i.e. the emission of radiofrequency radiation by excited protons to return to its thermalized state. There are two characteristic times associated to the relaxation of the spin:

- The T1 or spin-lattice relaxation time refers to the average time interval necessary for a spin to go from the excited antiparallel state back to the parallel

state i.e. the magnetization corresponding to direction of the magnetic field. Its typical values are in the second-millisecond range and it essentially controls the intensity of the de-excitation signal. Its importance radiates in that it is the time that is necessary to wait between radiofrequency pulses to excite the system again. While in an isolated 1H nucleus this time is indefinitely long when this nucleus is a sample its interaction with the surrounding matter (the lattice) allows the relaxation time to be finite and characteristic of the surrounding tissue in the case of MRI.

- The T2 or spin-spin relaxation time refers to the average time at which the magnetization component perpendicular to the magnetic field decays. This is naturally associated to the precession of the different nuclei in the sample that can move with some degree of coordination (in-phase) or in an arbitrary way (with a random phase). Thus, it is important to realize that the precession of these nuclei is correlated and that is very dependent on the chemical structure where these protons are embedded. Thus, the T2 is used to probe the biochemical environment of the sample.

1.3. Overview of quantitative methods used in the field of structural MRI

After the acquisition and visual quality checking of the images different methods for examining structural anomalies may be applied. These techniques may be based on manual or computerized methodology. In the early days of MRI, methods were based on subjective qualitative estimations instead of objective quantitative analysis. Qualitative methods are useful in diagnostic of gross structural abnormalities on a single subject while, on the other hand, quantitative studies are recommended in order to compare brain anatomy between groups, as the objectivity of these criteria permits replication and are optimal to find more subtle differences.

In this introduction two main techniques used in quantitative analysis will be presented: a)the region of interest (ROI) and b) voxel-based morphometry (VBM).

1.3.1. Region of interest analysis

The aim in the analysis of regions of interest is to obtain information in a particular region or set of regions using manual or semi automatic techniques. Usually, the brain may be rotated to align it with a particular plane, as anterior-posterior commissure plane, and then, for example, through hand tracing or point counting the following step would be to delineate the specific ROI falling within each two dimensional slice. The volume of the structure would be computed once each slice containing the region of interest is marked. These methods are generally labour intensive, time consuming and involve training the person in charge of it for each individual structure, making him or her reliable and less potential for bias when tracing. Further limitations are that when using manual tracing is not possible study large number of subjects, therefore, sample sizes tend to be small.

This type of method limits studying brain structures but is very robust when differences are found.

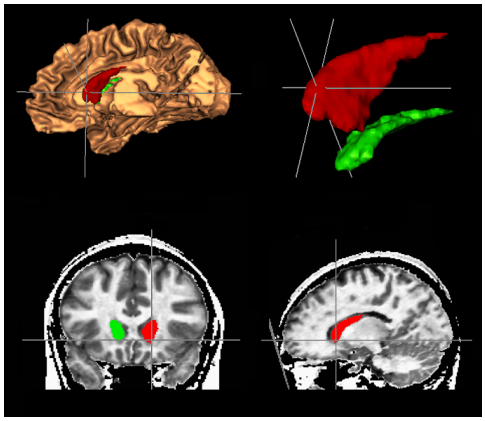

Figure 7. *ROI measures of caudate. (Author: Roberto Roiz- Santiañez).*

1.3.2. Voxel based morphometry

Presently, computational methods analysing global differences in the brain are divided into those that study brain shape or those that look for local anomalies in tissue composition after macroscopic differences in shape have been controlled for (Ashburner and Friston, 2000; Wright et al., 1995). Voxel based morphometry is included in the last group.

Classically voxel-based morphometry of MRI data involved spatial normalizing all the images to the same stereotactic space, extracting the grey matter from the normalized images, smoothing and finally performing a statistical analysis to localize, and make inferences about, group differences. (Ashburner and Friston, 2000; Wright et al., 1995).

Voxel-wise statistical tests are performed to compare the smoothed images where parametric or non-parametric statistics based on the general linear model may be applied to the data (Ashburner and Friston, 2000), (Bullmore et al., 1999; Nichols and Holmes, 2002). Statistical comparisons made at the level of each individual voxel between the brains of subject groups under study often involve complex statistical models, and corrections for multiple comparisons are also performed during a VBM analysis using the theory of Gaussian random fields so as to reduce the reporting of false positives

for instance by using correction based on family-wise error or field discovery rate methods (Friston et al., 1994b; Genovese et al., 2002)- Significant regions of difference are localised and typically reported in a standard space as Talairach or MNI (Evans AC et al., 1993; Talairach and Tournoux, 1988).

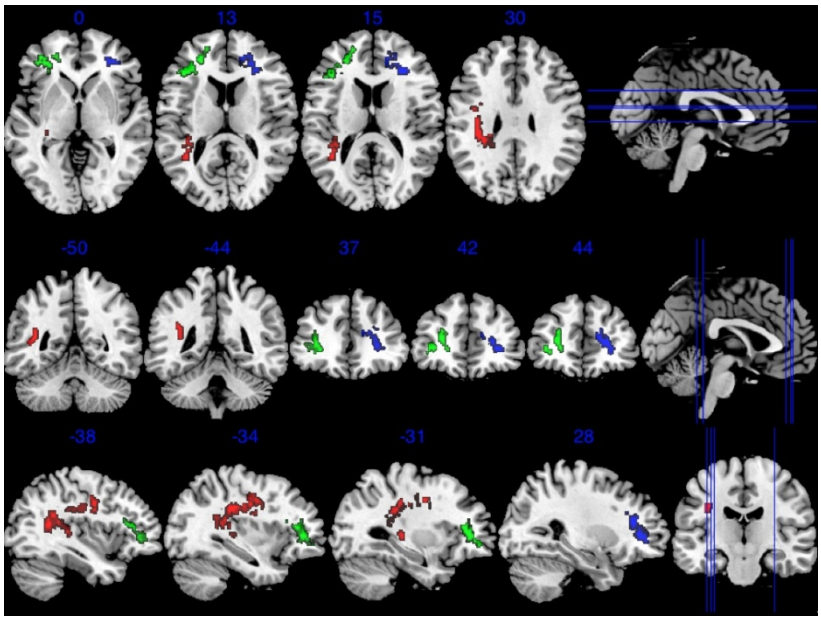

Figure 8. *White matter VBM study (Perez-Iglesias et al., 2010).*

In summary, VBM is able to identify regional differences in the tissue content of grey or white matter and has several advantages over ROI approaches. VBM is an automated and comprehensive technique that allows an unbiased examination of the entire brain on a voxel per voxel basis. It is less time and cost consuming, provides increased objectivity and it is able to identify subtle brain differences.

1.4. Schizophrenia spectrum disorders

Schizophrenia spectrum is a notably heterogeneous psychiatric disorder of the psychosis group that is defined by a reduced contact with reality of the subject accompanied by an extremely problematic and variable psychopathology influencing cognition, feelings, perception and other behavioural aspects (Sadock et al., 2009). These alterations change with time and are expressed differently by each patient, usually manifesting themselves through hallucinations, delirious beliefs, negative and deficitary symptomatology, social dysfunction and disorganized thought process and behaviour.

While its year-prevalence is around 0.5%, the risk of displaying schizophrenia at some point in life is close to 1% for the general population (Saha et al., 2005). The yearly schizophrenia spectrum incidence varies within the 7 to 20.1 per 100.000 inhabitants bracket depending on whether first schizophrenia episodes are recorded sensu stricto or considered in the more ample group of non-affective first psychotic episodes (Baldwin et al., 2005). Our group (Pelayo-Teran et al., 2008) found a yearly incidence of 1,38 in 100.000 for first non-afective psychotic episodes for the population within the age of risk. In the meta-analysis carried out by Aleman and coworkers (Aleman et al., 2003) or McGrath and coworkers (McGrath et al., 2004) can be seen that males have an increased probability of developing schizophrenia during life with a relative risk of 1.4 when compared to females, a fact consistent with our own studies in Cantabria where this relative risk was found to be 1.6 (Pelayo-Teran et al., 2008). Moreover, the male/female ratio increases as more restrictive constraints are imposed over the diagnosis of schizophrenia (Beauchamp and Gagnon, 2004; Tandon et al., 2008). Finally, we would like to mention that, as evidenced in several meta-analysis, bibliographic data reveals a systematic relationship between several social variables, like immigration or urban residence, to negative, stress-generating psychological, social and biological factors associated to social desintegration and the risk of developing

schizophrenia (Cantor-Graae and Selten, 2005; McGrath et al., 2004; van Os et al., 2010).

The initial symptoms of the disorder usually appear at an early adult age, usually concomitant with an important stage for the final development of the personality. Thus, the onset is often situated between the ages of 15 and 35 (50% below the age of 25) being infrequent after the age of 40 (Saha et al., 2005). Numerous studies, including our own, have shown that schizophrenia appears in males between 3 to 5 years before than in females (Pelayo-Teran et al., 2008), a fact apparently associated to a better social and familiar adjustment, as well as a more favourable evolution in this gender (Aleman et al., 2003; Atalay and Atalay, 2006; McGrath et al., 2004).

Historically, psychoses have been often described as disorders following a chronic course with a notable deficit in social and psychic functions, frequent re-incidences and a strong tendency towards developing treatment resistance. This point of view is clearly seen in a series of works demonstrating that the usual evolution course was characterized by the low proportion of patients experiencing significant improvement or recovery (20%-40%). This fact was later strongly vindicated in an exhaustive meta-analysis work over the full 20th century bibliography about the outcome of the treatment showing that only 40% of the patients had shown improvements after 5-6 years of treatment (Hegarty et al., 1994). However, this negative outline has been recently revisited in the meta-analysis carried out by Menezes and coworkers (Menezes et al., 2006) in which they show that treatment right after first psychotic episodes resulted in a negative outcome in only a 27.1% of the cases while 42.2% of them displayed a positive outcome. Nevertheless, and in spite of this optimistic vision of schizophrenia outcome in recent bibliography, there is still a strong tendency towards a chronic evolution of the disorder and strong deficits in the psycho-social functionality of the patients. As a consequence this disorder is associated with a large disability degree (Ertugrul and Ulug, 2002) being considered, globally, as the third disability cause in a multicentric, international study (Ustun et al., 1999) and one of the most important by WHO (WHO World Health Report, 2001). Moreover, it is also well-known that the families of the

patients endure a strong stress and overload due to the illness symptoms (Schulze and Rossler, 2005).

Side-by-side with these devastating consequences for the patients and their families, schizophrenia has also a very significant economic cost for the community. For example, Knapp and coworkers (Knapp et al., 2004) show in their bibliographic review on the economic impact of schizophrenia the important costs associated to the disease. When comparing the direct and the indirect costs it was shown that the later are the main responsible for the large expenses associated to the disorder (Andlin-Sobocki and Rossler, 2005; Wu et al., 2005). In western countries it is estimated that the cost could reach up to 2% of the GDP (Black and Andreasen, 2014). In this way, this disorder has a large cost in Spain, where the factors that determine its high cost are similar to those found in the studies carried out in other countries (Vazquez-Polo et al., 2005).

1.5. Neuroimaging and schizophrenia spectrum disorders

The first published neuroimaging study was carried out in chronic schizophrenia patients using computed tomography images and they found enlargement of the lateral ventricles (Johnstone et al., 1976). Since then the advance of neuroimaging techniques and the introduction of MRI in hospitals made the neuroimaging research on mental disorders grow. The first study using magnetic resonance imaging in schizophrenia was published in 1984 (Smith et al., 1984) with negative results.

In the last meta-analysis studying brain volumes in schizophrenia, Haijma et al (Haijma et al., 2013) studied results for over 18000 subjects. They found a marked reduction in total grey matter and volume increases of total CSF (Cerebrospinal Fluid), especially in the third ventricle. White matter reduction was similar in the medicated and medicated-naïve sample, while grey matter reduction was larger in the first group. This evidence, along with studies in high-risk populations (Koutsouleris et al., 2009) and families (Boos et al., 2007) supports the hypothesis of an early interruption in brain development in schizophrenia (Murray and Lewis, 1987; Weinberger, 1987).

These brain morphometric alterations appear to meet the criteria for endophenotypes in psychotic disorders (Gottesman and Gould, 2003; Prasad and Keshavan, 2008). However, the specificity for schizophrenia of these reported brain anomalies is uncertain. Moreover, there is overwhelming evidence that psychotic disorders are pathophysiologically heterogeneous (Kapur et al., 2012) which hampers the search for biomarkers to aid early diagnosis, stratification and the measurement of disease progression. Indeed this lack of biomarkers is perceived by industry as a key barrier to the development of novel treatments. Neuroimaging research may provide such objective and quantitative measurements.

Three topics, relevant in clinical practice in schizophrenia spectrum disorders have been the focus of the studies carried out with VBM approach and exposed in the present thesis: First, the age of onset of non-affective psychosis. As stated before, the typical age of onset for schizophrenia is late adolescence or early twenties, known as early onset schizophrenia (Rapoport and Gogtay, 2011). There is evidence implicating the disruption of normal neurodevelopmental processes, suggesting that early brain insults could have affect normal brain development in contrast to those who manifests non-affective psychosis late in life. Thus, variability in age of onset may explain the heterogeneity of brain structural abnormalities in schizophrenia. Second, and in line with the previous topic, differential diagnosis of psychotic disorders. Based on the heterogeneous clinical presentations, symptoms are insufficient for the diagnosis and management of non-affective psychosis. Structural neuroimage could represent a useful tool for diagnosis and management of non-affective psychosis. Third, insight in non-affective psychosis. Many persons with schizophrenia spectrum psychosis experience poor insight of their illness and, as a result, are at risk for treatment non-adherence and numerous negative outcomes. The etiology of poor insight has not yet been fully elucidated. The recent theory concerning the roots of poor insight in schizophrenia has proposed that it may result from impairments in frontal brain structures. The frontal lobe contains most of the dopamine-sensitive neurons in the cerebral cortex. This brain region has been implicated in higher cognitive skills.

1.5.1. Age of onset in non-affective psychosis

Given that neurodevelopment continues throughout adult life (Tanaka et al., 2012; Uematsu et al., 2012) it could be hypothesized that the disease process may interfere with the normal brain development leading to specific brain anomalies related to the age at which the illness manifests (Gogtay et al., 2011). Early disease onset has been associated with an "accelerated brain aging" effect in schizophrenia and affective disorders as a result form a

disturbance of normal brain maturation processes (Koutsouleris et al., 2013). Age of onset has been conceptualized as a proxy measure of the severity of non-affective psychosis (DeLisi, 1992). An earlier onset has been associated with a poorer clinical outcome (Hoff et al., 1996; Sato et al., 2004) and more severe cognitive impairments (Jeste et al., 1998; Rajji et al., 2009). Most of the previous studies investigating the effect of age of onset in brain structure have focused on early-onset psychosis (Gogtay et al., 2011; Jung et al., 2012; Matsumoto et al., 2001).

1.5.2. Differences in diagnosis in first episode non-affective psychosis

Major diagnosis classification systems retain categorical distinctions between several psychotic disorders that share substantial clinical features. It has been proved difficult to identify natural boundaries between psychotic disorders (Murray and Lewis, 1987; Murray et al., 2004) and a continuum approach to non-affective psychosis has been argued.

Previous region of interest (ROI) studies from our group in an overlapping sample revealed that - compared to healthy volunteers - patients with schizophrenia at the first break showed (1) a significant increase in lateral ventricle and cortical CSF volumes and decrease in total brain tissue and thalamic volumes (Crespo-Facorro et al., 2009), and (2) a diffuse pattern of reduced thickness (encompassing frontal, temporal and parietal heteromodal association cortices) accompanied by a marked thinning of sulci (Roiz-Santianez et al., 2012). Our group has also addressed this issue by performing a series of manually delineated ROI studies in first-episode patients. Reduced thalamic volume (Crespo-Facorro et al., 2007), right postcentral gyrus volume (Ferro et al., 2014) ,right insular cortex thinning (Roiz-Santianez et al., 2010a), but no differences in temporal pole (Roiz-Santianez et al., 2010b) and insular volumes (Crespo-Facorro et al., 2010) were observed in patients.

Nonetheless ROIs studies may neglect brain abnormalities in several other regions of the brain and may not be sensitive to alterations crossing predefined anatomical boundaries. In this regard, the VBM approach may reveal

the existence of morphological alterations in bran regions in an unbiased manner (Perlini et al., 2012).

1.5.3. Insight in non-affective psychosis

Lack of insight is considered a cardinal symptom in non-affective psychoses (Arango and Amador, 2011). Approximately 50-80% of first episode non-affective psychosis (FEP) patients present lack of insight into their condition, which remains after improvement of psychotic symptoms (Ayesa-Arriola et al., 2014; Crumlish et al., 2005; Saeedi et al., 2007). This leads to a failure to recognize the need for treatment, which has the compounding effect of treatment nonadherence (Buckley et al., 2007), thus representing a significant concern. Such observations have been documented as having a substantial impact on long-term functioning (Lincoln et al., 2007).

Recently, there has been a growing interest in exploring brain abnormalities underlying lack of insight in non-affective psychosis. Owing to the similarities between impaired insight in psychosis and anosognosia in neurological disorders, frontal lobe dysfunction has been implicated as a potential mechanism subserving poor insight (Kumar et al., 2014; Shad et al., 2004) and the majority of neuroimaging studies in schizophrenia spectrum disorders have focused on investigating the role of the prefrontal cortex. Several studies have reported significant correlations of poor insight with decreases in dorsolateral prefrontal grey matter volumes (GMV) (Laroi et al., 2000; Shad et al., 2004). These data have contributed to the development of a neural network of insight which encompasses the cingulate, frontal, parietal and temporal cortices (Antonius et al., 2011; Bedford et al., 2012; Liemburg et al., 2012; Raij et al., 2012) (van der Meer et al., 2013) (Kim et al., 2012). However, the studies with which this network has been defined have notable limitations, including small sample sizes.

2.RATIONALE, HYPOTHESIS AND OBJECTIVES

2.1. Rationale

Establishing the biological basis of a disease or disorder is an important step to advance in its diagnosis and find new possible routes for its treatment. In the case of psychiatric disorders the development of imaging techniques that allow the objective and unbiased research of "*in vivo*" subjects provides the optimal tools to look for the root of the problem. Our particular focus will be the early stages of schizophrenia spectrum psychosis since, at this point, no extraneous effects, due e.g. to medication or chronicity, have yet appeared veiling the underlying biological causes. In order to carry out this study we will use voxel-based morphometry, a technique based on magnetic resonance imaging, that will enable us to map the various structures of the brain in space, supporting this information with data on the kind of tissue (white, grey matter) associated with a position. Thus, this tool is optimal for the search of biomarkers trails of the disorder.

The age at which the first psychotic outbreak occurs is an important variable that may strongly impact the later evolution of the disorder. It has been shown that patients with an early onset of schizophrenia spectrum disorders has significantly greater levels of cognitive impairment and higher impulsivity (Kao and Liu, 2010). Several neuroimaging works examine these early stages, concentrating in its appearance at youth or even at the paediatric level (Kravariti et al., 2003; Rapoport and Gogtay, 2011). Other studies have investigated the effect of the age of onset in chronic patients, trying to associate it with the later evolution of the disorder (Ongur et al., 2009). However, to our knowledge no previous study has tried to establish the effect of the age of onset in young adults who have just been diagnosed with a first episode of non-affective psychosis.

Presently diagnosis in psychotic disorders is carried out based on symptoms, but a search for objective, quantitative and clinically meaningful measurements is needed. Looking at different manifestations of non-affective psychosis in FEP patients may help to advance in the understanding of the

neurobiological differences between diagnoses and, therefore help in the founding of quantitative measures.

Finally, we will study a factor that has an important influence on the quality of life and treatment of the patients: their own awareness of the disorder, the so-called *insight*. It has been observed that patients with higher insight display better cognitive skills and prognosis than those with lower insight into their problem (Lincoln et al., 2007). This factor is also correlated with the willingness and ability to follow the treatment (Buckley et al., 2007). It has been speculated that low insight is associated with grey matter deficits when compared to healthy controls and patients with higher insight. However, most of these studies have been carried on chronic patients (Orfei et al., 2013) or much smaller samples than the one here presented (Berge et al., 2011). During this work we will investigate the results of brain imaging to determine whether the awareness of the disorder has a physical basis.

2.2. Hypotheses

The main hypothesis in this work is that patients with a first psychotic episode display reduced grey matter levels when compared to an average obtained from a group of the general population with their same social and economic class. While this hypothesis is relatively well established we will concentrate on the following, more particular, aspects of this statement:

Hypothesis 1: Patients that are diagnosed with schizophrenia will display larger reductions in grey matter volume than other disorders of the psychotic spectrum.

Hypothesis 2: Patients with a younger age of onset will show a significant reduction in grey matter volume in relation to both patients that onset later in life and healthy controls.

Hypothesis 3: Patients with low insight display reduced grey matter volumes with respect to comparable healthy controls and patients with higher insight.

2.3. Objectives

Objective 1: To evaluate whether there are significant structural differences in patients diagnosed with non-affective psychosis depending on their age of onset.

Objective 2: To explore similarities/differences of the various disorders in the non-affective psychosis spectrum using voxel-based morphometry.

Objective 3: To determine whether brain structural abnormalities can be quantifiably related to the lack of insight.

3.METHODS

3.1. Study setting

Data for the present thesis were obtained from a large epidemiological intervention program of first-episode of psychosis: Programa de Atención a las Fases Iniciales de Psicosis (PAFIP) conducted at the department of Psychiatry of the University Hospital Marques de Valdecilla (HUMV), Santander, Spain. This program has a care intervention and a research branches. The care intervention branch has as objective to assist all patients from the Santander area that present a first episode of non-affective psychosis during the first three years. In order to accomplish that, a pharmacological protocol (Crespo-Facorro et al., 2008), individual psychotherapeutic interventions and psychoeducation for individuals and their families are provided. From the research point of view, PAFIP is a prospective and naturalistic study that pursues the objective of improving the knowledge of the initial phases of non-affective psychosis in the following areas: clinical, neurocognitive, neuroimaging, immunological and genetics.

3.2. Ethical and legal issues

The local institutional review board in accordance with the Declaration of Helsinki approved this program. Participation in the study is preceded by a thorough interview by an investigator of the program during which the patient is informed about the entire course of the study. It is emphasized that participation is voluntary and treatment alternatives aside PAFIP are explained to the patient. Patients are given sufficient time to read all the provided information and counsel with partners or relatives, also to clarify any questions with the investigator. Regarding data privacy, patients are informed about coding with no reference to their names o clinical history number. They are informed that this consent can be revoked at any time without citing reasons. A copy of the consent is given to the participant and he or she is asked to sign the written consent (appendices 1 and 2). In case of no agreement in signing the inform consent the subject is not included in the program.

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3.3. Participants

3.3.1. Patients

The subject sample that takes part in this study are patients that were referred to PAFIP, met the inclusion criteria and undertook an MRI between March 2002 and January 2005.

To be included in the PAFIP program, patients have to meet the following criteria:

1. Experiencing a first episode of schizophrenia spectrum psychosis.
2. Diagnoses. The studied group was part of the DSM-IV schizophrenia spectrum disorders: schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and psychosis not otherwise specified, excluding those psychotic disorders directly caused by a general medical condition or the use of substances including prescription drugs (Appendix 3). The initial diagnosis was confirmed using the structured interview SCID–I performed by an experienced research psychiatrist 6 months after the first contact.
3. No prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks.
4. Age between 15 and 55 years.
5. Live in Cantabria.
6. Presence of psychotic symptoms, from moderate to severe, according to at lest one of the five items in the scale of positive symptoms (Andreasen, 1984)

Patients were excluded if:

1. Had a history of brain injury or neurological illness, mental retardation, or
2. Fulfilled DSM-IV diagnosis of drug dependence (except nicotine dependence).

3.3.2. Healthy controls

A group of healthy controls (HC) was also recruited from the same catchment area through advertisements. Exclusion criteria were current or past history of psychiatric, neurological or general medical illnesses, including substance dependence and significant loss of consciousness, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Healthy volunteers were selected to have a similar distribution in age, gender, laterality index, drug history and years of education as the patient population. The absence of psychosis in first-degree relatives was also an inclusion criterion. After a detailed description of the study, each subject gave written informed consent to participate.

3.4 Sociodemographic and clinical characteristics

Social and demographic information was collected using a questionnaire specifically designed for the study. A member of the research team carried out this process at the moment of admission in the program, both with the patient as well as with the reference relative. The questionnaire includes important information including, among other items: age, gender, period of education, urban/rural origin, as well as data on cohabitation and family support (Appendix 4).

Clinical evaluation was carried out by the same psychiatrist. The following tests were carried out:

1. The Spanish version of the Brief Psychiatric Rating Scale - BPRS - (Overall and Gorman, 1962). The BPRS scale evaluates the characteristics of

the main psychiatric symptoms. The version employed consists of 24 items that are individually evaluated in a scale ranging from 1 to 7. A score of 1 is equivalent to "symptom absence", 2 "very slight", 3 "slight", 4 "moderate", 5 "moderately severe", 6 "severe" and 7 "extremely severe".

2. The Spanish version of the Scale for the Assessment of Positive Symptoms - SAPS- (Andreasen, 1984). This scale has 5 items related to delirium, hallucinations, extravagant behaviour, formal thought disorders and inappropriate affection (Appendix 5).

3. The Spanish version of Scale for the Assessment of Negative Symptoms - SANS - (Andreasen, 1983). This scale consists of 5 items related to the symptoms alogia, affective flattening, apathy, anhedonia and attention (Appendix 6).

4. The Spanish version of the psychiatric interview SCID-I (The Structured Clinical Interview for DSM-IV Axis I Disorders). This tool consists in a psychiatric interview that allows diagnosing the psychiatric disorders included in the Axis I of DSM-IV.

In this work we used SAPS and SANS as the main scales to measure the patient's clinical severity. To obtain a more specific value for the psychotic clinical severity the scores for the positive, negative and disorganized clinical dimensions that can be calculated from SANS and SAPS (Flaum and Andreasen, 1995; Grube et al., 1998). In this way the score corresponding to the positive dimension is the result of the sum of the scores corresponding to "hallucinations" and "delirium" in the SAPS scales; the score corresponding to the negative dimension is measured as the sum of the SANS items "alogia", "apathy", "asociability" and "affective flattening"; finally the disorganized dimension is obtained from the sum of the items "extravagant behavior", "formal though disorders" and "inappropriate affection".

The same psychiatrist confirmed the diagnosis 6 months after the first contact through a structured psychiatric interview using, as previously indicated, the SCID-I interview (The Structured Clinical Interview for DSM-IV Axis I Disorders).

Premorbid information was also collected through a questionnaire specifically designed for the study. This process was supervised by the medical staff associated to the PAFIP program and was carried out both with patients and their relatives. The obtained information included, essentially, the evaluation of the previous psychiatric and psychotic record both in the patient and close relatives as well as an evaluation of the symptoms and clinic manifestation of the onset of the disorder.

The duration of the untreated psychotic episode (DUP) was defined as the duration, in months, from the appearance of the first psychotic symptom that was continuously sustained and the administration of a proper treatment.

The duration of the untreated disorder (DUI) was defined as the duration, in months, from the appearance of the first nonspecific symptom related to psychosis and that could be associated to a deterioration of the previous function level of the patient and the start of the adequate treatment.

Duration of prodromal period (DPP) was defined as the period from the first unspecific symptoms related to psychosis (as defined above) to the first continuous (present most of the time) psychotic symptom.

Age of onset of psychosis was defined as the age at which the emergence of the first continuous (present most of the time) psychotic symptom.

Finally, handedness was assessed by the Edinburgh Inventory (Oldfield, 1971).

3.5. Insight assesment

The shortened version of the Scale of Unawareness of Mental Disorder (SUMD) (Amador et al., 1994) was used to measure insight in our FEP patients (appendix 7). The SUMD is a semi-structured interview, which provides scores on insight dimensions. The dimension insight into mental illness was selected for the purpose of this study. This dimension ranges from 1 to 5, with higher scores indicating less awareness. Good insight was defined as a score of 1, and

poor insight was defined as a score greater than 1. Patients were classified in two groups: good vs. poor insight.

3.6. Imaging acquisition

High-resolution three-dimensional (3D) T1-weighted images were acquired on a 1.5-T whole-body scanner (SIGNA, GE, Milwaukee, WI, USA) at the University Hospital Marques of Valdecilla, Santander, Spain. Three-dimensional T1-weighted images, using a spoiled gradient recalled acquisition in the steady state (GRASS) (SPGR) sequence, were acquired in the coronal plane with the following parameters: TE = 5 msec, TR = 24 msec, NEX = 2, rotation angle = 45°, FOV = 26 x 19.5 cm, slice thickness =1.5 mm and a matrix of 256 x 192. Images were acquired in the coronal plane covering the whole brain. All subjects were scanned using the same protocol on the same scanner.

3.7. Imaging analysis preprocessing

Data was transferred from the Radiology Department to the computer at the Neuroimaging Unit. After a visual inspection of the images using Osirix (http://www.osirix-viewer.com/) all images were converted from DICOM to NIFTI format using Chris's Roden dcm2nii conversion program (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html).

Structural images were pre-processed using SPM5 package (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) running in MATLAB (MathWorks, Natic, MA) and Christian's Gaser VBM toolbox http://www.neuro.uni-jena.de/.

3.7.1. Segmentation

Segmentation is the procedure by which the original brain image for each subject is partitioned into grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) and three other background classes that are not saved.

Gasser's approach is based on an adaptive Maximum A Posterior (MAP) technique without the need for a priori information about tissue probabilities. It starts with an initial segmentation of the three pure classes (GM, WM and CSF) followed by a Partial Volume Estimation (PVE) of two mixed types (Tohka et al., 2004). As a consequence, each intensity value in the resulting image is represented by a weighted sum of random variables, each of them describing a pure tissue class. The MAP estimation is adaptive in the sense that local variations of the parameters (i.e., means and variance) are modelled as slowly varying spatial functions (Rajapakse et al., 1997). This not only accounts for intensity inhomogeneities but also for other local variations of intensity.

Furthermore, to improve the quality of segmentation a Hidden Markov Random Field (HMRF) model (Cuadra et al., 2005) was applied to the segmented tissue. This model provides spatial constraints based on neighbouring voxels of a 3x3x3 cube. The center voxel has 26 neighbours and Markov Random Field energy can be calculated by counting the number of neighbours of one tissue class. The idea is to remove isolated voxels of one tissue class, which are unlikely to be member of this tissue type. This procedure also closes holes in a cluster of connected voxels of one tissue type.

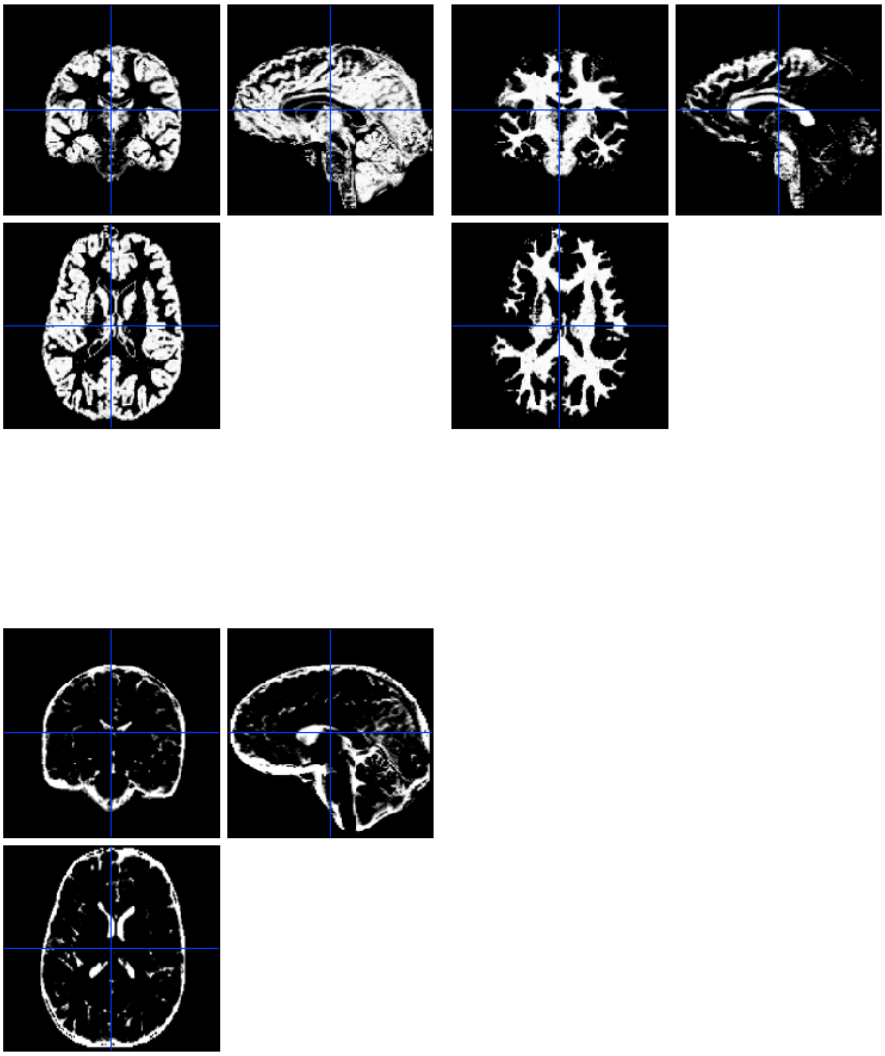

Figure 9. *Segmentation images for one subject without priors and with Hidden Markov Random Field applied. Top left: Grey matter, top roght: white mmater, bottom left: CSF.*

3.7.2. Spatial Normalization

The following step is spatial normalization, in which the individual tissue segments (in the case of the present work grey matter) are brought into a common space via registration into a standard stereotactic atlas to ensure correspondence across different brains. Since voxel based morphometry techniques started to be used different approaches have being developed, being DARTEL one of the most accurate (Klein et al., 2009).

DARTEL stands for Diffeomorphic Anatomical Registration Through Exponential Lie algebra (Ashburner, 2007). In short, the registration procedure starts by creating an initial template created by the mean of all the images. Afterwards, the images are registered to this initial template and averaged again creating a more detailed mean template than the previous one. This step of registration and template generation is repeated several times (usually 6), giving as a result highly detailed mean template.

After repeating this procedure six times and images are warped to the final template and the obtained deformation fields were applied to the GM images to register them to MNI standard space. In our case voxel size 1 × 1 × 1.

Spatial normalization changes the volume locally of the tissue segments. In fact, DARTEL registration leaves only very small differences between template and individual images (and thus across individual images). However, the original anatomical differences are coded in the deformation fields.

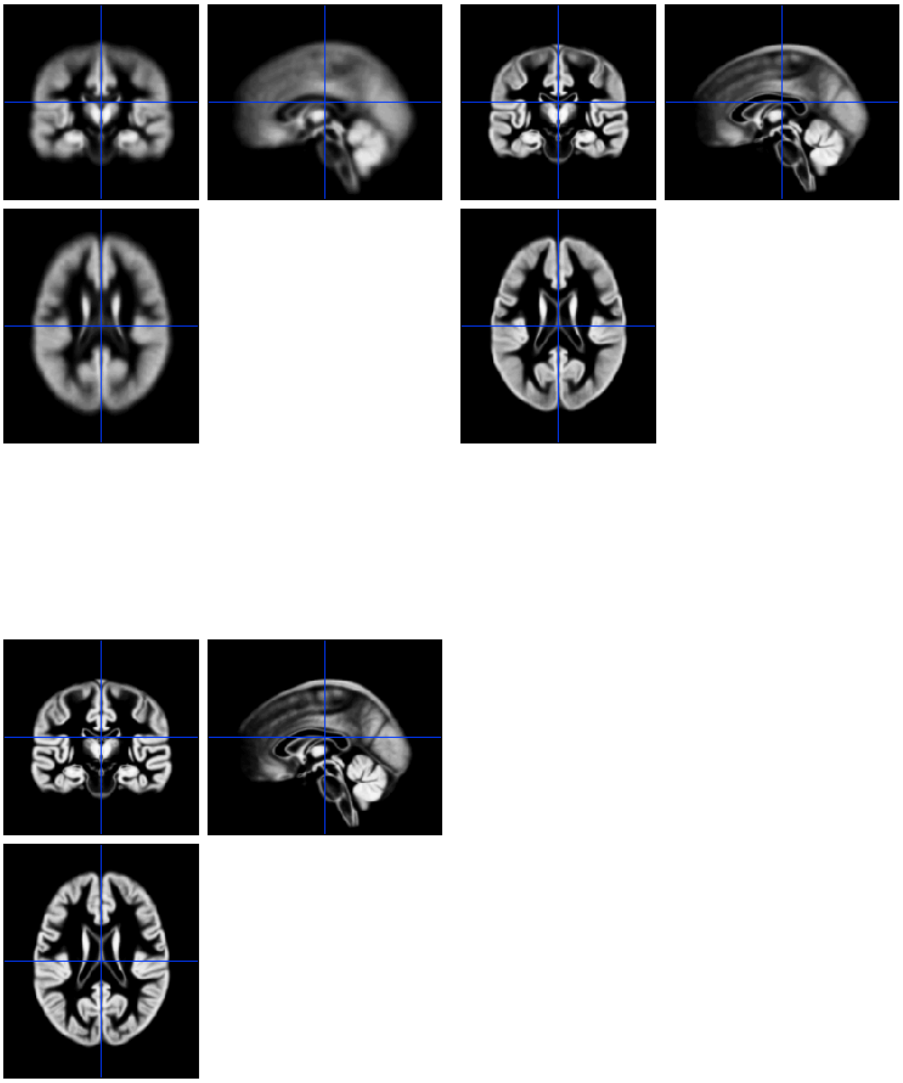

Figure 10. *Templates generated by DARTEL from 0, (top left) 3 (top right) to the final 6 (bottom).*

3.7.3. Modulation

The following step we carried out is modulation in order to assess GMV differences. Since spatial normalisation expands and contracts some brain regions modulation is used to scale by the amount of contraction, so that the total amount of grey matter in the modulated GM remains the same, as it would be in the original images. This step is recommended when we want to study differences in volume as we do in this thesis. Modulation is performed by multiplying the normalized grey matter segments with the Jacobian determinant from the deformation matrix.

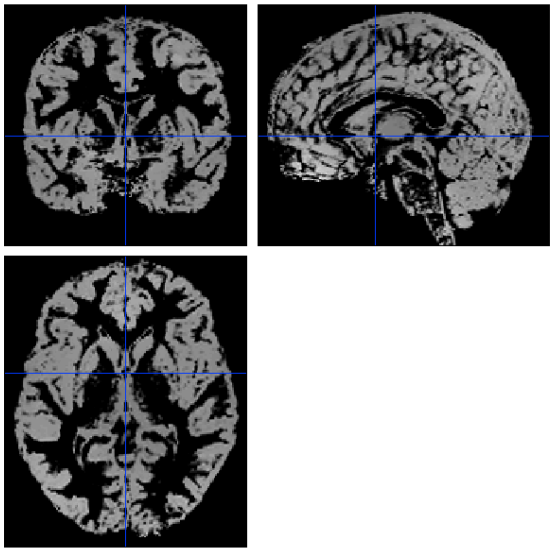

Figure 11. *Modulated image.*

3.7.4. Spatial smoothing

The last step before statistical analysis is spatial smoothing. This process involves averaging voxels in an image with neighbours, which blurs the sharp edges. This smearing effect of smoothing compensates for the registration errors, also increases the sensitivity and specifity of the statistical test. Smoothing increases the signal to noise ratio and creates a local weight average of the surrounding pixels (Gaser et al., 2001; Salmond et al., 2000). Also is critical as reenders the data more normally distributed so that they conform more closely to a Gaussian field model. This is imperative when Gaussian field theory is used to make statistical inferences about regionally specific effects (for instance assign p values) as is done in VBM. Smoothing in SPM involves three-dimensional convolution of an imaging with a Gaussian kernel which has the shape of a normal distribution curve. Full Width at Half Maximum (FWHM) is the measured that defines the width of the Gaussian curve.

In our case, as we used DARTEL and have a very good registration, smoothing was carried out with a 5 mm FWHM Gaussian kernel. Once smoothing is done pre-processing is completed.

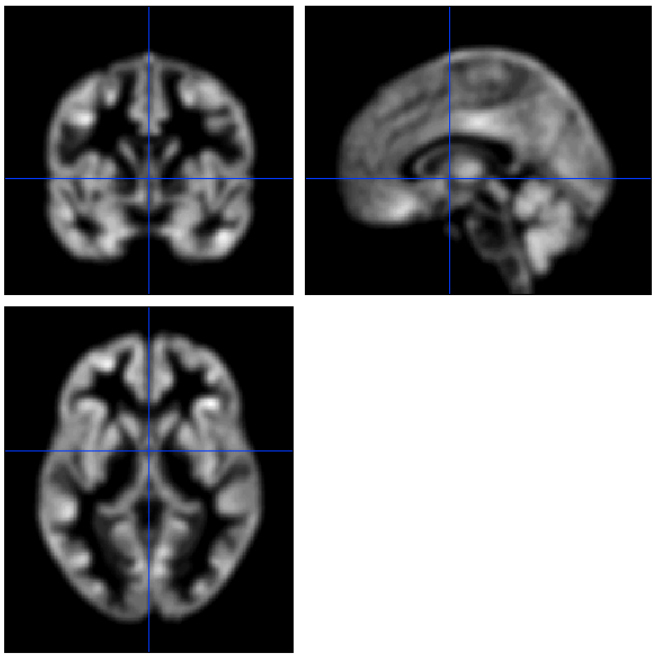

Figure 12. *Image smoothed with a 5x5x5 kernel.*

3.8. Statistical analysis

3.8.1. Statistical analysis of clinical and sociodemographic data.

Statistical analysis of clinical and sociodemographic data was carried out using the statistical software IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp.

In order to analyze differences between groups two test were used:

- T-test for continuous variables.
- Chi square for categorical variables.

3.8.2. Statistical analysis of imaging data

Imaging statistical analysis was performed within the framework of the General Linear Model (GLM) (Horton, 1978) using SPM.

A variable Y can be explained by a linear combination of basic functions

$$Y = X\beta + \varepsilon$$

Where Y represents the matrix of the measurements, X de design matrix, β the parameters we want to estimate and ε the error. We assumed that the error is identically distributed, independent and follows a Gaussian distribution of 0 mean and standard deviation determined.

GLM applied to imaging (Friston et al., 1994a) allows us to carry out statistical inferences (named contrasts in imaging).

Y (grey matter) = β_1 (Group 1) + β_2 (Group 2) + β_3 (covariates) + β_4 (total intracranial volume) + ε

All analysis in this thesis were carried out within the framework of the General Linear Model, several analysis were designed to investigate grey volume differences between healthy controls versus psychotic patients. Age at scan, gender and total intracranial volume were entered as covariates of no interest in the statistical design in order to regress out possible effects of these parameters on between-group volume differences.

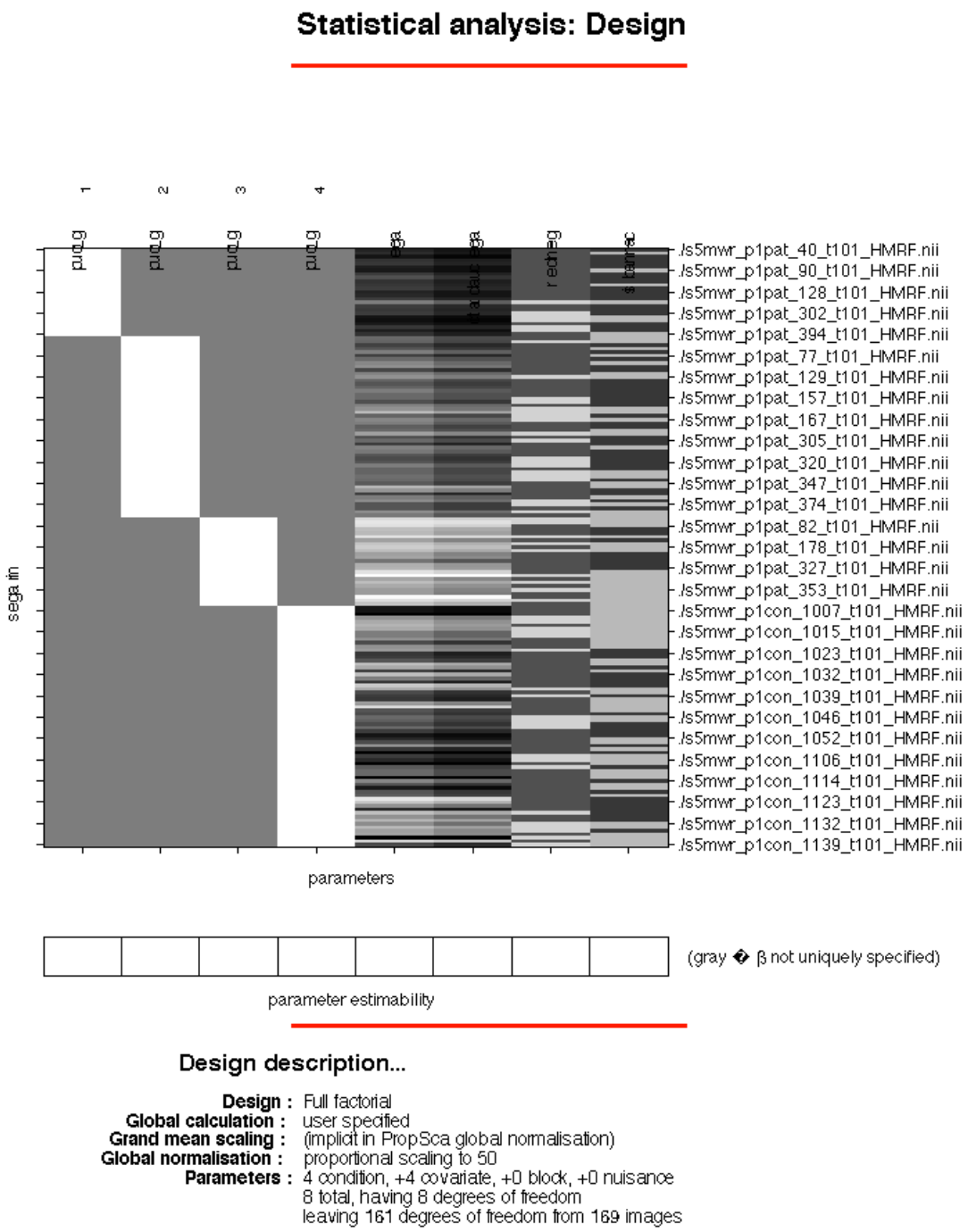

Figure 13. *Example of a full factorial design in SPM.*

In order to asses differences between groups, first a primary cluster-forming voxel-level threshold of $p<0.01$ (uncorrected) was applied. The threshold for significance was set at an uncorrected voxel-level $p < 0.001$ in combination with a cluster-level $p < 0.05$ corrected for the whole brain volume. All clusters sizes were adjusted for smoothness non-uniformity by means of the VBM5 toolbox (Hayasaka et al., 2004). Anatomical regions covered by significant clusters were identified using automated anatomical labelling (Tzourio-Mazoyer et al., 2002).

4.RESULTS

4.1. Comparison of grey matter volume between schizophrenia spectrum patients and a healthy control sample

4.1.1. Sample

From February 2001 to December 2007, 264 subjects were included in the PAFIP program. Of these, 153 accepted to participate in the MRI study. Of those, we discarded 14 non-right subjects, 20 subjects of age 40 or older and 3 subjects for bad quality data. Therefore, a final set of 101 right-handed patients with high quality MRI scans was analyzed in this study.

Sociodemographic and clinical data for first episode of non-affective psychosis patients and healthy controls subjects are described in table 1. There were no statistically significant differences in relevant socio-demographic characteristics. All subjects were Caucasians.

	First Episode of Psychosis	Healthy Volunteers	
	N=101	N=69	Statistics
Males, N(%)	67 (66.3)	48 (69.6)	χ= 0.20; p= 0.66
Age at MRI, mean (SD), years	26.93 (5.58)	26.16 (5.96)	F=0.75 ; p=0.39
Height, mean (SD), cm[1]	169.87 (9.13)	172.64 (8.08)	F= 4.10; p=0.045
Age at onset, mean (SD), years	26.38 (5.89)	-	-
Interval inclusion-mri, mean (SD) weeks	4.43 (3.59)	-	-
Low parental socieconomic status,N (%)[2]	51 (50.5)	27 (40.3)	χ=1.85 ; p=0.17
Low academic level, N (%)	51 (50.5)	25 (36.8)	χ=3.10 ; p=0.08
Alcohol users, N (%)[3]	64 (63.4)	43 (64.2)	χ=0.01 ; p=0.91
Cannabis users, N (%)[4]	56 (55.4)	27 (39.7)	χ=4.03 ; p=0.045
Tobacco users, N (%)[4]	62 (61.4)	39 (57.4)	χ=0.27 ; p=0.60
DUP, mean, (SD), months	7.71 (12.83)	-	-
DUI, mean, (SD), months	20.40 (27.34)	-	-
DDP, mean, (SD), months	12.63 (22.02)	-	-
Symptomatology (total scores)			-
Negative dimension	4.47 (4.98)	-	-
SANS	6.36 (5.1)	-	-
SAPS	13.79 (4.16)	-	-
Positive dimension	7.47 (2.33)	-	-
Disorganized dimension	6.32 (3.18)	-	-

Abbreviations: DUP, duration of untreated psychosis; DUI, duration of untreated ilness; DPP, duration of premorbid period.

[1]Based in data from 100 first episode of psychosis patients and 68 healthy volunteers.

[2]Based in data from 100 first episode of psychosis patients and 69 healthy volunteers.

[3]Based in data from 101 first episode of psychosis patients and 67 healthy volunteers.

[4]Based in data from 101 first episode of psychosis patients and 68 healthy volunteers.

Table 1 . *Sociodemographic and clinical characteristics for the whole sample.*

4.1.2. Grey matter volume differences: VBM analysis

Whole brain grey matter differences between patients with a first episode of psychosis against controls (pcFWE <0.035) are shown in Table 2. Ten clusters of grey matter volume loss in patients were identified in frontal, temporal and occipital lobes. No significant grey matter increments were observed when comparing patients against healthy controls.

Table 2. *Grey matter volume deficits in FES patients vs Healthy Controls.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 19535; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: −50,-53,-37; P_{FWE} = 0.040				
ParaHippocampal	97 (0.50; 1.24)	2.91; 2.57 (0.15)		
Lingual	527 (2.70; 3.14)	3.88; 2.73 (0.32)		
Occipital Mid	1390 (7.12; 5.31)	3.82; 2.87 (0.30)		
Occipital Inf	266 (1.36; 3.53)	3.75; 2.81 (0.37)		
Fusiform	2025 (0.22; 0.46)	4.35; 2.89 (0.43)		
Angular	43 (6.67; 3.30)	3.60; 2.69 (0.35)		
Temporal Mid	1303 (6.67; 3.30)	3.87; 2.75 (0.31)		
Temporal Inf	1539 (7.88; 6.01)	4.47; 3.13 (0.51)		
Cerebelum Crus1	7745 (39.65; 37.19)	5.11; 3.19 (0.59)		
Cerebelum Crus2	1382 (7.07; 9.12)	4.70; 3.06 (0.52)		
Cerebelum_4_5	3 (0.02; 0.03)	2.50; 2.42 (0.06)		
Cerebelum_6	1960 (10.03; 14.46)	3.92; 2.85 (0.34)		
Cerebelum_7b	414 (2.12; 8.85)	4.17; 3.07 (0.48)		
Cerebelum_8	296 (1.52; 1.96)	4.05; 2.90 (0.48)		
Cluster 2: k_c = 4515; P_{cFWE} = 0.006; Voxel maximum x,y,z [mm]: 54,-7,36; P_{FWE} = 0.077				
Precentral			1437 (31.82; 5.31)	5.10; 3.41 (0.68)
Rolandic Oper			108 (2.39; 1.01)	3.40; 2.60 (0.23)
Postcentral			2680 (59.35; 8.76)	5.11; 3.26 (0.64)
Parietal Inf			30 (0.66; 0.28)	4.53; 3.36 (0.69)
SupraMarginal			29 (0.64; 0.18)	4.92; 3.32 (0.66)
Heschl			20 (0.44; 1.00)	3.08; 2.68 (0.21)
Temporal Sup			90 (1.99; 0.36)	3.15; 2.67 (0.21)
Cluster 3: k_c = 9403; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 49,-69,-6; P_{FWE} = 0.49				
Cuneus			1 (0.01; 0.01)	2.44; 2.44 (0.00)
Occipital Sup			751 (7.99; 6.64)	4.91; 3.16 (0.54)
Occipital Mid			2765 (29.41; 16.47)	5.11; 3.21 (0.63)
Occipital Inf			40 (0.43; 0.51)	4.86; 3.18 (0.67)
Fusiform			196 (2.08; 0.97)	4.49; 3.03 (0.55)
Angular			1 (0.01; 0.01)	2.46; 2.46 (0.00)
Temporal Mid			2095 (22.28; 5.94)	5.10; 3.37 (0.70)
Temporal Inf			3116 (33.14; 10.95)	4.93; 3.23 (0.62)
Cluster 4: k_c = 3197; P_{cFWE} = 0.035; Voxel maximum x,y,z [mm]: 17,-85,7; P_{FWE} = 0.510				
Calcarine	1307 (40.88; 7.24)	5.07; 3.29 (0.65)	1146 (35.85; 7.70)	5.01; 3.28 (0.62)
Cuneus	259 (8.10; 2.12)	5.03; 3.40 (0.69)	255 (7.98; 2.24)	5.04; 3.33 (0.66)
Lingual	71 (2.22; 0.42)	4.48; 3.21 (0.68)	48 (1.50; 0.26)	3.51; 2.68 (0.29)
Occipital Sup			60 (1.88; 0.55)	4.14; 3.12 (0.50)
Occipital Mid			14 (0.44; 0.05)	3.60; 2.84 (0.32)
Precuneus			1 (0.03; 0.00)	4.22; 3.99 (0.33)

Clusters were characterized by their extend kc and significance PFWE, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels k, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported.Abbreviations: k= number of voxels, HC healthy controls, Inf Inferior, Mid Middle, Oper Opercular and Sup Superior.

4.2. Effect of age of onset of psychosis in grey matter volume

4.2.1. Sample

In order to study grey matter differences patients were stratified into age of onset groups based on percentile rules. Group 1, 25th percentile, formed by 17.08 to 21.41 years old at illness onset, called early-adult onset group (N=25); Group 2, from 25th to 75th percentiles, composed of 21.48 to 30.10 years old age of onset, called intermediate adult onset group (N=51); Group 3, 75th percentile, formed by 30.35 to 39.78 years old at illness onset, as late adult onset group (N=25). A forth group was that formed by healthy controls, age from 15.18 to 37.68 years old (N=69).

Group characteristics are shown in table 3.

	First Episode of Psychosis	<25	25-75	>75	Healthy Volunteers	
	N=101	N=25	N=51	N=25	N=69	Statistics
Males, N(%)	67 (66.3)	19 (76,0)	32 (62,7)	16 (64,0)	48 (69,6)	χ= 0.46; p= 0.93
Age at MRI, mean (SD), years	26.93 (5.58)	20,55 (2,15)	26,48 (2,80)	34,24 (3,17)	26,16 (5,96)	F=41,82 ; p=0.000 *
Height, mean (SD), cm	169.87 (9.13)	170,65 (6,00)	170,87 (9,81)	167,08 (9,91)	172,64 (8,08)	F=2,53; p=0,059
Age at onset, mean (SD), years	26.38 (5.89)	19,63 (1,27)	25,68 (2,41)	34,57 (3,50)	-	F=223,78; p=0.000 *
Interval inclusion-mri, mean (SD) weeks	4.43 (3.59)	6,31 (4,58)	3,78 (3,28)	3,86 (2,29)	-	F=4,947; p=0,009 *
Low parental socieconomic status,N (%)		8 (33,3)	31 (60,8)	12 (48,0)	27 (40,3)	
Low academic level, N (%)	51 (50.5)					χ=9.48 ; p=0.15
Alcohol users, N (%)	64 (63.4)	19 (76,0)	34 (66,7)	11 (44,0)	43 (64,2)	χ=6.03 ; p=0.11
Cannabis users, N (%)	56 (55.4)	18 (72,0)	30 (58,8)	8 (32,0)	27 (39,7)	χ=12,50 ; p=0.006 *
Tobacco users, N (%)	62 (61.4)	15 (60,0)	31 (60,8)	16 (64,0)	39 (57,4)	χ=0,37 ; p=0.95
DUP, mean, (SD), months[1]	7.71 (12.83)	9,25 (17,88)	7,44 (10,78)	6,72 (10,96)	-	F= 0,263 ; p=0.769
DUI, mean, (SD), months[1]	20.40 (27.34)	22,77 (25,16)	18,36 (24,80)	22,26 (34,29)	-	F= 0,286; p=0.752
DDP, mean, (SD), months[1]	12.63 (22.02)	13,22 (17,99)	10,93 (20,67)	15,55 (28,00)	-	F=0,376 ; p=0.688
Symptomatology (total scores)[2]						
Negative dimension	4,53 (4,99)	6,00 (5,97)	4,22 (4,77)	3,72 (4,21)	-	F= 1.529; p=0.222
SANS	6,46 (5,16)	8,24 (5,93)	6,31 (5,17)	4,96 (3,81)	-	F= 2,644; p=0.076
SAPS	13,70 (4,23)	14,72 (4,17)	13,57 (4,31)	12,96 (4,11)	-	F=1.136 ; p=0.325
Positive dimension	7,45 (2,33)	7,72 (2,59)	7,61 (2,23)	6,84 (2,27)	-	F=1.140 ; p=0.324
Disorganized dimension	6,26 (3,23)	7,00 (3,30)	5,96 (3,32)	6,12 (2,96)	-	F= 0.897; p=0.411

Abbreviations: NSNA, Non-specific non-afective;DUP, duration of untreated psychosis; DUI, duration of untreated ilness; DPP, duration of premorbid period.
[1]Based data from 51 schizophrenia, 29 schizophreniform, 20 other psychosis patients and 69 healthy volunteers.
[2]Based data from 51 schizophrenia, 29 schizophreniform, 20 other psychosis patients.

Table 3. *Sociodemographic and clinical characteritics for the diagnoitc study groups.*

4.2.2. Voxel based morphometry analysis

No GMV increases were found in any of the patient groups compared to HC, nor in the following comparisons: [early adult onset > intermediate adult onset], [early adult onset > late adult onset], [early adult onset < late adult onset], [intermediate adult onset < late adult onset]. There was no gender-by-group interaction. Following we show all positive results.

4.2.2.1. Results from the analysis GMV healthy controls greater than GMV early-adult onset group.

We found large overall grey matter reductions in FEP patients when comparing them to healthy control subjects and five clusters where identified (P_{cFWE} <0.045) Table 4.

The first cluster contained close to 20000 voxels and was located in the right hemisphere, mainly in pre- and post- central gyri, temporal pole and insula, but reaching also frontal and parietal structures.

The second cluster was located in the right parietal lobe, mainly in the left angular gyrus.

The third cluster was found bilaterally at the cingulum (mid part mostly), supplementary motor area and paracentral lobe.

The fourth cluster was located in the left hemisfere, running though temporal and occipital lobes until the cerebrellum.

The fifth and last cluster was located at the calcarine sulcus.

Table 4. *SPM results of grey matter analysis for greater GMV in healthy controls than patients with early age on onset.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 19736; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 54,-2,32; P_{FWE} = 0.058				
Postcentral			5405 (27.39; 17.67)	4.74; 2.91 (0.49)
Temporal Sup			3305 (16.75; 13.15)	4.38; 2.85 (0.38)
Precentral			2737 (13.87; 10.12)	4.57; 2.81 (0.40)
Insula			2053 (10.40; 14.50)	4.18; 2.88 (0.37)
Rolandic Oper			1344 (6.81; 12.62)	4.01; 2.79 (0.36)
Temporal Pole Sup			1095 (5.55; 10.23)	3.75; 2.78 (0.31)
Heschl			862 (4.37; 43.27)	4.13; 2.95 (0.39)
Frontal Inf Orb			470 (2.38; 3.44)	4.37; 2.74 (0.41)
SupraMarginal			415 (2.10; 2.63)	4.12; 2.69 (0.30)
Frontal Inf Oper			262 (1.33; 2.34)	3.87; 3.02 (0.40)
Temporal Mid			254 (1.29; 0.72)	3.95; 2.98 (0.41)
Frontal Inf Tri			38 (0.19; 0.22)	3.91; 2.94 (0.35)
Parietal Inf			32 (0.16; 0.30)	4.06; 3.12 (0.47)
Putamen			29 (0.15; 0.34)	3.62; 2.94 (0.35)
Cluster 2: k_c = 2989; P_{cFWE} = 0.045; Voxel maximum x,y,z [mm]: 48,-64,44; P_{FWE} = 0.433				
Angular			2277 (76.19; 16.25)	4.33; 2.75 (0.37)
Parietal Sup			297 (9.94; 1.67)	4.38; 2.94 (0.53)
Parietal Inf			290 (9.70; 2.70)	4.25; 2.75 (0.34)
Cluster 3: k_c = 5496; P_{cFWE} = 0.002; Voxel maximum x,y,z [mm]: -7,-26,46; P_{FWE} = 0.452				
Cingulum Mid	2989 (54.39; 19.25)	4.38; 2.78 (0.38)	326 (5.93; 1.85)	
Supp Motor Area	1083 (19.71; 6.31)	4.33; 2.81 (0.32)	21 (0.38; 0.11)	2.85; 2.64 (0.16)
Paracentral Lobule	401 (7.30; 3.72)	3.38; 2.74 (0.24)	194 (3.53; 2.90)	3.47; 2.78 (0.29)
Cingulum Ant	220 (4.00; 1.96)	3.24; 2.71 (0.24)		
Precuneus	21 (0.38; 0.07)	3.30; 2.80 (0.25)	73 (1.33; 0.28)	3.41; 2.83 (0.24)
Cluster 4: k_c = 13617; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -52,-57,-24; P_{FWE} = 0.475				
Occipital Mid	3078 (22.60; 11.77)	4.13; 3.07 (0.40)		
Temporal Inf	2762 (20.28; 10.79)	4.38; 2.85 (0.39)		
Temporal Mid	2761 (20.28; 6.98)	4.07; 2.74 (0.32)		
Cerebelum Crus 1	1646 (12.09; 7.90)	3.78; 2.63 (0.20)		
Fusiform	1311 (9.63; 7.09)	3.92; 2.87 (0.34)		
Occipital Inf	1230 (9.03; 16.34)	3.81; 2.88 (0.34)		
Angular	155 (1.14; 1.65)	2.98; 2.59 (0.16)		
Cerebelum Crus 2	70 (0.51; 0.46)	3.19; 2.70 (0.23)		
Cerebelum 7b	37 (0.27; 0.79)	3.10; 2.67 (0.20)		
Cluster 5: k_c = 13617; P_{cFWE} = 0.006; Voxel maximum x,y,z [mm]: 16,-84,3; P_{FWE} = 0.640				
Calcarine	1331 (30.15; 7.37)	4.26; 2.81 (0.33)	1599 (36.22; 10.74)	4.38; 2.78 (0.36)
Cingulum Post			5 (0.11; 0.19)	3.10; 2.85(0.24)

Clusters were characterized by their extend kc and significance PFWE, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels k, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: k= number of voxels, HC healthy controls, Inf Inferior, Mid Middle,Orb Orbital, Oper Opercular and Sup Superior.

4.2.2.2. Results from the analysis GMV healthy controls greater than GMV intermediate adult onset group.

When analysing the largest group of patients (n=50), with ages of onset between 21.48 and 30.10 years old, against healthy controls, we found a decrease of grey matter in patients mostly located in the cerebellum (P_{cFWE} <0.004).

Table 5. *SPM results of grey matter analysis for greater GMV in healthy controls than patients with intermediate age on onset.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 4704; P_{cFWE} = 0.004; Voxel maximum x,y,z [mm]: -51,-55,-40; P_{FWE} = 0.079				
Cerebelum Crus 1	2418 (51.40; 11.61)	4.94; 3.06 (0.61)		
Cerebelum Crus 2	1150 (24.44; 7.59)	4.61; 3.03 (0.51)		
Cerebelum 6	493 (10.48; 3.64)	3.37; 2.67 (0.23)		
Cerebelum 7b	357 (7.59; 7.63)	4.75; 3.16 (0.63)		
Cerebelum 8	190 (4.04; 1.26)	4.61; 2.98 (0.61)		
Fusiform	15 (0.32; 0.08)	2.84; 2.52 (0.14)		
Temporal Inf	3 (0.06; 0.01)	2.45; 2.40 (0.04)		

Clusters were characterized by their extend kc and significance PFWE, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels k, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: k= number of voxels, HC healthy controls, Inf Inferior.

4.2.2.3. Results from the analysis GMV healthy controls greater than GMV late adult onset group

We found seven clusters where the volume of grey matter was reduced in patients with a late age of onset with respect to healthy controls (P_{cFWE} <0.039). Table 6.

The first and largest cluster was located in the right cerebellum, occipital lobe (inferior and middle parts) and parahippocampal gyrus.

The second cluster was centered in the left occipital lobe, including the calcarine sulcus.

The third cluster extends from the left cerebellum, through the occipital lobe (fusiform and lingual gyri) to the temporal lobe.

The following two clusters were located in the right hemisphere: the fourth in the middle and superior parts of the occipital and temporal lobes, plus the cuneus and angular gyri. The fifth cluster was centered in the parietal lobe, including its inferior and superior parts and the angular gyrus.

The sixth cluster was located in the left precentral and postcentral gyri.

The seventh and final cluster was located in the fontal lobe bilaterally and also includes parts of the middle and anterior cingulum.

Table 6. *SPM results of grey matter analysis for greater GMV in healthy controls than patients with late age on onset.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 13637; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 26, -58, -13; P_{FWE} = 0.455				
Cerebelum 6			3905 (28.64; 27.19)	4.22; 2.83 (0.38)
Fusiform			3475 (25.48; 17.25)	4.19; 2.83 (0.39)
Cerebelum Crus 1	6 (0.04; 0.03)	3.68 (2.75; 0.42)	1619 (11.87; 7.64)	4.22; 2.83 (0.40)
Occipital Inf			1504 (11.03; 19.01)	4.22; 2.81 (0.37)
Lingual			957 (7.02; 5.20)	3.96; 2.74 (0.33)
Occipital Mid			668 (4.90; 3.98)	3.62; 2.85 (0.34)
Cerebelum Crus 2			258 (1.89; 1.52)	3.26; 2.63 (0.21)
Cerebelum 4 5			114 (0.84; 1.66)	3.89; 2.90 (0.42)
Cerebelum Crus 2	105 (0.77; 0.69)	3.77; 2.66 (0.28)		
ParaHippocampal			29 (0.21; 0.32)	3.72; 2.85 (0.36)
Cerebelum 7b			16 (0.12; 0.37)	2.84; 2.59 (0.18)
Calcarine			13 (0.10; 0.09)	3.35; 2.84 (0.31)
Temporal Mid			1 (0.01; 0.00)	3.10; 3.06 (0.05)
Cluster 2: k_c = 3087; P_{cFWE} = 0.039; Voxel maximum x,y,z [mm]: -21,-97,2; P_{FWE} = 0.564				
Occipital Mid	2563 (82.14; 9.69)	4.05; 2.82 (0.38)		
Calcarine	385 (12.47; 2.13)	3.28; 2.62 (0.21)		
Occipital Sup	38 (1.23; 0.35)	3.69; 2.81 (0.38)		
Occipital Inf	14 (0.45; 0.19)	2.47; 2.41 (0.05)		
Lingual	7 (0.23; 0.04)	2.93; 2.69 (0.26)		
Cluster 3: k_c = 8478; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -33,-87,-33; P_{FWE} = 0.672				
Cerebelum Crus 1	4191 (49.43; 20.13)	4.22; 2.76 (0.32)		
Cerebelum 6	1077 (12.70; 7.95)	4.20; 2.95 0.32)		
Fusiform	867 (10.23; 4.69)	4.05; 2.79 (0.37)		
Temporal Inf	858 (10.12; 3.35)	4.22; 3.14 (0.49)		
Cerebelum Crus 2	513 (6.05; 3.39)	4.20; 3.04 (0.48)		
Lingual	307 (3.62; 1.83)	3.62; 2.65 (0.25)		
Occipital Inf	243 (2.87; 3.23)	3.89; 2.82 (0.37)		
Cerebelum 7b	129 (1.52; 2.76)	3.17; 2.64 (0.19)		
Cerebelum 8	92 (1.09; 0.61)	3.26; 2.70 (0.24)		
Occipital Mid	61 (0.72; 0.23)	2.71; 2.50 (0.09)		
Temporal Mid	14 (0.17; 0.04)	2.56; 2.44 (0.06)		
Cluster 4: k_c = 3648; P_{cFWE} = 0.017; Voxel maximum x,y,z [mm]: 31,-82,35; P_{FWE} = 0.922				
Occipital Mid			2023 (55.45; 12.05)	4.05; 2.84 (0.39)
Temporal Mid			579 (15.87; 1.64)	3.72; 2.66 (0.25)
Occipital Sup			512 (14.03; 4.53)	4.20; 2.87 (0.42)
Cuneus			295 (8.09; 2.59)	4.22; 2.94 (0.47)
Angular			93 (2.55; 0.66)	3.82; 2.90 (0.49)
Parietal Sup			10 (0.27; 0.06)	3.00; 2.63 (0.24)
Cluster 5: k_c = 4987; P_{cFWE} = 0.003; Voxel maximum x,y,z [mm]: 19,-56,63; P_{FWE} = 0.988				
Parietal Sup			2940 (58.95; 16.54)	4.20; 2.87 (0.40)
Angular			1937 (38.84; 13.82)	3.88; 2.72 (0.32)
Parietal Inf			77 (1.54; 0.72)	3.77; 2.75 (0.40)
Occipital Sup			34 (0.68; 0.30)	3.40; 2.66 (0.29)
Cluster 6: k_c = 3465; P_{cFWE} = 0.022; Voxel maximum x,y,z [mm]: -30,-26,63; P_{FWE} = 0.989				
Precentral	2497 (72.07; 8.85)	4.22; 2.86 (0.41)		
Postcentral	952 (27.48; 3.06)	4.20; 2.72 (0.31)		
Paracentral Lobule	1 (0.03; 0.01)	3.01; 3.01 (0.00)		
Cluster 7: k_c = 8780; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 21,67,12; P_{FWE} = 0.998				
Frontal Sup Medial	2467 (28.10; 10.31)	4.09; 2.78 (0.33)	2387 (27.19; 13.98)	4.19; 2.82 (0.36)
Frontal Sup	187 (2.13; 0.65)	3.87; 2.83 (0.34)	1800 (20.50; 5.55)	4.22; 2.86 (0.43)
Frontal Med Orb	54 (0.62; 0.94)	3.46; 2.62 (0.25)	782 (8.91; 11.42)	3.88; 2.73 (0.31)
Frontal Sup Orb			259 (2.95; 3.25)	3.87; 2.76 (0.36)
Frontal Mid			127 (1.45; 0.31)	4.16; 2.77 (0.36)
Frontal Mid Orb			107 (1.22; 1.32)	3.15; 2.62 (0.21)
Cingulum Mid	4 (0.05; 0.03)	2.85; 2.57 (0.21)	78 (0.89; 0.44)	3.46; 2.69 (0.25)
Cingulum Ant	39 (0.44; 0.35)	3.48; 2.69 (0.26)	75 (0.85; 0.71)	3.42; 2.73 (0.25)

Abbreviations: k= number of voxels, HC healthy controls, Ant Anterior, Inf Inferior, Mid Middle, Orb Orbital and Sup Superior.

4.2.2.4. Results from the analysis GMV intermediate adult onset group greater than GMV early-adult onset group.

We found one single cluster where the volume of grey matter was reduced in patients with a late age of onset with respect patients with intermediate age of onset (P_{cFWE} <0.001). This cluster mostly occupies the fusiform gyrus, cerebellum and occipital lobe.

Table 7. *SPM results of grey matter analysis for greater GMV in patients with intermediate age on onset than patients with early age on onset.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 8694; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 25,-88,-16; P_{FWE} = 0.637				
Fusiform			2149 (24.72; 10.67)	4.17; 2.83 (0.35)
Cerebelum 6			2036 (23.42; 14.18)	3.89; 2.60 (0.23)
Occipital Inf			1800 (20.70; 22.75)	4.12; 2.84 (0.41)
Occipital Mid			906 (10.42; 5.40)	3.75; 2.86 (0.36)
Cerebelum Crus 1			664 (7.64; 3.13)	4.14; 2.76 (0.42)
Lingual			520 (5.98; 2.83)	4.25; 2.89 (0.45)
Vermis 6			361 (4.15; 12.16)	3.03; 2.59 (0.17)
Vermis 7			68 (0.78; 4.38)	2.85; 2.53 (0.14)
Calcarine			52 (0.60; 0.35)	3.16; 2.70 (0.21)
Cerebelum 4 5			22 (0.25; 0.32)	2.84; 2.56 (0.15)
Occipital Sup			6 (0.07; 0.05)	2.68; 2.52 (0.11)
Vermis 4 5			4 (0.05; 0.08)	2.70; 2.56 (0.13)

Clusters were characterized by their extend *kc* and significance *PFWE*, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation *x,y,z* [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: *k*= number of voxels, Inf Inferior, Mid Middle and Sup Superior.

4.2.2.5. Results from the analysis GMV intermediate adult onset group greater than GMV in the late adult onset group.

A single cluster where grey matter volume is reduced in early onset FEP patients versus intermediate onset FEP patients in the precental and postcentral gyrus (P_{cFWE} <0.037).

Table 8. *SPM results of grey matter analysis for greater GMV in patients with intermediate age on onset than patients with late age on onset.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 3121; P_{cFWE} = 0.037; Voxel maximum x,y,z [mm]: 49,-4,36; P_{FWE} = 0.996				
Precentral			1089 (34.89; 4.03)	3.71; 2.88 (0.37)
Postcentral			1819 (58.28; 5.95)	3.66; 2.80 (0.30)
SupraMarginal			48 (1.54; 0.30)	2.93; 2.55 (0.15)

Clusters were characterized by their extend *kc* and significance *PFWE*, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation *x,y,z* [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: *k*= number of voxels.

4.2.2.6. Gradiation analisis HC > FEP late adult onset> intermediate adult onset group > early-adult onset group

When doing a contrast analysis following the hypothesis that the decrease of grey matter volume would be linear as the age of onset is younger a total of 3 clusters were revealed (P_{cFWE} <0.049) occupying the following regions: Cluster 1 included the right precentral gyrus and the postcentral gyrus. The second cluster was localized in the left fusiform gyrus, extended to middle occipital gyrus and left cerebellum (tuber). The last cluster included the right superior temporal gyrus, claustrum and insula.

Table 9. *SPM results of grey matter analysis between groups of age of onset and healthy controls (HC> late > intermediate > early onset).*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 2922; P_{cFWE} = 0.049; Voxel maximum x,y,z [mm]: −6,18,60; P_{FWE} = 0.988				
Precentral			1083 (37.06; 4.00)	3.93; 2.81 (0.36)
Postcentral			1740 (59.54; 5.69)	3.99; 2.83 (0.38)
Cluster 2: k_c = 7104; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -49,-74,-8; P_{FWE} = 0.908				
Occipital Mid	2578 (36.29, 9.85)	3.93; 2.80 (0.35)		
Occipital Inf	1374 (19.34; 18.25)	3.99; 2.97 (0.41)		
Fusiform	449 (6.32; 2.43)	3.10; 2.59 (0.18)		
Temporal Mid	1282 (18.05; 3.24)	3.52; 2.67 (0.26)		
Temporal Inf	1123 (15.81; 4.39)	3.86; 274 (0.34)		
Cerebellum Crus	37 (0.52, 0.18)	3.00; 2.58 (0.19)		
Cluster 3: k_c = 3338; P_{cFWE} = 0.027; Voxel maximum x,y,z [mm]: 54,2,-6; P_{FWE} = 0.951				
Frontal Inf Oper			2 (0.06; 0.02)	2.85; 2.76 (0.13)
Rolandic Oper			165 (4.94; 155)	3.53; 2.73 (0.28)
Insula			997 (29.87; 7.04)	3.97; 2.83 (0.36)
Putamen			5 (0.15; 0.06)	3.61; 2.83 (0.46)
Temporal Sup			851 (25.49; 3.39)	3.97; 2.79 (0.39)
Temporal Pole Sup			486 (14.56; 4.54)	3.88; 2.92 (0.42)

Clusters were characterized by their extend *kc* and significance *PFWE*, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation *x,y,z* [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: *k*= number of voxels, HC healthy controls, *Inf* Inferior, *Mid* Middle, *Oper* Opercular and *Sup* Superior.

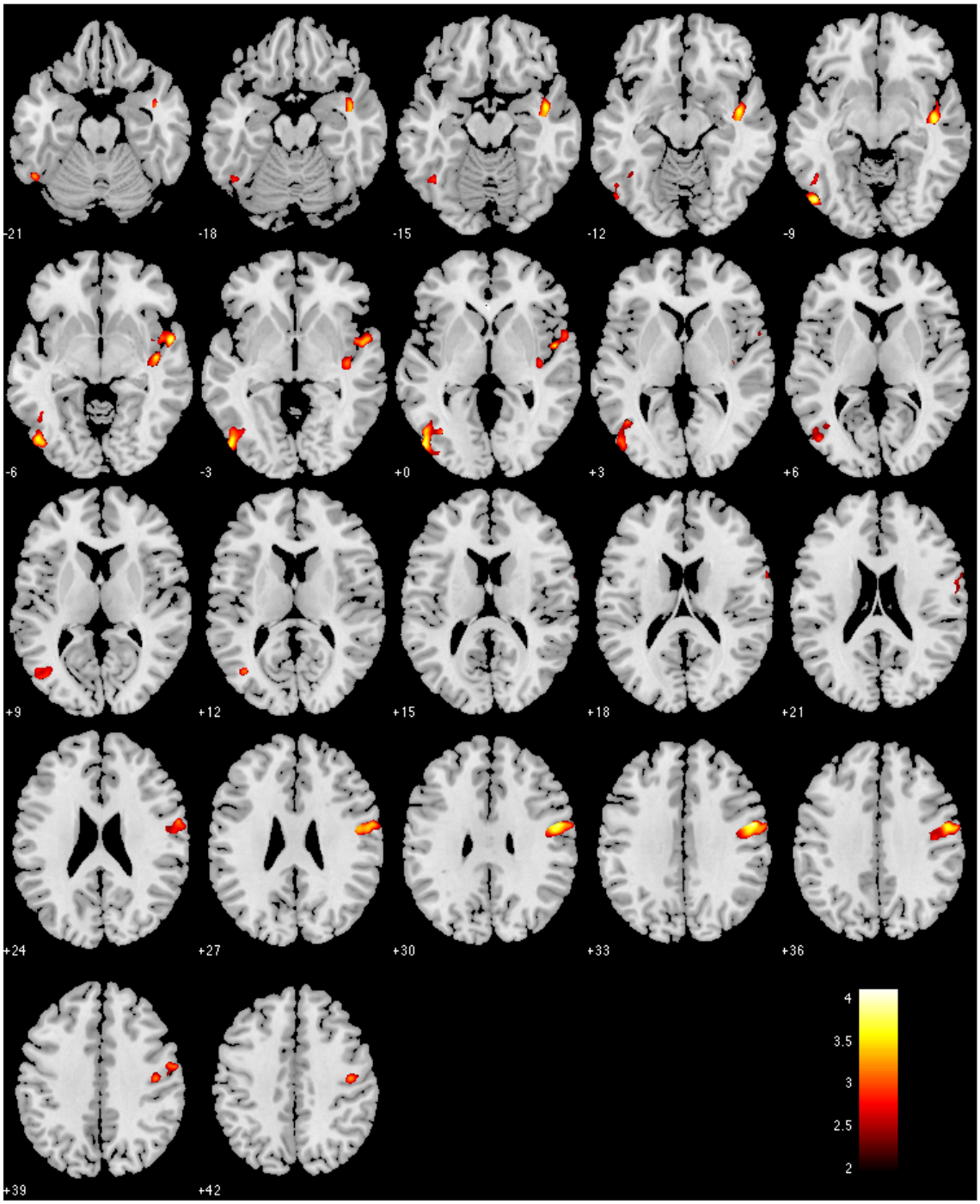

Figure 14. *Gradual reduction with age of onset following the contrast (HC>late onset> intermediate onset > early onset) at p<0.05 cluster-level corrected.*

4.3. Specific brain structural abnormalities in schizophrenia spectrum disorders

4.3.1. Sample

In order to study the effect of diagnosis, patients were split in 3 groups according to their confirmed axis I diagnoses: schizophrenia (SZ), schizophreniform disorder (SZF) and Non-Specified Non-Affective psychosis (NSNA). Six months after study enrolment, axis I diagnoses were: schizophrenia (SZ) (N = 51; 50.5%), schizophreniform disorder (SZF) (N=30; 29.7%), schizoaffective disorder (N=3; 3%), brief reactive psychosis (N = 11; 10.9%) and not otherwise specified psychosis (N = 6; 5.9%). Patients with schizoaffective disorder, brief reactive psychosis and not otherwise specified psychosis were subsumed in the group of other psychosis (NSNA) (N = 20; 19.8%). All three patient groups had similar severity levels of psychopathology (all p N 0.18) and did not differ in gender, age, academic level or age of onset. Bonferroni post-hoc analysis showed that schizophrenia patients had significantly longer DUP, DUI and DPP periods than SZF and NSNA patients. Demographic and clinical data are summarized in table 10.

Table . 10. *Sociodemographic and clinical characteritics for the diagnoitc study groups*

	First Episode of Psychosis	Schizophrenia	Schizophreniform	NSNA	Healthy Volunteers	
	N=101	N=51	N=30	N=20	N=69	Statistics
Males, N(%)	67 (66.3)	35 (68,6)	19 (63.3)	13 (65)	48 (69.6)	χ= 0.46; p= 0.93
Age at MRI, mean (SD), years	26.93 (5.58)	27.31 (5.73)	26.15 (6.46)	27.16 (3.47)	26.16 (5.96)	F=0.51 ; p=0.67
Height, mean (SD), cm	169.87 (9.13)	169.29 (8.36)	169.84 (10.58)	171.38 (9.07)	172.64 (8.08)	F= 1.63; p=0.19
Age at onset, mean (SD), years	26.38 (5.89)	26.74(6.39)	25.47 (6.3)	32.59 (3.54)	-	F=0.51 ; p=0.6
Interval inclusion-mri, mean (SD) weeks	4.43 (3.59)	4.50 (3.79)	5.42 (3.64)	2.75 (2.27)	-	F=3.53 ; p=0.03
Low parental socieconomic status,N (%)[1]	51 (50.5)	24 (48)	14 (46.7)	13 (65)	27 (40.3)	χ=3.83 ; p=0.28
Low academic level, N (%)	51 (50.5)	28 (54.9)	16 (53.3)	7 (35)	25 (36.8)	χ=5.82 ; p=0.12
Alcohol users, N (%)	64 (63.4)	34 (66.7)	17 (56.7)	13 (65)	43 (64.2)	χ=0.86 ; p=0.84
Cannabis users, N (%)	56 (55.4)	29 (56.9)	13 (43.3)	14 (70)	27 (39.7)	χ=7.53 ; p=0.06
Tobacco users, N (%)	62 (61.4)	35 (68,6)	16 (53.3)	11 (55)	39 (57.4)	χ=2.54 ; p=0.47
DUP, mean, (SD), months[2]	7.71 (12.83)	11.71 (16.17)	4.17 (6.49)	2.8 (5.05)	-	F= 5.55 ; p=0.005 ***
DUI, mean, (SD), months[2]	20.40 (27.34)	29.73 (32.08)	11.41 (16.27)	9.63 (17.77)	-	F= 6.81; p=0.002 ***
DDP, mean, (SD), months[2]	12.63 (22.02)	18.01 (27.15)	7.16 (11.82)	6.83 (14.86)	-	F=3.26 ; p=0.04
Symptomatology (total scores)[3]						
Negative dimension	4.47 (4.98)	5.22 (5.32)	4.13 (5.06)	3.4 (3.83)	-	F= 1.09; p=0.34
SANS	6.36 (5.1)	7.00 (5.51)	6.33 (5.14)	5.25 (4.22)	-	F= 0.83; p=0.44
SAPS	13.79 (4.16)	14.12 (4.46)	13.83 (4.24)	12.45 (3.52)	-	F=1.14 ; p=0.32
Positive dimension	7.47 (2.33)	7.82 (2.25)	7.3 (2.45)	6.7 (2.27)	-	F=1.78 ; p=0.18
Disorganized dimension	6.32 (3.18)	6.29 (3.42)	6.53 (3.43)	5.75 (2.40)	-	F= 0.36; p=0.70

Abbreviations: NSNA, Non-specific non-afective;DUP, duration of untreated psychosis; DUI, duration of untreated ilness; DPP, duration of premorbid period.

[1]Based data from 50 schizophrenia, 30 schizophreniform, 20 other psychosis patients and 67 healthy volunteers.

[2]Based data from 51 schizophrenia, 29 schizophreniform, 20 other psychosis patients and 69 healthy volunteers.

[3]Based data from 51 schizophrenia, 29 schizophreniform, 20 other psychosis patients.

4.3.2. VBM analysis

In the VBM analysis of healthy controls (HC) versus each of the diagnoses groups no significant grey matter increments were observed in any of the clinical groups compared to HC. Furthermore, no differences were found when comparing diagnoses groups pair-wise.

4.3.2.1. Analysis of GMV in healthy controls versus schizophrenia patients.

SZ patients showed a decrease in grey matter volume in seven clusters in both hemispheres (pcFWE <0.034).

Two clusters were located in the right hemisphere; the first one had a local maximum in the temporal lobe, in the fusiform gyrus (45,-65,-7) and extended to the inferior frontal gyrus. The second cluster in the right cerebrum was localized in the inferior frontal gyrus (35,24,8) and included also two local maxima more than 8.0 mm apart in the putamen and claustrum.

Five clusters were located in the left hemisphere. The first one started on the temporal lobe, fusiform gyrus and included also the cerebellar tonsil and culmen.

The following two clusters are located in the frontal lobe, the first one was located in the superior frontal gyrus and extended to the medial frontal gyrus and superior frontal gyrus and the second one was located in the superior frontal gyrus and extended to the inferior frontal gyrus. The sixth cluster was located in the left insula where it had two local maxima more than 8.0 mm apart and extended to the inferior frontal gyrus. The seventh cluster included the middle occipital gyrus and the middle temporal gyrus, (Table 11).

Table 11. SPM results of grey matter analysis between first episode of schizophrenia patients and healthy controls (HC>SZ).

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 6065; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 50,-68,-7; P_{FWE} = 0.479				
Temporal Inf			3450 (56.89; 12.12)	4.08; 2.89 (0.38)
Temporal Mid			2019 (33.29; 5.72)	3.71; 2.71 (0.29)
Occipital Inf			191 (3.15; 2.41)	4.02; 2.90 (0.42)
Occipital Mid			60 (0.99; 0.36)	2.86; 2.56 (0.15)
Fusiform			23 (0.38; 0.11)	3.29; 2.68 (0.28)
Cluster 2: k_c = 3174 ; P_{cFWE} = 0.034; Voxel maximum x,y,z [mm]: 39,28,1; P_{FWE} = 0.768				
Insula			1671 (52.64;11.80)	4.08; 2.91 (0.40)
Frontal Inf Tri			355 (11.18; 2.06)	4.08; 2.90 (0.36)
Putamen			228 (7.18; 2.68)	4.06; 3.01 (0.45)
Frontal Inf Orb			156 (4.91; 1.14)	3.85; 2.83 (0.36)
Frontal Inf Oper			13 (0.41; 0.12)	3.09; 2.82 (0.21)
Cluster 3: k_c = 6505 ; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -43,-60,-15; P_{FWE} = 0.806				
Cerebelum Crus1	3383 (52.01; 16.25)	4.08; 2.80 (0.36)		
Temporal Inf	1039 (15.97; 4.06)	4.02; 3.10 (0.42)		
Fusiform	871 (13.39; 4.71)	4.10; 2.93 (0.42)		
Cerebelum Crus2	480 (7.38; 3.17)	3.68; 2.77 (0.30)		
Lingual	204 (3.14; 1.22)	3.36; 2.72 (0.25)		
Cerebelum 6	174 (2.67; 1.28)	3.43; 2.70 (0.26)		
Cerebelum 7b	75 (1.15; 1.60)	2.78; 2.56 (0.12)		
Occipital Inf	73 (1.12; 0.97)	3.90; 2.93 (0.41)		
Cerebelum 8	40 (0.61; 0.26)	2.78; 2.51 (0.10)		
Cluster 4: k_c = 12868 ; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -12,43,49; P_{FWE} = 0.853				
Frontal Sup Medial	4338 (33.71; 18.12)	4.10; 2.81 (0.37)	2994 (23.27; 17.54)	4.28; 2.86 (0.39)
Supp Motor Area	1192 (9.26; 6.94)	4.29; 2.98 (0.43)	1374 (10.68; 7.24)	4.32; 3.10 (0.45)
Frontal Sup	1880 (14.61; 6.53)	4.08; 2.81 (0.38)	20 (0.16; 0.06)	3.60; 2.74 (0.34)
Cingulum Ant	58 (0.45; 0.52)	3.43; 2.66 (0.25)	610 (4.74; 5.81)	4.03; 2.89 (0.38)
Cingulum Mid	16 (0.12; 0.10)	3.03; 2.77 (0.20)	250 (1.94; 1.42)	3.43; 2.75 (0.28)
Frontal Mid	9 (0.07; 0.02)	3.91; 3.13 (0.53)		
Cluster 5: k_c = 4560 ; P_{cFWE} = 0.005; Voxel maximum x,y,z [mm]: -32,51,14; P_{FWE} = 0.926				
Frontal Mid	3347 (71.98; 8.60)	4.08; 2.90 (0.38)		
Frontal Mid Orb	591 (12.71; 8.32)	3.75; 2.79 (0.37)		
Frontal Inf Tri	404 (8.69; 2.00)	4.02; 2.91 (0.39)		
Frontal Sup	229 (4.92; 0.80)	4.08; 3.05 (0.48)		
Frontal Inf Orb	25 (0.54; 0.18)	3.15; 2.60 (0.25)		
Frontal Sup Orb	17 (0.37; 0.22)	3.57; 2.72 (0.35)		
Cluster 6: k_c = 4775 ; P_{cFWE} = 0.004; Voxel maximum x,y,z [mm]: -42,3,1; P_{FWE} = 0.972				
Insula	3040 (63.66; 20.45)	4.08; 2.91 (0.39)		
Temporal Sup	541 (11.33; 2.95)	3.93; 2.86 (0.37)		
Frontal Inf Tri	357 (7.48; 1.76)	3.71; 2.85 (0.33)		
Frontal Inf Oper	292 (6.12; 3.52)	3.86; 3.00 (0.35)		
Temporal Pole Sup	141 (2.95; 1.37)	3.45; 2.79 (0.33)		
Frontal Inf Orb	96 (2.01; 0.71)	4.02; 2.90 (0.49)		
Rolandic Oper	12 (0.25; 0.15)	3.41; 2.90 (0.30)		
Temporal Mid	11 (0.23; 0.03)	2.76; 2.53 (0.12)		
Cluster 7: k_c = 6065 ; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -44, -73, 7; P_{FWE} = 0.999				
Occipital Mid	1713 (53.78; 6.55)	4.08; 2.83 (0.40)		
Temporal Mid	1326 (41.63; 3.35)	4.08; 2.96 (0.40)		

Abbreviations: k= number of voxels, HC healthy controls,SZ schizophrenia, Ant Anterior, Inf Inferior, Mid Middle, Orb Orbital, Oper Opercular, Tri Triangular and Sup Superior.

4.3.2.2. Analysis of GMV in healthy controls versus schizophreniform patients.

Patients diagnosed with schizophreniform disorder revealed a decrease in GM in the left cerebellum (cerebellar tonsil and culmen) as shown in the table 12 (K_c= 5716,P_{cFWE} <0.001).

Table 12. *SPM results of grey matter analysis between schizophreniform patients and healthy controls (HC>SZF).*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 5716 ; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -49,-57,-33; P_{FWE} = 0.460				
Cerebelum Crus1	2907 (50.86; 13.96)	4.40; 2.94 (0.50)		
Cerebelum 6	1623 (28.39; 11.98)	3.82; 2.76 (0.31)		
Cerebelum Crus2	752 (13.16; 4.96)	3.82; 2.75 (0.32)		
Cerebelum 7b	139 (2.43; 2.97)	3.66; 2.76 (0.31)		
Fusiform	99 (1.73; 0.54)	3.56; 2.67 (0.24)		
Cerebelum 4 5	72 (1.26; 0.80)	2.66; 2.44 (0.06)		
Cerebelum 8	62 (1.08; 0.41)	3.46; 2.86 (0.32)		
Lingual	24 (0.42; 0.14)	3.01; 2.58 (0.18)		
Temporal Inf	16 (0.28; 0.06)	3.26; 2.71 (0.26)		

Clusters were characterized by their extend *kc* and significance *PFWE*, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation *x,y,z* [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: *k*= number of voxels, HC healthy controls, SZF schizophreniform, *Inf* Inferior.

4.3.2.3. Analysis of GMV in healthy controls versus non-schizophrenia non-affective psychosis patients.

This contrast identified six clusters of grey matter reductions in patients when compared to healthy controls (P_{cFWE} <0.033). Subjects with non-schizophrenia non-affective psychosis had a grey matter volume reduction bilaterally in the cerebellum (culmen and cerebellar tonsil) and right cuneus. One cluster was localized in the left middle occipital gyrus and left cuneus. Another cluster included the left middle occipital gyrus and the middle temporal gyrus. The fifth cluster was centered in the left temporal lobe and extends to the superior temporal gyrus and the insula. The last cluster was in the parietal lobe with maxima in superior and inferior lobules.

Table 13. *SPM results of grey matter analysis between non-specific non-affective psychosis patients and healthy controls (HC>NSNA).*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 8124; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: -42,-51,-26; P_{FWE} = 0.212				
Cerebelum Crus 1	2440 (30.04; 11.72)	4.27; 2.86 (0.34)		
Fusiform	1678 (20.66; 9.08)	4.66; 2.79 (0.37)		
Cerebelum 8	535 (6.59; 3.54)	3.68; 2.87 (0.30)		
Temporal Inf	456 (5.61; 1.78)	3.91; 2.73 (0.26)		
Cerebelum Crus 2	444 (5.47; 2.93)	3.41; 2.77 (0.28)		
Cerebelum 7b	352 (4.33; 7.52)	3.61; 2.91 (0.31)		
Cerebelum 4 5	246 (3.03; 2.73)	3.09; 2.62 (0.17)		
ParaHippocampal	79 (0.97; 1.01)	2.68; 2.47 (0.09)		
Hippocampus	71 (0.87; 0.95)	2.84; 2.49 (0.12)		
Lingual	22 (0.27; 0.13)	2.69; 2.49 (0.10)		
Thalamus	1 (0.01; 0.01)	2.37; 2.37 (0.00)		
Occipital Inf	1 (0.01; 0.01)	2.37; 2.37 (0.00)		
Cluster 2: k_c = 18277; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 11,-56,-5; P_{FWE} = 0.284				
Calcarine	1814 (9.93; 10.04)	4.55; 2.86 (0.40)	3144 (17.20; 21.12)	4.66; 2.81 (0.3)
Lingual	422 (2.31; 2.52)	3.74; 2.89 (0.31)	2915 (15.95; 15.84)	4.31; 2.87 (0.35)
Occipital Mid	343 (1.88; 1.31)	4.39; 2.97 (0.41)	2689 (14.71; 16.02)	4.35; 2.69 (0.27)
Fusiform	2 (0.01; 0.01)	2.59; 2.55 (0.06)	1537 (8.41; 7.63)	3.67; 2.81 (0.29)
Occipital Sup	145 (0.79; 1.33)	4.48; 3.00 (0.50)	1188 (6.50; 10.51)	3.79; 2.66 (0.23)
Cuneus	1074 (5.88; 8.80)	3.79; 2.68 (0.24)	1131 (6.19; 9.93)	4.16; 2.70 (0.28)
Cerebelum 4 5			424 (2.32; 6.16)	3.64; 2.77 (0.27)
ParaHippocampal			407 (2.23; 4.49)	3.50; 2.76 (0.28)
Precuneus	291 (1.59; 1.03)	3.70; 2.64 (0.25)	148 (0.81; 0.57)	4.23; 2.72 (0.36)
Vermis	176 (0.96; 3.31)	4.25; 2.97 (0.40)		
Occipital Inf	91 (0.50; 1.21)	3.07; 2.63 (0.20)		
Cerebelum 6	73 (0.40; 0.54)	3.59; 2.90 (0.34)	32 (0.18; 0.22)	3.27; 2.85 (0.30)
Cerebelum Crus 1	42 (0.23; 0.20)	3.68; 3.09 (0.36)		
Angular			6 (0.03; 0.04)	2.97; 2.67 (0.23)
Cluster 3: k_c = 5016; P_{cFWE} = 0.003; Voxel maximum x,y,z [mm]: -25,-96,14; P_{FWE} = 0.639				
Occipital Mid	3837 (76,50; 14.67)	3.68; 2.81 (0.30)		
Occipital Sup	904 (18.02; 8.27)	3.56; 2.66 (0.22)		
Cuneus	174 (3.47; 1.43)	3.13; 2.61 (0.19)		
Cluster 4: k_c = 3195; P_{cFWE} = 0.033; Voxel maximum x,y,z [mm]: -52,-78,4; P_{FWE} = 0.926				
Temporal Mid	1294 (40.50; 3.27)	3.68; 2.87 (0.34)		
Occipital Mid	1194 (37.37; 4.56)	3.56; 2.88 (0.27)		
Occipital Inf	468 (14.65; 6.22)	3.27; 2.81 (0.01)		
Cluster 5: k_c = 4512; P_{cFWE} = 0.006; Voxel maximum x,y,z [mm]: -43,-9,-7; P_{FWE} = 0.988				
Temporal Pole Sup	1880 (41.67; 18.29)	3.68; 2.86 (0.30)		
Temporal Sup	1233 (27.33; 6.71)	3.39; 2.68 (0.23)		
Rolandic Oper	344 (7.62; 4.34)	3.37; 2.85 (0.26)		
Insula	242 (5.36; 1.63)	3.38; 2.64 (0.25)		
Heschl	156 (3.46; 8.67)	3.40; 2.73 (0.24)		
Temporal Mid	28 (0.62; 0.07)	3.28; 2.87 (0.28)		
Temporal Pole Mid	27 (0.60; 0.45)	3.21; 2.73 (0.23)		
Cluster 6: k_c = 3532; P_{cFWE} = 0.021; Voxel maximum x,y,z [mm]: -19,-67,52; P_{FWE} = 1.000				
Parietal Sup	1931 (54.67; 11.69)	3.68; 2.90 (0.32)		
Angular	1213 (34.34; 12.93)	3.68; 2.82 (0.27)		
Parietal Inf	241 (6.82; 1.23)	3.51; 2.86 (0.26)		
Precuneus	119 (3.37; 0.42)	3.46; 3.02 (0.29)		

Clusters were characterized by their extend *kc* and significance *PFWE*, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation *x,y,z* [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: *k*= number of voxels, HC healthy controls, NSNA other psychosis, *Inf* Inferior, *Mid* Middle, *Oper* Opercular and *Sup* Superior.

6.2.4. Diagnosis analysis: Gradual reduction of GMV Healthy Control > No-Specific Non-Affective Psychosis > Schizophreniform > Schizophrenia

A gradual reduction of grey matter depending on diagnose was tested with the following contrast: HC>NSNA>SZF>SZ. This contrast showed a gradual decrease in GM in 4 clusters (pcFWE <0.031). Cluster 1 showed three local maxima in the left frontal lobe, 2 in the inferior frontal gyrus and one in the middle frontal gyrus. The second cluster had two local maxima in the right fusiform gyrus and one local maximum in the middle occipital gyrus. Cluster number 3 was located in the right parietal lobe: postcentral gyrus, right frontal lobe, precentral gyrus and right superior temporal gyrus. The last cluster included the left superior frontal gyrus and the right superior frontal gyrus as well as the right medial frontal gyrus. These results are shown in table 14 and figure 15.

Table 14. *SPM results of grey matter analysis between schizophrenia spectrum groups and healthy controls HC>NSNA>SZF>SZ.*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = *3945;* P_{cFWE} = *0.012;* *Voxel maximum x,y,z [mm]: −41,54,2;* P_{FWE} = *0.748*				
Frontal Mid	2868 (72.70; 7.37)	4.07; 2,79 (0.34)		
Frontal Mid Orb	466 (11.81; 5.56)	4.09; 2.98 (0.43)		
Frontal Inf Tri	465 (11.79; 2.30)	3.82; 2.79 (0.35)		
Frontal Inf Orb	89 (2.26; 0.66)	3.16; 2.65 (0.21)		
Frontal Sup	1 (0.03; 0.00)	2.63; 2.63 (0.00)		
Cluster 2: k_c = *3254;* P_{cFWE} = *0.031;* *Voxel maximum x,y,z [mm]: 49,-54,-16;* P_{FWE} = *0.820*				
Occipital Mid			19 (0.58; 0.11)	3.22; 2.68 (0.27)
Occipital Inf			3 (0.09; 0.04)	2.73; 2.51 (0.20)
Fusiform			49 (1.51; 0.24)	3.24; 2.68 (0.24)
Temporal Mid			549 (16.87; 1.56)	3.38; 2.62 (0.20)
Temporal Inf			2416 (74.25; 8.49)	4.09; 2.86 (0.37)
Cluster 3: k_c = *3752;* P_{cFWE} = *0.015;* *Voxel maximum x,y,z [mm]: 62,-8,16;* P_{FWE} = *0.962*				
Precentral			982 (26.17; 6.63)	4.16; 2.92 (0.43)
Rolandic Oper			411 (10.95; 3.86)	3.69; 2.78 (0.33)
Postcentral			1649 (43.94; 5.39)	3.73; 2.76 (0.31)
SupraMarginal			13 (0.35; 0.08)	2.74; 2.53 (0.08)
Heschl			18 (0.48; 0.90)	3.32; 2.81 (0.30)
Temporal Sup			672 (17.91; 2.67)	4.09; 3.01 (0.42)
Cluster 4: k_c = *3983;* P_{cFWE} = *0.011;* *Voxel maximum x,y,z [mm]: -6,18,60;* P_{FWE} = *0.988*				
Frontal Sup	5 (0.13; 0.02)	3.89; 3.09 (0.59)	9 (0.23, 0.03)	3.73; 3.07 (0.49)
Supp Motor Area	616 (15.46; 3.59)	4.16; 2.97 (0.45)	782 (19.63, 4.12)	3.72; 2.75 (0.33)
Frontal Sup Medial	642 (6.12; 2.68)	4.00; 2.86 (0.38)	1469 (6.88; 8.60)	4.03; 2.81 (0.34)
Cingulum Ant			293 (7.36; 2.79)	4.09; 3.00 (0.43)
Cingulum Mid	2 (0.05; 0.01)	3.20; 2.83 (0.53)	144 (3.61; 0.82)	3.68; 2.84 (0.36)

Clusters were characterized by their extend kc and significance PFWE, corrected for cluster extend and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected PFWE value of the maximum voxel. For anatomical regions within clusters, the number of voxels k, the percentage of the cluster covered by the region %clust, the percentage of the region covered by the cluster %reg and height threshold T Max,mean (SD) were reported. Abbreviations: k= number of voxels, HC healthy controls,, SZ schizophrenia, SZF schizophreniform, NSNA other psychosis, Ant Anterior, Inf Inferior, Mid Middle, Orb Orbital, Oper Opercular, Tri Triangular, Sup Superior and Supp Supplementary.

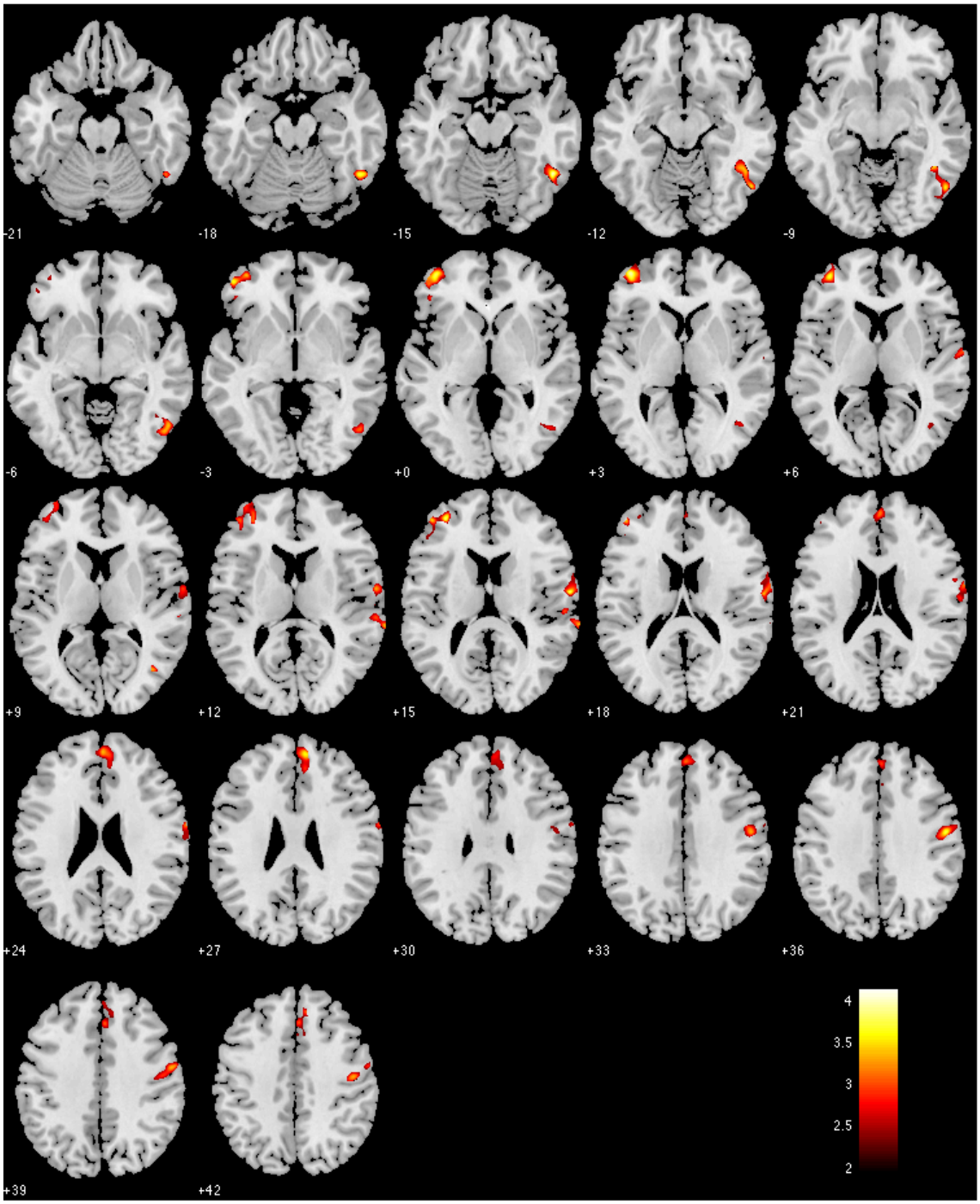

Figure 15. *Areas of reduced GMV by diagnosis (HC>NSNA> SZF > SZ) at p<0.05 cluster-level corrected.*

4.4. Effect of lack of insight in grey matter volume in first episode of non-affective psychosis patients.

4.4.1. Sample

In this analysis the sample is smaller (157 instead of 170) because there was no insight information for the whole initial sample. Patients were grouped by the insight of mental illness assessment. Finally there was a group of 34 patients with good insight, a second group of 54 patients classified as having poor insight and 69 healthy controls.

Demographics and clinical characteristics are shown in table 15:

Table 15. Socio-demographic and clinical characteristics of the study groups.

	IMI=good N=34	IMI=poor N=54	Healthy Volunteers N=69	Statistics	
Males, N(%)	24 (70,6)	35 (64,8)	48 (69,6)	χ^2=0,434	0,805
Age at MRI, mean (SD), years	27,5 (6,0)	26,5 (5,6)	26,2 (6,0)	F=0,582	0,560
Height, mean (SD), cm[1]	170,5 (9,6)	169,3 (8,6)	172,6 (8,1)	F=2,348	0,099
Age at onset, mean (SD), years	27,0 (6,2)	25,4 (5,3)		F=1,531	0,219
Intervalo inicio-mri, mean (SD) weeks	4,3 (3,3)	4,8 (4,0)		F=0,370	0,544
Low parental socioconomic status,N (%)[2]	19 (55,9)	22 (41,5)	40 (59,7)	χ^2=4,117	0,128
Education, mean (SD), years	10,7 (3,2)	9,6 (2,9)	10,6 (2,6)	F=2,349	0,099
Alcohol users, N (%)[3]	22 (64,7)	36 (66,7)	43 (64,2)	χ^2=0,085	0,958
Cannabis users, N (%)[4]	18 (52,9)	35 (64,8)	39 (57,4)	χ^2=1,347	0,510
Tobacco users, N (%)[4]	19 (55,9)	31 (57,4)	27 (39,7)	χ^2=4,513	0,105
DUP, mean, (SD), months	5,1 (8,2)	9,8 (15,8)		F=2,548	0,114
DUI, mean, (SD), months	14,6 (18,3)	25,7 (33,3)		F=3,152	0,079
DDP, mean, (SD), months	9,6 (14,5)	15,8 (27,2)		F=1,508	0,223
Symptomatology (total scores)					
Negative dimension	4,7 (5,0)	4,4 (4,9)		F=0,079	0,779
SANS	6,9 (4,7)	6,0 (5,3)		F=0,535	0,466
SAPS	13,6 (4,4)	13,9 (4,3)		F=0,108	0,743
Positive dimension	7,5 (2,4)	7,3 (2,3)		F=0,072	0,789
Disorganized dimension	6,1 (3,4)	6,5 (3,1)		F=0,402	0,528

Abbreviations: DUP, duration of untreated psychosis; DUI, duration of untreated ilness; DPP, duration of premorbid period.

[1]Based in data from 87 first episode of psychosis patients and 68 healthy volunteers.

[2]Based in data from 87 first episode of psychosis patients and 67 healthy volunteers.

[3]Based in data from 88 first episode of psychosis patients and 67 healthy volunteers.

[4]Based in data from 88 first episode of psychosis patients and 68 healthy volunteers.

4.4.2. VBM analysis

In the VBM analysis of healthy controls (HC) versus each group of FEP patients differentiated by illness insight no significant grey matter increments were observed in any of the clinical groups compared to HC.

4.4.2.1 Analysis of GMV in healthy controls versus patients with poor insight

This contrast identified two clusters of grey matter reductions in patients (P_{cFWE} <0.001).

The first cluster occupies from the superior medial frontal gyrus to the supplementary motor area and anterior and middle part of the cingullum. Table 16 and figure 16.

Table 16. *SPM results of grey matter analysis between patients with poor illness insight and healthy controls (HC > poor insight).*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 10590; P_{cFWE} < 0.001; Voxel maximum x,y,z [mm]: 8,36,42; P_{FWE} = 0.174				
Superior Medial frontal gyrus	2423 (22.88; 10.12)	4.68; 2.88 (0.48)	4175(39.43;24.46)	4.73; 2.88 (0.47)
Supplementary motor area	904 (8.54;5.26)	4.72; 3.00(0.48)	1214 (11.46; 6.40)	4.47; 2.97 (0.42)
Cingulum, anterior part	108 (1.02; 0.96)	4.46; 2.71 (0.38)	862 (8.14; 8.219	4.56; 2.85 (0.48)
Cingullum, middle part	32 (0.30; 0.21)	3.26; 2.69(0.24)	746 (7.04; 4.23)	4.22; 2.85 (0.45)
Superior frontal gyrus	29 (0.27; 0.10)	4.63; 3.06 (0.55)	7 (0.07; 0.02)	3.48; 3.23 (0.22)
Cluster 2: k_c = 4604; P_{cFWE} < 0.006; Voxel maximum x,y,z [mm]: -10,-92,-3; P_{FWE} = 0.269				
Calcarine fissure	1993 (43.29; 11.03)	4.59; 2.79 (0.45)	1752 (38.05; 11.77)	4.56; 2.87 (0.48)
Cuneus	193 (4.19; 1.58)	2.66; 2.47 (0.07)	131 (2.85; 1.15)	2.71; 2.48 (0.09)
Lingual gyrus	81 (1.76; 0.48)	3.80; 2.58 (0.32)	182 (3.95; 0.99)	2.84; 2.50 (0.10)
Superior occipital gyrus	52 (1.13;0.48)	3.23; 2.68 (0.25)		
Middle occipital gyrus	75 (1.63; 0.29)	3.85; 2.79 (0.39)		
Inferior occipital gyrus	31 (0.67; 0.41)	2.63; 2.45 (0.08)		

Clusters were characterized by their extent *Kc* and significance *PcFWE*, corrected for cluster extent and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected *PFWE* value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered %clust, the percentage of the region covered by the cluster %reg.

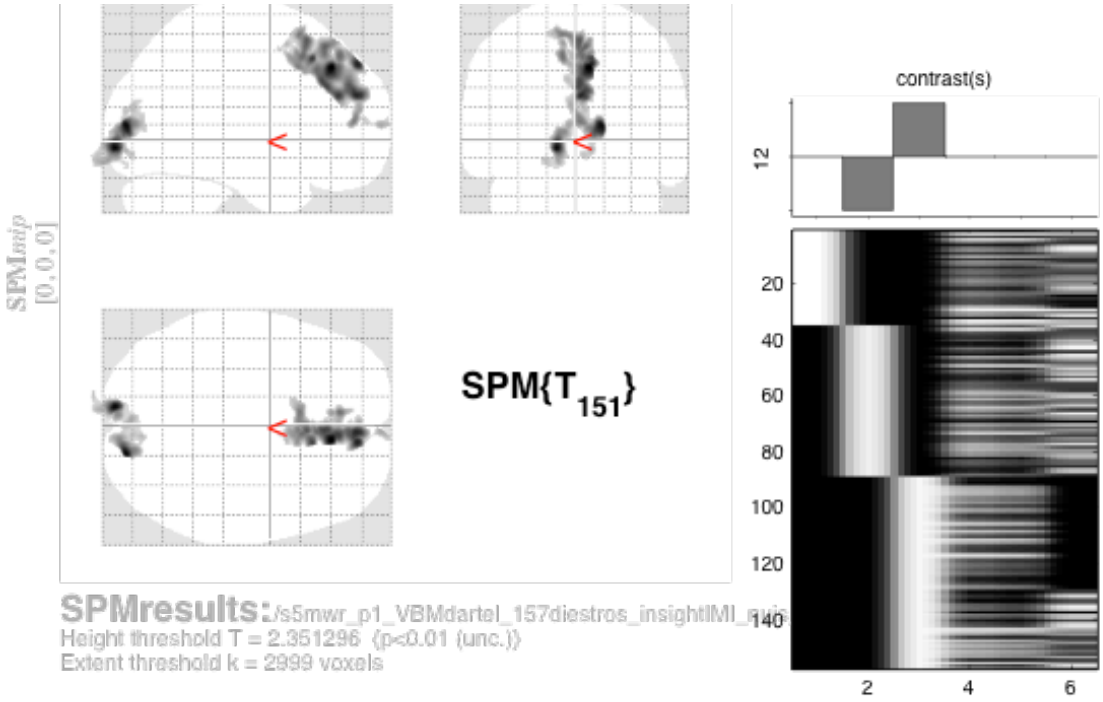

Figure 16. *SPM results for the contrast HC>Poor Insight FEP patients.*

4.4.2.2 Analysis of GMV in patients with good insight versus patients with poor insight

In the comparison of patients with good insight versus patients with poor insight, the last group showed a reduction of grey matter volume in the occipital and temporal lobes (P_{cFWE} <0.001). Table 17 below and figure 17.

Table 17. *SPM results of grey matter analysis between patients with good illness insight and poor insight (good insight > poor insight).*

Anatomical region	Left		Right	
	Extent	T	Extent	T
	K(%clust;%reg)	Max; mean (SD)	K(%clust;%reg)	Max; mean (SD)
Cluster 1: k_c = 5834; P_{cFWE} = 0.001; Voxel maximum x,y,z [mm]: 16,-95,26; P_{FWE} = 0.306				
Middle occipital gyrus			2945 (50.48; 17.55)	3.90; 2.87 (0.37)
Superior occipital gyrus			1661 (28.47; 14.69)	4.52; 3.19 (0.51)
Cuneus			466 (7.99; 4.09)	4.05; 2.79 (0.37)
Middle temporal gyrus			420 (7.20; 1.19)	3.24; 2.61 (0.18)

Clusters were characterized by their extent *Kc* and significance *PcFWE*, corrected for cluster extent and smoothness non-stationarity, as well as by the localisation x,y,z [mm] and corrected *PFWE* value of the maximum voxel. For anatomical regions within clusters, the number of voxels *k*, the percentage of the cluster covered %clust, the percentage of the region covered by the cluster %reg

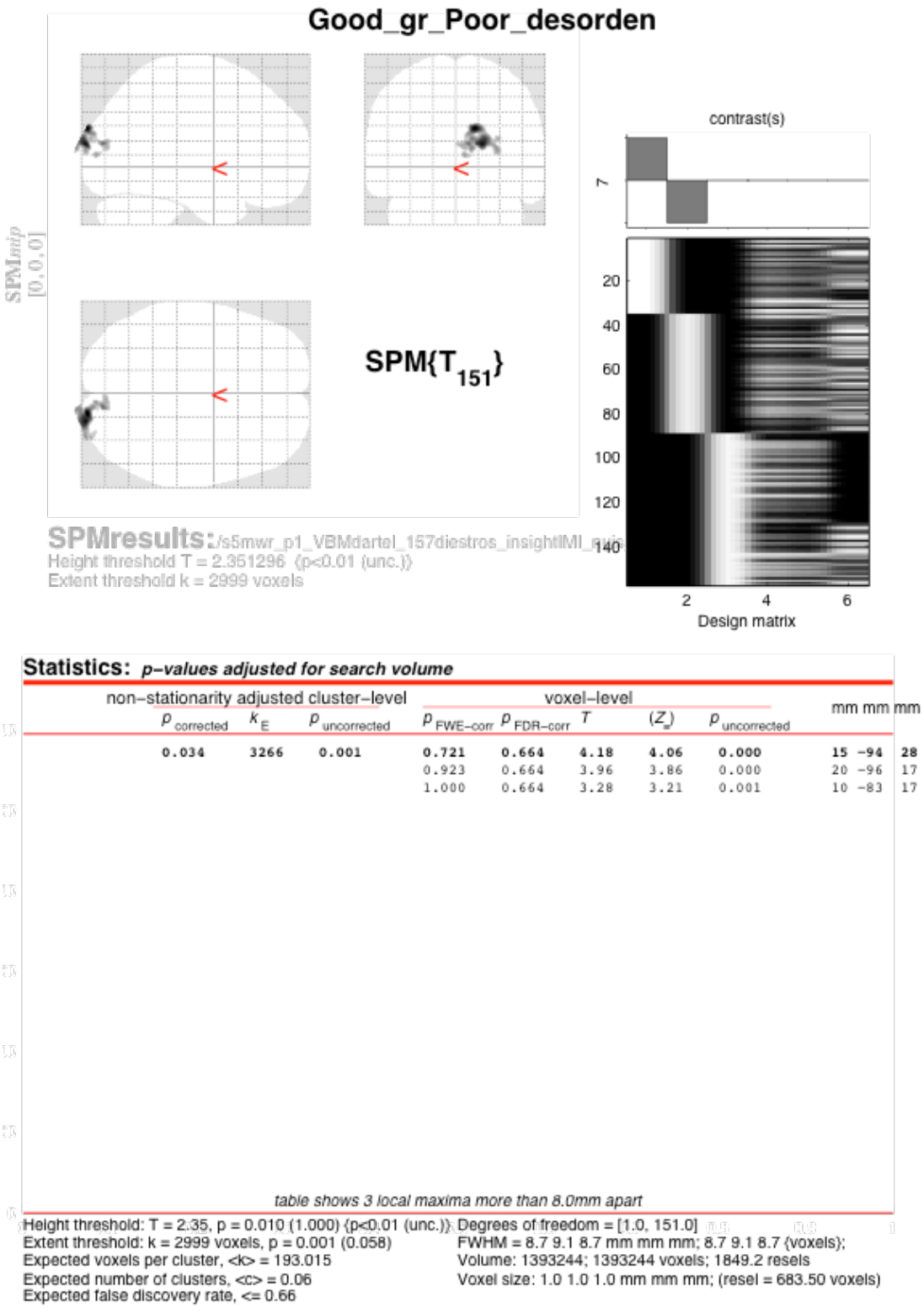

Figure 17. *SPM results for the contrast Good Insight >Poor Insight FEP patients.*

5.DISCUSSION

5.1. Grey matter volume differences between First Episode of Schizophrenia Spectrum Patients and Healthy Controls

In a large sample of right-handed, Caucasian, under 40 years old patients with a first episode of schizophrenia spectrum disorders, we found that first episode of non-affective psychosis show a reduction of grey matter in the frontal, temporal and occipital lobes, left insula and cerebellum

The presence of morphological brain alterations at the time of onset of the illness supports the primary neurodevelopment disorder theory in schizophrenia, which states that schizophrenia is the behavioural outcome of an aberration in neurodevelopmental processes that begins before the onset of clinical symptons and is caused by a combination of environmental and genetic factors (Rapoport and Gogtay, 2011).

The results of our study in FEP confirm the presence of decrease in GMV already at the onset of the disease of some deficits observed in chronic patients as medial frontal gyrus, superior temporal gyrus, insula and cerebellum (Honea et al., 2005). Such morphological changes, present early in the course of the illness, are therefore unlikely to be a consequence of chronicity nor neuroleptic exposure. This differences are widespread, and, as our data reveal, reforce the idea of a distribution of cortical circuits that are disturbed. Our results of global grey matter deficits are in concordance with recent meta-analysis (Haijma et al., 2013)

Moreover, FEP showed a decrease in cerebellar volume with respect to healthy controls.The cerebellum connects with other brain structures and might be a critical node in a cortical-cerebellar-thalamic–cortical circuit necessary for a correct coordination of brain processes. The cognitive dysmetry theory (Andreasen et al., 1998) has suggested that disruption of this circuit is a fundamental deficit in the pathology of schizophrenia .

5.2. Effect of Age of Onset in grey matter volume

In a sample of 101 first episode of schizophrenia spectrum patients under 40 years old, separated in three groups depending in their age at onset of illness by percentiles, and 69 healthy controls we found that age of onset of psychosis is an important factor revealing a decrease in each of the patients group versus healthy controls and most importantly a gradual decrease of grey matter in the following contrast: healthy controls > late onset > intermediate onset > early onset in frontal, temporal and occipital lobes, insula and cerebellum.

We found also reductions of grey matter pair-wise in the early and late onset groups versus the intermediate onset group

We found a gradation of grey matter volume, being the patients with early onset more affected (reduced volume) and patients with late onset having being more protected in these brain areas: right postcentral and precental gyrus, right insula, right superior temporal gyrus and left occipital pole (inferior, middle and fusiform gyrus). If we consider the possibility of a disruption in the normal process of brain development as a key factor contributing to the onset of psychosis, it would be expected that those cases with an earlier developmental interference might show an earlier illness onset. Total and grey matter volume of superior temporal gyrus was significantly lower in patients with early-onset schizophrenia and positively correlated with the age at onset (Matsumoto et al., 2001). In chronic patients no correlation was found between age of onset and grey matter volume (Assuncao Leme et al., 2013). It is noteworthy the reduction of GMV in the right postcentral gyrus were our group, using an ROI approach, also found structural abnormalities (Ferro et al., 2014).

The insula is widely interconnected with cortical and limbic areas, being a major component of the "limbic integration cortex" (Mesulam and Mufson, 1982). Furthermore, recent studies show that the insula is a key component of a general salience network (Palaniyappan et al., 2012), and that insular

dysfunction and altered between networks interactions might be a characteristic factor of schizophrenia (Manoliu et al., 2013). Insula volume reduction has been shown both in VBM studies (Ellison-Wright et al., 2008; Honea et al., 2005) and in regions of interest studies (Crespo-Facorro et al., 2000) (Duggal et al., 2005). In a recent article, Takahashi et al. (Takahashi et al., 2009) found a progressive pathological process in the insular cortex during the early, but not the late, phase after the onset of the illness. Our group has previously described, using manual ROI methods, insular cortical thinning in FEP vs. healthy controls (Roiz-Santianez et al., 2010a) and decrease of insular volume (Crespo-Facorro et al., 2000). Grey matter volume abnormalities in the right insula have been associated with a higher risk for transition to psychosis in subjects at high clinical risk (Smieskova et al., 2012).

Age of onset is being known to have and influence in the outcome. Earlier age of onset have been reported to be correlated with poorer cognitive performance, increased severity of symptoms, behavioral deterioration, less responsiveness to antipsychotics, and greater likelihood of rehospitalization (Jeste et al., 1998; Rabinowitz et al., 2006; Tuulio-Henriksson et al., 2004). This could be in concordance with the results of this study.

5.3. Differences grey matter volume reduction between diferent diagnoses in schizophrenia spectrum disorders

After confirming the existence of brain structural abnormalities present at the early phases of the illness in patients with a first episode of schizophrenia spectrum psychosis we investigated the specificity of brain structural abnormalities in diagnosis by using voxel based morphometry in a sample of schizophrenia spectrum patients at their first break of the illness.

In a sample of 51 schizophrenics, 30 patients diagnosed of schizophreniform disorder and 20 patients non-schizophrenic non-affective psychosis and 69 healthy controls we found reductions of GMV of each of the diagnosis groups when compared pair wise with the healthy control groups but no differences between them.

The main result is a gradual reduction of grey matter related to diagnosis (HC > NSNA > SZF> SZ) in the fronto-temporal-parietal network in FEP that is more severe in patients with a diagnosis of schizophrenia. In a recent investigation from our group using a ROI approach to investigate brain structural characteristics, we observed that the brain changes found in patients at the first break of a non-affective psychotic disorder are robustly associated with the diagnoses of schizophrenia and schizophreniform disorder and are independent of relevant intervening variables (Crespo-Facorro et al., 2009).

These results confirmed our hypothesis that schizophrenia individuals may show a discernible pattern of grey matter volume reductions when compared to other non-affective psychoses and to healthy volunteers.

5.4. Effect of lack of insight in grey matter volume in non-affective psychosis

The last analysis of this thesis aimed to investigate grey matter abnormalities underlying lack of insight in patients with a first-episode of non-affective psychosis.

Interestingly, we found a reduction in grey matter volume in the middle and superior right occipital gyrus, cuneus and middle temporal gyrus in patients with poor insight when compared to those with good insight.

Moreover, there were bilateral reductions in patients with poor insight when compared to healthy controls in superior medial frontal gyrus, cingulum, supplementary motor area, calcarine fissure, cuneus and lingual gyrus. Also reductions were found in the right hemisphere in the occipital gyrus in its inferior, middle and superior parts.

Hence, our findings agree partially with previous neuroimaging studies of insight in FEP subjects (Berge et al., 2011; Buchy et al., 2011; Cooke et al., 2008; Morgan et al., 2010). In particular, a positive association of awareness of symptoms and their attribution to a mental illness with grey matter volumes in the left superior and middle temporal gyrus and the right inferior temporal and lateral parietal gyri had been reported, including a correlation of the right superior temporal gyrus grey matter volume with the ability to recognise experiences as abnormal (Cooke et al., 2008). Occipital brain structures have been linked to visual and associative perception (Kleinschmidt, 2004). Previous research had found that this area is affected in neglect patients, particularly in those who after right-hemisphere stroke ignore their contralateral arm or avoid accepting that they had suffered a seizure (Kortte and Hillis, 2009). Neglect was critically associated with white matter abnormalities in the occipital lobe, which corresponds to a white matter tract connecting the parahippocampal gyrus with the angular gyrus of the parietal lobe (Bird et al., 2006). Thus, our findings of reductions of GMV mainly in the temporal and occipital lobes appear to be consistent with other studies examining constructs related to insight.

However, previous research has also implicated aberrant functioning with the prefrontal cortex as an underlying feature of lack of insight. We did not find strong evidence of structural abnormalities within key regions of the neural network proposed (i.e., cingulate) (Antonius et al., 2011; Bassitt et al., 2007) (Berge et al., 2011; Cooke et al., 2008; Flashman et al., 2001; Ha et al., 2004; Kumar et al., 2014; Orfei et al., 2013; Sapara et al., 2007; Shad et al., 2004). An explanation for these inconsistencies may be that most of previous studies have compare chronic patients and healthy controls, using small sample sizes. However, our large sample size allowed us to make comparisons between subgroups of FEP patients with good and poor insight, as well as comparisons between these subgroups and controls. In this direction, we found that a reduction in GMV in the frontal lobe was exclusively observed when comparing patients with poor insight and healthy controls, but neither when the comparisons were conducted between subgroups of patients depending on their insight nor when comparing good insight patients and healthy controls. This could suggest that reductions in frontal grey matter would be more strongly related to illness severity, attending the poor insight subgroup presented a longer duration of untreated illness (mean 31.26 months), a known factor related with brain abnormalities in FEP patients (Crespo-Facorro et al., 2007), while temporal and occipital lobes reductions may underlie impaired insight per se. We consider these results as relevant information on which to base further investigation.

5.5.Limitations

Some potential limitations should be considered.

First, VBM methodology has limitations concerning spatial normalization, smoothing and the template of choice (Davatzikos, 2004). This problem has been addressed by a cautious methodological choice of preprocessing parameters (i.e. use of DARTEL) and statistical options that are likely to have led to reliable VBM results (Klein et al., 2009; Kubicki et al., 2002). Additionally, the inclusion of a large sample represents a significant improvement with respect to other studies, which utilized smaller samples.

Second, although our patients were minimally treated (mean= 4.43 weeks) the effect of antipsychotic medication in grey matter volume should not be neglected(Roiz-Santianez et al., 2015) .

Third, the non-specified non-affective psychosis group encompassed patients with three different diagnoses (schizoaffective disorder, brief reactive psychosis and not otherwise specified psychosis), which may vanish likely differences between these nosological categories.

6.CONCLUSIONS

As general conclusions we have found:

1. There was an overall reduction of grey matter volume in the first episode of non-affective psychosis sample in relation to the healthy control sample.
2. None of the different groups of patients in the different analysis showed more grey matter volume than the healthy control group.

In this work we set three main objectives:

Objective 1: *To evaluate whether there are significant structural differences in patients diagnosed with non-affective psychosis depending on their age of onset.*

The conclusions relevant to this objective are:

1. There are is a gradiation in grey matter volume with age of onset, being the patients that onset at a younger age the ones more affected by this reduction.
2. The linear decrease in grey matter following the contrast (healthy controls > late onset > intermediate onset > early onset)is found only in frontal, temporal and occipital lobes, insula and cerebellum.

Objective 2: *To explore similarities/differences of the various disorders in the non-affective psychosis spectrum using voxel-based morphometry.*

The conclusions relevant to this objective are:

3. Patients with diagnosis of schizophrenia show a more pronounce reduction of grey matter volume than any other schizophrenia spectrum disorder.

4. A gradual reduction of grey matter is found related to diagnosis when in the frontal, temporal, parietal and occipital lobes with schizophrenia patients being the most affected. (Healthy Controls > Non-Specific Non- Affective > Schizophreniform > Schizophrenia)

Objective 3: *To determine whether brain structural abnormalities can be quantifiably related to the lack of insight.*

The conclusions relevant to this objective are:

5. There is a significant reduction in grey matter volume in patients with poor insight in superior medial frontal gyrus, supplementary motor area and anterior and middle part of the cingullum when compared to healthy controls.
6. Patients with poor insight showed a reduction of grey matter volume in the occipital and temporal lobes when compared to patients with good insight.

7.RESUMEN EN ESPAÑOL

La esquizofrenia es una compleja enfermedad altamente incapacitante y que afecta aproximadamente a un 1% de la población general. El establecimiento de las bases biológicas de la enfermedad es un paso importante para avanzar en su diagnóstico y encontrar nuevas rutas posibles para su tratamiento.

Los últimos metanálisis que han estudiado las alteraciones cerebrales en esquizofrenia han encontrado una marcada reducción de la materia gris total y un aumento del volumen de líquido cefalorraquídeo (Haijma et al., 2013). Estas alteraciones morfométricas parecen cumplir los criterios para ser considerados endofenotipos en los trastornos psicóticos (Gottesman and Gould, 2003; Prasad and Keshavan, 2008)

En el caso de los trastornos psiquiátricos el desarrollo de las técnicas de imagen permite la investigación objetiva e imparcial de sujetos "in vivo" proporciona las herramientas óptimas para buscar la raíz del problema. Nuestro enfoque particular serán las primeras fases de la psicosis ya que, en este momento no existen confusores debidos a la medicación u otras causas asociadas a la cronicidad. Para llevar a cabo este estudio vamos a utilizar la morfometría basada en voxel, una técnica basada en la resonancia magnética, que nos permitirá trazar las diversas estructuras del cerebro en el espacio, el apoyo a esta información con datos sobre el tipo de tejido (blanco , la materia gris) asociado con una posición. Por lo tanto, esta herramienta es óptima para la búsqueda de biomarcadores senderos del trastorno.

La edad en que se produce el primer brote psicótico es una variable importante que pueda afectar fuertemente la evolución posterior de la enfermedad. Se ha demostrado que los pacientes con un inicio precoz de los trastornos del espectro esquizofrénico tiene significativamente mayores niveles de deterioro cognitivo y una mayor impulsividad (Kao and Liu, 2010). Varios estudios de neuroimagen han examinado estas primeras etapas, concentrándose en su aparición en la adolescencia o incluso a nivel pediátrico

(Kravariti et al., 2003; Rapoport and Gogtay, 2011). Otros estudios han investigado el efecto de la edad de inicio en pacientes crónicos, tratando de asociarlo con la evolución posterior de la enfermedad (Ongur et al., 2009). Sin embargo, a nuestro conocimiento ningún estudio previo ha tratado de establecer el efecto de la edad de inicio en adultos que acaban de ser diagnosticados con un primer episodio de psicosis.

Actualmente en los trastornos psicóticos el diagnóstico se lleva a cabo en base a los síntomas, pero existe la necesidad de una búsqueda de herramientas de medida cuantitativas y clínicamente significativas. Un estudio de los pacientes con diferentes diagnósticos de psicosis no afectivas puede ayudar a avanzar en la comprensión de las diferencias neurobiológicas entre los diagnósticos y, por lo tanto, ayudar en la búsqueda de dichas medidas cuantitativas.

Por último, vamos a estudiar un factor que tiene una influencia importante en la calidad de vida y el tratamiento de los pacientes: su propia conciencia de la enfermedad. Se ha observado que los pacientes con una buena conciencia de enfermedad tienen una mejor cognición y pronóstico que aquellos con una mala conciencia de enfermedad (Lincoln et al., 2007). Este factor también se correlaciona con la voluntad y la capacidad de seguir el tratamiento (Buckley et al., 2007). Se ha especulado que una propia conciencia de enfermedad se asocia con déficits de materia gris en comparación con los controles sanos y pacientes con mejor conciencia. Sin embargo, la mayoría de estos estudios se han realizado en pacientes crónicos (Orfei et al., 2013) o muestras mucho menores a la que aquí se presenta (Berge et al., 2011). Durante este trabajo vamos a investigar los resultados de las imágenes del cerebro para determinar si la conciencia de la enfermedad tiene una base fisiológica.

Se llevaron a cabo resonancias magnéticas estructurales de 101 pacientes con un primer episodio psicótico y 69 sujetos control sanos comprables sociodemográficamente. Los pacientes recibieron exámenes clínicos y la severidad de sus síntomas fue medida con las escalas BPRS, SAPS y SANS.

Además el diagnóstico fue confirmado a los seis meses de inclusión en el programa PAFIP.

Las imágenes obtenidas de la adquisición de resonancia magnética se inspeccionaron para descartar artefactos y grandes anormalidades en cada sujeto y a continuación todas las imágenes fueron procesadas con el programa SPM (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) que corre MATLAB (MathWorks, Natic, MA) y se hizo uso del VBM toolbox http://www.neuro.uni-jena.de/:

Primero las imágenes cerebrales de cada individuo son segmentadas en materia gris, materia blanca y fluido cefalorraquídeo aplicando un modelado Hidden Markov Random Field (Cuadra et al., 2005) que, quitando los vóxeles aislados que podrían haber sido erróneamente clasificados minimiza el ruido en el proceso de segmentación. Seguidamente se introducen todas las imágenes de los sujetos del estudio en la herramienta DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) (Ashburner, 2007) del programa SPM donde se crea una plantilla mediante un proceso iterativo de creación de plantillas específicas de nuestra muestra y registro de las imágenes a esas plantillas, con esto se consiguen una serie de plantillas y los campos de deformación de cada sujeto para llegar a la plantilla común. Seguidamente se aplica un proceso de corrección, llamado modulación, de la intensidad de las imágenes segmentadas. Durante la normalización algunos vóxeles cambian de volumen. Para preservar su volumen asociado, la intensidad de cada uno de estos se multiplicará por el valor correspondiente de la deformación. Así, al hacer el análisis final podremos ver las diferencias en la cantidad absoluta, volumen, de materia gris. Finalmente, como paso previo a la estadística, las imágenes segmentadas son suavizadas, reduciendo la relación señal–ruido. Esto se hace promediando la intensidad de cada voxel con el de los colindantes, esto se realiza mediante el producto de convolución de la función de distribución de la intensidad con una gaussiana. La amplitud del núcleo gaussiano isotrópico (caracterizado por la amplitud a media altura del máximo FWHM) determina la escala de máxima sensibilidad para evidenciar cambios morfológicos. Nosotros aplicamos un FWHM de 5 mm.

Las imágenes procesadas se analizaron bajo el Modelo Lineal General (GLM) y varios análisis fueron diseñados para investigar las diferencias en volumen de materia gris entre sujetos control sanos y pacientes psicóticos. En el diseño estadístico se introdujeron la edad en el momento de la adquisición de la imagen, el género y el volumen intracraneal total como covariables para poder descartar posibles efectos de estos parámetros en las diferencias de volumen intergrupales. Primero aplicamos un umbral al nivel de voxel de $p<0.01$ para facilitar la formación de clusters. Entonces aplicamos una inferencia a nivel de cluster con un umbral de $p<0.05$ corregido por familywise error para corregir por comparaciones múltiples. Además ajustamos por la no uniformidad del suavizado el tamaño de los clusters usando la herramienta VBM 5 (Hasaka 2004). Finalmente, una vez obtenidos resultados positivos, las regiones anatómicas cubiertas por clusters significativos se identificaron usando el marcado anatómico automático (AAL) (Tzourio-Mazoyer et al., 2002).

En este trabajo hemos encontrado los siguientes resultados principales:

1. Los pacientes muestran un menor volumen de materia gris respecto a los voluntarios sanos en los lóbulos frontal, temporal y occipital, en la ínsula izquierda y el cerebelo.
2. La edad de inicio es un factor importante y se observa un descenso gradual del volumen de materia gris al separar grupos por este factor en los lóbulos frontal, temporal y occipital, en la ínsula izquierda y el cerebelo.
3. Al estudiar a los pacientes según los diferentes diagnósticos de los pacientes en el espectro de la psicosis no afectiva hay una reducción gradual en los lóbulos frontal, temporal, parietal y occipital siendo los pacientes diagnosticados de esquizofrenia los que presentan una mayor reducción de volumen.

4. Los pacientes con una pobre conciencia de enfermedad presentan diferencias en los lóbulos temporal y occipital al ser comparados con pacientes con una buena conciencia de enfermedad.

Para mayor detalle de los resultados consultar tablas 1-17 de la sección "Results".

Con lo que concluimos que:

1. Existe una reducción total de volumen de materia gris en la muestra total de pacientes con un primer episodio de psicosis relación con la muestra de controles sanos.
2. Ningún grupo o subgrupo de pacientes muestra áreas cerebrales de mayor volumen de materia gris que el grupo control.
3. Observamos una gradación en el volumen de materia gris con la edad de inicio, siendo los pacientes que inicio a una edad menor los más afectados por esta reducción.
4. La disminución lineal en la materia gris tras el contraste (controles sanos> inicio tardío> inicio intermedio> inicio temprano) se encuentra en el lóbulo frontal, lóbulos temporal y occipital, la ínsula y el cerebelo.
5. Los pacientes con diagnóstico de esquizofrenia muestran una reducción más pronunciada de volumen de materia gris que cualquier otro trastorno del espectro de la esquizofrenia.
6. Una reducción gradual de la materia gris se encuentra relacionada con el diagnóstico (HC> NSNA> SZF > SZ) en los lóbulos frontal, temporal, parietal y occipital.
7. Hay una reducción significativa en el volumen de materia gris en pacientes con mala conciencia de enfermedad en la circunvolución frontal medial, área motora suplementaria y cíngulo en comparación con los controles sanos.

8. Los pacientes con mala conciencia de enfermedad mostraron una reducción del volumen de materia gris en los lóbulos occipital y temporal, en comparación con los pacientes con buena conciencia de enfermedad.

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APPENDICES

APPENDIX 1

General consent of the program

Protocolo de atención clínica e investigación de los primeros episodios psicóticos de Cantabria (PAFIP)

Se solicita su autorización para ser incluido en un programa de tratamiento en el Servicio de Psiquiatría del Hospital Universitario "Marqués de Valdecilla".

El programa incluye una parte de investigación que implica la realización de algunas pruebas psicológicas, de análisis de laboratorio y de resonancia magnética cerebral, que se repetirán a lo largo de las revisiones y que ayudarán a complementar el estudio de su enfermedad.

Algunas de las pruebas practicadas no son imprescindibles y sirven para complementar el proyecto en su parte investigadora. Aunque Ud. puede beneficiarse de la realización de las mismas, sobre todo, sirven para un mejor conocimiento de la enfermedad que padece.

Ud. participa voluntariamente en este programa y puede retirarse de él sin tener que dar explicación alguna. En este caso, pasaría a recibir el tratamiento especializado convencional.

Este protocolo ha sido aprobado por el Comité Ético del Hospital Universitario "Marqués de Valdecilla", que tiene por misión velar por las normas éticas que regulan los estudios médicos para seguridad de los pacientes participantes en los mismos.

Nombre del participante: _____

He recibido información adaptada a mi nivel de entendimiento de los extremos indicados anteriormente, así como de las posibles alternativas de tratamiento, con sus pros y contras. Estoy satisfecho de la información recibida y de haber obtenido respuestas claras sobre las dudas planteadas.

_____ _____
(Firma del participante) (Fecha)

_____ _____
(Firma del representante legal del participante) (Fecha)

MEDICO INFORMANTE

Yo he explicado y discutido con él paciente o su representante legalmente autorizado los puntos anteriormente expuestos. En mi opinión el paciente ha entendido los objetivos, procedimientos, riesgos, beneficios y obligaciones referentes a su participación en este protocolo.

_____ _____

(Nombre y firma del médico) (Fecha)

APPENDIX 2

MRI Consent

RESONANCIA

Solicitud de Consentimiento informado para el proyecto de investigación sobre Fases Tempranas de los Trastornos Psicóticos (Programa PAFIP)

CONFIDENCIAL

Estimado Sr. D.

Usted está siendo invitado a participar en un estudio de investigación. Antes de que tome una decisión es importante que entienda por qué se hace la investigación y qué implica para usted. Tómese su tiempo para leer la siguiente información y pregúntenos cualquier duda que tenga al respecto. Gracias por su colaboración.

Objeto y beneficios de la investigación

Todavía no se conocen con exactitud las causas que provocan que la gente desarrolle un trastorno psicótico. Un trastorno psicótico significa que una persona experimenta o siente cosas que no necesariamente son verdad o reales.

Estudios recientes sugieren que estructuras de las sustancias gris y blanca cerebrales podrían estar implicadas en el desarrollo de esta enfermedad, pero la información de que disponemos aún no es concluyente. Por eso, es importante repetir este tipo de investigaciones en el mayor número posible de personas. El estudio de la estructura cerebral nos aportará un mejor conocimiento de las posibles causas de los trastornos psicóticos y nos puede proporcionar información para el desarrollo en un futuro de nuevas líneas de tratamiento.

Procedimiento

Esta investigación implica la realización de una resonancia magnética (RM). El tiempo aproximado de la prueba es de unos 30 minutos. Una resonancia magnética toma múltiples imágenes de su cerebro y para poder obtener imágenes de buena calidad necesitamos que usted permanezca lo más quieto posible. Durante la prueba de RM usted va a oír ruidos, pero que en ninguna forma van a causarle ningún daño. La RM no utiliza rayos X, por lo que no existen los riesgos asociados a este tipo de técnica ya que no se usa ninguna radiación. La RM es un potente imán y por lo tanto atrae objetos metálicos. Usted no podrá realizar esta prueba, por ejemplo, si ha tenido alguna vez una herida en sus ojos por algún tipo de material metálico o tiene algún tipo de objeto metálico (como tornillos o placas metálicas) insertado en su cuerpo tras una operación o si tiene un marcapasos. Como precaución le pedimos que nos haga saber si usted puede estar embarazada.

Algunas personas se sienten incómodas en el escáner porque el espacio es limitado. Usted va a estar en contacto en todo momento con el personal técnico. Si usted se siente incómodo o angustiado, háganoslo saber y podemos finalizar la prueba en cualquier momento.

No hay ninguna restricción en la dieta o en su actividad habitual ni antes ni después del escáner. Si toma medicación, debe continuar tomándola como habitualmente.

Comunicación de resultados

En raras ocasiones, esta prueba puede poner de manifiesto alguna anomalía. Estos estudios de RM son revisados por un radiólogo. Si encontrásemos algún hallazgo anormal se lo haríamos saber.

Garantías de confidencialidad

Los datos que se obtengan serán totalmente confidenciales y serán utilizados exclusivamente con fines investigadores y docentes con el objetivo de mejorar el conocimiento de trastornos psiquiátricos específicos. Su intimidad quedará salvaguardada en todo momento, y ni el nombre, ni cualquier otro dato que pueda llevar a la identificación de los participantes serán utilizados en ninguno de los trabajos que se deriven de esta investigación.

Derecho a rehusar o abandonar

Su colaboración es totalmente voluntaria. Si en algún momento desea retirarse del estudio podrá hacerlo, sin tener que dar explicación alguna.

El Servicio de Psiquiatría del Hospital Universitario Marqués de Valdecilla en colaboración con el Servicio de Radiología, es quien organiza esta investigación. Además, el estudio aquí descrito ha sido aprobado por el Comité Ético de este hospital.

Si tiene alguna duda sobre lo que acaba de leer o sobre cualquier otro aspecto de esta investigación, por favor háganoslo saber antes de firmar esta hoja de consentimiento informado.

1. Confirmo que he leído y entendido la hoja de información y he realizado todas las preguntas que he precisado. ☐
2. Entiendo que mi participación en el presente estudio es voluntaria y tengo derecho a abandonar en cualquier momento. ☐
3. En inusual caso de que se encuentre casualmente una anomalía en las pruebas que me van a hacer deseo ser informado de ello: Si ☐ No ☐
4. Accedo a tomar parte en el presente estudio. ☐

_____	_____	_____
Nombre	Fecha	Firma y DNI
_____	_____	_____
Nombre de la persona que recoge el consentimiento (si distinta al investigador)	Fecha	Firma
_____	_____	_____
Nombre del investigador principal	Fecha	Firma

APPENDIX 3

DSM-IV-TR criteria for schizophrenia (APA, 2001)

A. Síntomas característicos: Deben darse al menos dos de los siguientes, cada uno de ellos presente durante una porción significativa de tiempo durante el periodo de un mes (o menos si es tratado satisfactoriamente):
- Delirios.
- Alucinaciones.
- Habla desorganizada (con frecuencia descarrilamiento o incoherencia).
- Comportamiento exageradamente desorganizado o catatónico.
- Síntomas negativos, es decir, afecto plano, alogia o abulia.
Nota: Solamente se requiere un síntoma de los anteriores si los delirios son desorganizados o las alucinaciones consisten en voces que comentan el comportamiento o pensamiento de la persona, o dos más fuentes que conversan entre ellas.
B. Alteraciones en el funcionamiento sociolaboral: Durante la mayor parte del tiempo desde el inicio del trastorno, una o más áreas importantes del funcionamiento como -trabajo, relaciones interpersonales o el cuidado personal- están marcadamente por debajo del nivel alcanzado antes del inicio (o cuando el inicio es en la infancia o la adolescencia, existe fracaso para alcanzar el nivel de realización interpersonal, académico u ocupacional esperado).
C. Duración: Signos continuos del trastorno persisten durante al menos 6 meses. En este periodo de 6 meses debe incluir al menos durante un mes los síntomas que reúnen los criterios del apartado A (síntomas de la fase activa), y puede incluir períodos prodómicos o residuales cuando el criterio A no se cumple en su totalidad. Durante estos periodos, las señales del trastorno pueden manifestarse a través de síntomas negativos, o dos o más síntomas de los listados en el criterio A están presentes de forma atenuada (p. ej., afecto

embotado, experiencias perceptuales inusuales).
D. Exclusión del diagnóstico de trastorno esquizoafectivo y de trastorno afectivo: El trastorno esquizoafectivo y el trastorno de humor con síntomas psicóticos han sido excluidos porque: 1) ningún episodio de depresión mayor o de manía ha estado presente al mismo tiempo que los síntomas de la fase activa; o 2) si estos episodios han ocurrido durante la fase activa de los síntomas, su duración ha sido más breve que la duración de los periodos activos o residuales.
E. Exclusión de las alteraciones secundarias al uso de sustancias o a condiciones médicas: El trastorno no se debe a un trastorno psicótico inducido o secundario al uso de sustancias (p. ej., abuso de drogas, medicación) o a condiciones médicas.
F. Relación con un trastorno del desarrollo: Si hay una historia de autismo u otro trastorno del desarrollo, solamente se hace el diagnóstico adicional de esquizofrenia si están presentes delirios o alucinaciones, durante al menos un mes (o menos si son tratados satisfactoriamente).

APPENDIX 4

Sociodemographic questionare

INFORMACIÓN SOCIODEMOGRÁFICA

1.1	Raza	**1** Caucásica **2** Etnia gitana **3** Árabe **4** Negra **5** Asiática **6** Hispana **7** Otros	☐
1.2	Lugar de nacimiento	_____	☐☐☐☐☐
1.3	Tipo de zona	**1** Zona urbana (> 10.000 habitantes) **2** Zona intermedia (2.001-10.000) **3** Zona rural (< 2.000)	☐
1.4	Estado civil	**1** Soltero **2** Casado o pareja estable **3** Separado o divorciado **4** Viudo	☐
1.5	Máximo nivel académico alcanzado	**1** Analfabetos (no sabe leer ni escribir en ningún idioma) **2** Sin estudios (sabe leer y escribir pero fue menos de 5 años a la escuela) **3** Primer grado (fue a la escuela 5 años o más pero sin completar EGB, ESO o Bachiller elemental) **4** ESO, EGB o Bachillerato elemental **5** Bachiller superior, BUP, Bachiller LOGSE, COU, PREU **6** FP grado medio, FP I, Oficialía industrial o equivalente **7** FP grado superior, FP II, Maestría industrial o equivalente **8** Diplomatura, Arquitectura o Ingeniería Técnicas; 3 cursos aprobados de Licenciatura, Ingeniería o Arquitectura. **9** Licenciatura, Arquitectura, Ingeniería o equivalente **10** Doctorado	☐☐
1.6	Calificación media	**1** Alto (sobresaliente / notable) **2** Medio **3** Bajo	☐
1.7	¿Tuvo apoyo especial en el colegio?	**1** Sí **2** No **3** No disponible este recurso	☐
1.8	¿Está estudiando en la actualidad?	**1** Sí **2** No	☐
1.9	**Estudiantes:** ¿Qué estudios está realizando actualmente? *(Se pueden señalar hasta 3 casillas)*		

1- Enseñanzas iniciales para adultos (alfabetización, educ. básica) ☐
2- Programas de garantía social ☐
3- ESO ó Educación secundaria para adultos ☐
4- Bachillerato, BUP y COU ☐
5- Escuela oficial de idiomas ☐
6- Enseñanzas artísticas de grado elemental o medio ☐
7- Formación profesional de grado medio o estudios equivalentes ☐
8- Formación profesional de grado superior, FP II o equivalente ☐
9- Diplomatura universitaria, Arquitectura o Ingeniería técnica o equivalente ☐
10- Licenciatura universitaria, Arquitectura o Ingeniería o equivalente ☐
11- Estudios de postgrado, máster, MIR o análogo ☐
12-Doctorado ☐

Otros cursos de formación:

13- Curso del INEM, Escuela Taller u otro curso para desempleados ☐
14- Curso de formación promovido por la empresa (sólo para ocupados) ☐
15- Otros cursos no mencionados antes (de informática, preparación de oposiciones, idiomas en academias, cursos culturales o recreativos) ☐

PADRE

1.10 Fecha de nacimiento del padre ☐☐/☐☐/☐☐

1.11 Estado del padre ☐

1 Vivo
2 Fallecido
3 Desconocido

1.12 Estudios del padre ☐☐

1 Analfabetos (no sabe leer ni escribir en ningún idioma)
2 Sin estudios (sabe leer y escribir pero fue menos de 5 años a la escuela)
3 Primer grado (fue a la escuela 5 años o más pero sin completar EGB, ESO o Bachiller elemental)
4 ESO, EGB o Bachillerato elemental
5 Bachiller superior, BUP, Bachiller LOGSE, COU, PREU
6 FP grado medio, FP I, Oficialía industrial o equivalente
7 FP grado superior, FP II, Maestría industrial o equivalente
8 Diplomatura, Arquitectura o Ingeniería Técnicas; 3 cursos aprobados de Licenciatura, Ingeniería o Arquitectura.
9 Licenciatura, Arquitectura, Ingeniería o equivalente
10 Doctorado

1.13 ¿Cuál es la actividad que está realizando actualmente?:

1 Estudiante
2 Ocupado
3 Ocupado: Temporalmente ausente del trabajo (ILT)
4 Parado buscando el primer empleo
5 Parado que ha trabajado antes
6 Cobrando una pensión de incapacidad permanente o invalidez
7 Cobrando una pensión de viudedad u orfandad
8 Cobrando una pensión de jubilación o prejubilado
9 Realizando tareas de voluntariado social
10 Realizando las tareas del hogar
11 Otra situación

☐☐

1.14 Profesión/Ocupación del padre: _____
(aunque esté ya retirado)

1.15 Señale su ocupación:
Ver anexo

0 Fuerzas armadas
1 Dirección de las empresas y de las administraciones públicas
2 Técnicos y profesionales científicos e intelectuales
3 Técnicos y profesionales de apoyo
4 Empleados de tipo administrativo
5 Trabajadores de los servicios de restauración, personales, protección y vendedores de los comercios
6 Trabajadores cualificados en la agricultura y en la pesca
7 Artesanos y trabajadores cualificados de las industrias manufactureras, la construcción, y la minería, excepto los operadores de instalaciones y maquinaria
8 Operadores de instalaciones y maquinaria, y montadores
9 Trabajadores no cualificados

☐

MADRE

1.16 Fecha de nacimiento de la madre ☐☐/☐☐/☐☐

1.17 Estado de la madre

1 Viva
2 Fallecida
3 Desconocido

☐

1.18 Estudios de la madre

1 Analfabetos (no sabe leer ni escribir en ningún idioma)
2 Sin estudios (sabe leer y escribir pero fue menos de 5 años a la escuela)
3 Primer grado (fue a la escuela 5 años o más pero sin completar EGB, ESO o Bachiller elemental)
4 ESO, EGB o Bachillerato elemental
5 Bachiller superior, BUP, Bachiller LOGSE, COU, PREU
6 FP grado medio, FP I, Oficialía industrial o equivalente
7 FP grado superior, FP II, Maestría industrial o equivalente
8 Diplomatura, Arquitectura o Ingeniería Técnicas; 3 cursos aprobados de Licenciatura, Ingeniería o Arquitectura.
9 Licenciatura, Arquitectura, Ingeniería o equivalente
10 Doctorado

☐☐

1.19 ¿Cuál es la actividad que está realizando actualmente?:

1 Estudiante
2 Ocupada
3 Ocupada: Temporalmente ausente del trabajo (ILT)
4 Parada buscando el primer empleo
5 Parada que ha trabajado antes
6 Cobrando una pensión de incapacidad permanente o invalidez
7 Cobrando una pensión de viudedad u orfandad
8 Cobrando una pensión de jubilación o prejubilado
9 Realizando tareas de voluntariado social
10 Realizando las tareas del hogar
11 Otra situación

1.20 Profesión/Ocupación de la madre
(aunque ya esté retirada)

1.21 Señale su ocupación:
Ver anexo

0 Fuerzas armadas
1 Dirección de las empresas y de las administraciones públicas
2 Técnicos y profesionales científicos e intelectuales
3 Técnicos y profesionales de apoyo
4 Empleados de tipo administrativo
5 Trabajadores de los servicios de restauración, personales, protección y vendedores de los comercios
6 Trabajadores cualificados en la agricultura y en la pesca
7 Artesanos y trabajadores cualificados de las industrias manufactureras, la construcción, y la minería, excepto los operadores de instalaciones y maquinaria
8 Operadores de instalaciones y maquinaria, y montadores
9 Trabajadores no cualificados

1.22 Nivel socioeducativo de los padres

1 Familia acomodada – Educación elevada – Rango social elevado
2 Profesionales liberales – Licenciados – Puestos directivos
3 Pequeños negocios – Trabajadores cualificados - Bachiller
4 Educación inferior a 2º grado – Poca cualificación
5 Estudios básicos – Trabajo sin cualificación
6 Desconocido

2. ALOJAMIENTO

2.1 ¿Dónde vive habitualmente? _____

2.2 Tipo de zona

1 Zona urbana (> 10.000 habitantes)
2 Zona semiurbana (2.001-10.000)
3 Zona rural (< 2.000)
4 Itinerante

2.3 ¿Desde hace cuántos años vive en este lugar?

2.4 ¿Dónde residió la mayor parte de su infancia-juventud? _____

2.5 Tipo de zona

1 Zona urbana (> 10.000 habitantes)
2 Zona semiurbana (2.001-10.000)
3 Zona rural (< 2.000)

2.6 ¿Con quién vive habitualmente?

1 Vive solo (+/- hijos)
2 Con la esposa/o (+/- hijos)
3 Vive en pareja
4 Vive con los padres
5 Vive con otros familiares
6 Vive con otros

☐

2.7 Si vive con su **familia:**
(pregunta 2.4 = 2,3,4,5)

¿Cuántos adultos viven ahí, excluyendo al paciente?
(mayores de 18 años)

Número de adultos ☐☐

¿Y cuántos niños, excluyendo al paciente?
(menores de 18 años)

Número de niños ☐☐

3. ACTIVIDAD LABORAL E INGRESOS DEL PACIENTE

3.1 ¿Cuál es la actividad que está realizando actualmente el paciente?

1 Estudiante
2 Ocupado
3 Ocupado: Temporalmente ausente del trabajo (ILT)
4 Parado buscando el primer empleo
5 Parado que ha trabajado antes
6 Cobrando una pensión de incapacidad permanente o invalidez
7 Cobrando una pensión de viudedad u orfandad
8 Cobrando una pensión de jubilación o prejubilado
9 Realizando tareas de voluntariado social
10 Realizando las tareas del hogar
11 Otra situación

☐☐

3.2 **Pacientes ocupados y parados**
(pregunta 3.1: del 2 al 5)
En los últimos 12 meses:

Número de semanas empleado- activo ☐☐

Número de semanas empleado- de baja laboral ☐☐

Número de semanas desempleado ☐☐

Total: 5 2

3.3 Profesión del paciente _____

3.4 **Si está ocupado:** (pregunta 3.1 = 2 ó 3) señale su ocupación: Ver anexo

0 Fuerzas armadas
1 Dirección de las empresas y de las administraciones públicas
2 Técnicos y profesionales científicos e intelectuales
3 Técnicos y profesionales de apoyo
4 Empleados de tipo administrativo
5 Trabajadores de los servicios de restauración, personales, protección y vendedores de los comercios
6 Trabajadores cualificados en la agricultura y en la pesca
7 Artesanos y trabajadores cualificados de las industrias manufactureras, la construcción, y la minería, excepto los operadores de instalaciones y maquinaria
8 Operadores de instalaciones y maquinaria, y montadores
9 Trabajadores no cualificados

☐

INGRESOS DEL PACIENTE

3.5 ¿Recibe algún tipo de pensión o ayuda económica?

1 Sí
2 No

☐

3.6 **<u>Si la respuesta es afirmativa:</u>** ¿qué tipo de ayuda recibe?:

1 Subsidio-Desempleo
2 Incapacidad transitoria
3 Invalidez
4 Jubilación
5 Ingresos mínimos de inserción
6 No contributiva
7 Hijo a cargo
8 Orfandad
9 Viudedad

☐

3.7 ¿Cuál es su **<u>principal</u>** fuente de ingresos?

1 Salario-ILT
2 Desempleo
3 Pensión
4 Dependencia familiar
5 Otros _____

☐

3.8 **Si 3.7 = 1, 2,3 (salario, desempleo, pensión)** ¿Cuáles son sus ingresos mensuales?

1 < 300 €
2 300 - 600 €
3 601 – 1500 €
4 1.501 – 2.000€
5 > 2.000 €

Ingresos netos ☐

APPENDIX 5

The Spanish version of Scale for the Assessment of Positive Symptoms - SAPS

_____
SAPS
1- ALUCINACIONES
• Alucinaciones auditivas 0 1 2 3 4 5
• Voces comentadoras 0 1 2 3 4 5
• Voces que conversan 0 1 2 3 4 5
• Alucinaciones táctiles/ cenestésicas 0 1 2 3 4 5
• Alucinaciones olfatorias 0 1 2 3 4 5
• Alucinaciones visuales 0 1 2 3 4 5
• GLOBAL 0 1 2 3 4 5..... ☐
2- IDEAS DELIRANTES
• Delirio de persecución 0 1 2 3 4 5
• Delirio de celos 0 1 2 3 4 5
• Delirio de culpa/ pecado 0 1 2 3 4 5
• Delirio de grandeza 0 1 2 3 4 5
• Delirio religioso 0 1 2 3 4 5

• Delirio somático	0 1 2 3 4 5
• Delirio de referencia	0 1 2 3 4 5
• Delirio de ser controlado	0 1 2 3 4 5
• Lectura de pensamiento	0 1 2 3 4 5
• Difusión del pensamiento	0 1 2 3 4 5
• Inserción del pensamiento	0 1 2 3 4 5
• Robo del pensamiento	0 1 2 3 4 5
• GLOBAL 5.....☐	0 1 2 3 4
3- CONDUCTAS EXTRAVAGANTES	
• Apariencia/ vestimenta	0 1 2 3 4 5
• Comportamiento social/ sexual	0 1 2 3 4 5
• Conductas agresivas/ agitación	0 1 2 3 4 5
• Conductas repetitivas/ estereotipias	0 1 2 3 4 5
• GLOBAL 5..... ☐	0 1 2 3 4
4- ALTERACIONES FORMALES DEL PENSAMIENTO	
• Descarrilamiento	0 1 2 3 4 5
• Tangencialidad/ Incoherencia	0 1 2 3 4 5
• Ilogicalidad	0 1 2 3 4 5

• Circunstancialidad	0 1 2 3 4 5
• Presión del habla	0 1 2 3 4 5
• Distraibilidad en el discurso	0 1 2 3 4 5
• Asociaciones fonéticas	0 1 2 3 4 5
• GLOBAL 5..... ☐	0 1 2 3 4
5- AFECTO INAPROPIADO 5..... ☐	0 1 2 3 4

APPENDIX 6

The Spanish version of Scale for the Assessment of Negative Symptoms - SAPS

SANS
1- APLANAMIENTO AFECTIVO
• Inexpresividad facial 0 1 2 3 4 5
• Descenso de movimientos espontáneos 0 1 2 3 4 5
• Descenso de gestos durante el discurso 0 1 2 3 4 5
• Pobre contacto visual 0 1 2 3 4 5
• Falta de respuesta emocional 0 1 2 3 4 5
• Falta de inflexiones vocales 0 1 2 3 4 5
• GLOBAL 0 1 2 3 4 5..... ☐
2- ALOGIA
• Pobreza en la cantidad del lenguaje 0 1 2 3 4 5
• Pobreza en el contenido del lenguaje 0 1 2 3 4 5
• Bloqueo del discurso 0 1 2 3 4 5
• Aumento en el tiempo de latencia al responder 0 1 2 3 4 5

• GLOBAL	0 1 2 3 4
5..... ☐	
3- AVOLICIÓN-APATÍA	
• Aseo/ higiene	0 1 2 3 4 5
• Faltas de asistencia al trabajo/ escuela	0 1 2 3 4 5
• Falta de energía física	0 1 2 3 4 5
• GLOBAL	0 1 2 3 4
5..... ☐	
4- ANHEDONIA-ASOCIABILIDAD	
• Interés y actividades recreativas	0 1 2 3 4 5
• Interés y actividad sexual	0 1 2 3 4 5
• Habilidad por establecer relaciones íntimas	0 1 2 3 4 5
• Relaciones con amigos	0 1 2 3 4 5
• GLOBAL	0 1 2 3 4
5..... ☐	
5- ATENCIÓN	
• Inatención en situaciones sociales	0 1 2 3 4 5
• Inatención durante la exploración	0 1 2 3 4 5
• GLOBAL	0 1 2 3 4

5..... ☐

APPENDIX 7

Spanish shortened version of the Scale of Unawareness of Mental Disorder -SUMD-

CUESTIONARIO SUMD

1. Conciencia de poseer un desorden ☐
2. Conciencia de los efectos de la medicación ☐
3. Conciencia de las consecuencias sociales del desorden ☐

Conciencia de poseer un desorden

Ítem no relevante

Conciencia

Conciencia intermedia

No hay conciencia

Conciencia de los efectos de la medicación

Ítem no relevante

Conciencia

Conciencia intermedia

No hay conciencia

Conciencia de las consecuencias sociales del desorden mental

Ítem no relevante
Conciencia
Conciencia intermedia
No hay conciencia

APPENDIX 8

Original publications related with this thesis

"Brain grey matter abnormalities related to lack of insight in psychosis: a voxel-based morphometry and meta-analytic investigation" Submitted

Diana Tordesillas-Gutierrez, Rosa Ayesa-Arriola, Jennifer L. Robinson, Javier Lopez-Morinigo , Anthony David, Jesus Pujol, Benedicto Crespo-Facorro

"Grey matter volume differences in non-affective psychosis and the effects of age of onset on grey matter volumes: A voxelwise study".

Tordesillas-Gutierrez D, Koutsouleris N, Roiz-Santiañez R, Meisenzahl E, Ayesa-Arriola R, Marco de Lucas E, Soriano-Mas C, Suarez-Pinilla P, Crespo-Facorro B

Schizophrenia Research May;164(1-3):74-82

IF: 3,923 / Q1

APPENDIX 9

List of publications from the candidate

1. FERRO A, ROIZ-SANTIÁÑEZ R, ORTÍZ-GARCÍA DE LA FOZ V, TORDESILLAS-GUTIÉRREZ D, AYESA-ARRIOLA R, DE LA FUENTE N, FAÑANÁS L, BRAMBILLA P, CRESPO-FACORRO B. A cross-sectional and longitudinal structural magnetic resonance imaging study of the post-central gyrus in first-episode schizophrenia patients. *Psychiatry Res-Neuroim*. 2015 Jan 30;231(1):42-9. IF: 2,424 / Q2

2. ROIZ-SANTIÁÑEZ R, ORTIZ-GARCÍA DE LA FOZ V, AYESA-ARRIOLA R, TORDESILLAS-GUTIÉRREZ D, JORGE R, VARELA-GÓMEZ N, SUÁREZ-PINILLA P, CÓRDOVA-PALOMERA A, NAVASA-MELADO JM, CRESPO-FACORRO B. No progression of the alterations in the cortical thickness of individuals with schizophrenia-spectrum disorder: a three-year longitudinal magnetic resonance imaging study of first-episode patients. *Psychol Med*. 2015 Oct;45(13):2861-71. IF: 5,938 / D1*

3. SUÁREZ-PINILLA P, ROIZ-SANTIAÑEZ R, ORTIZ-GARCÍA DE LA FOZ V, GUEST PC, AYESA-ARRIOLA R, CÓRDOVA-PALOMERA A, TORDESILLAS-GUTIERREZ D, CRESPO-FACORRO B. Brain structural and clinical changes after first episode psychosis: Focus on cannabinoid receptor 1 polymorphisms. *Psychiatry Res-Neuroim*. 2015 Aug 30;233(2):112-9. IF: 2,424 / Q2*

4. TORDESILLAS-GUTIERREZ D, KOUTSOULERIS N, ROIZ-SANTIAÑEZ R, MEISENZAHL E, AYESA-ARRIOLA R, MARCO DE LUCAS E, SORIANO-MAS C, SUAREZ-PINILLA P, CRESPO-FACORRO B. Grey matter volume differences in non-affective psychosis and the effects of age of onset on grey matter volumes: A voxelwise study. *Schizophr Res*. 2015 May;164(1-3):74-82. IF: 3,923 / Q1*

5. ROIZ-SANTIÁÑEZ R, AYESA-ARRIOLA R, TORDESILLAS-GUTIÉRREZ D, ORTIZ-GARCÍA DE LA FOZ V, PÉREZ-IGLESIAS R, PAZOS A, SÁNCHEZ E, CRESPO-FACORRO B. Three-year longitudinal population-based volumetric MRI study in first-episode schizophrenia spectrum patients. *Psychol Med*. 2014 Jun;44(8):1591-604. IF: 5,938 / D1

6. THOMPSON PM, STEIN JL, MEDLAND SE, HIBAR DP, VASQUEZ AA, RENTERIA ME, TORO R, JAHANSHAD N, SCHUMANN G, FRANKE B, WRIGHT MJ, MARTIN NG, AGARTZ I, ALDA M, ALHUSAINI S, ALMASY L, ALMEIDA J, ALPERT K, ANDREASEN NC, ANDREASSEN OA,APOSTOLOVA LG, APPEL K, ARMSTRONG NJ, ARIBISALA B, BASTIN ME, BAUER M, BEARDEN CE, BERGMANN O, BINDER EB, BLANGERO J, BOCKHOLT HJ, BØEN E, BOIS C, BOOMSMA DI, BOOTH T, BOWMAN IJ, BRALTEN J, BROUWER RM, BRUNNER HG, BROHAWN DG, BUCKNER RL, BUITELAAR J, BULAYEVA K, BUSTILLO JR, CALHOUN VD, CANNON DM, CANTOR RM, CARLESS MA, CASERAS X, CAVALLERI GL, CHAKRAVARTY MM, CHANG KD, CHING CR, CHRISTOFOROU A, CICHON S, CLARK VP, CONROD P, COPPOLA G, CRESPO-FACORRO B, CURRAN JE, CZISCH M, DEARY IJ, DE GEUS EJ, DEN BRABER A, DELVECCHIO G, DEPONDT C, DE HAAN L, DE ZUBICARAY GI, DIMA D, DIMITROVA R, DJUROVIC S, DONG H, DONOHOE G, DUGGIRALA R, DYER TD, EHRLICH S, EKMAN CJ, ELVSÅSHAGEN T, EMSELL L, ERK S, ESPESETH T, FAGERNESS J, FEARS S, FEDKO I, FERNÁNDEZ G, FISHER SE, FOROUD T, FOX PT, FRANCKS C, FRANGOU S, FREY EM, FRODL T, FROUIN V, GARAVAN H, GIDDALURU S, GLAHN DC, GODLEWSKA B, GOLDSTEIN RZ, GOLLUB RL, GRABE HJ, GRIMM O, GRUBER O, GUADALUPE T, GUR RE, GUR RC, GÖRING HH, HAGENAARS S, HAJEK T, HALL GB, HALL J, HARDY J, HARTMAN CA, HASS J, HATTON SN, HAUKVIK UK, HEGENSCHEID K, HEINZ A, HICKIE IB, HO BC, HOEHN D, HOEKSTRA PJ, HOLLINSHEAD M, HOLMES AJ, HOMUTH G, HOOGMAN M, HONG LE, HOSTEN N, HOTTENGA JJ, HULSHOFF POL HE, HWANG KS, JACK CR JR, JENKINSON M, JOHNSTON C, JÖNSSON EG, KAHN RS, KASPERAVICIUTE D, KELLY S, KIM S, KOCHUNOV P,

KOENDERS L, KRÄMER B, KWOK JB, LAGOPOULOS J, LAJE G, LANDEN M, LANDMAN BA, LAURIELLO J, LAWRIE SM, LEE PH, LE HELLARD S, LEMAÎTRE H, LEONARDO CD, LI CS, LIBERG B, LIEWALD DC, LIU X, LOPEZ LM, LOTH E, LOURDUSAMY A, LUCIANO M, MACCIARDI F, MACHIELSEN MW, MACQUEEN GM, MALT UF, MANDL R, MANOACH DS, MARTINOT JL, MATARIN M, MATHER KA, MATTHEISEN M, MATTINGSDAL M, MEYER-LINDENBERG A, MCDONALD C, MCINTOSH AM, MCMAHON FJ, MCMAHON KL, MEISENZAHL E, MELLE I, MILANESCHI Y, MOHNKE S, MONTGOMERY GW, MORRIS DW, MOSES EK, MUELLER BA, MUÑOZ MANIEGA S, MÜHLEISEN TW, MÜLLER-MYHSOK B, MWANGI B, NAUCK M, NHO K, NICHOLS TE, NILSSON LG, NUGENT AC, NYBERG L, OLVERA RL, OOSTERLAAN J, OPHOFF RA, PANDOLFO M, PAPALAMPROPOULOU-TSIRIDOU M, PAPMEYER M, PAUS T, PAUSOVA Z, PEARLSON GD, PENNINX BW, PETERSON CP, PFENNIG A, PHILLIPS M, PIKE GB, POLINE JB, POTKIN SG, PÜTZ B, RAMASAMY A, RASMUSSEN J, RIETSCHEL M, RIJPKEMA M, RISACHER SL, ROFFMAN JL, ROIZ-SANTIAÑEZ R, ROMANCZUK-SEIFERTH N, ROSE EJ, ROYLE NA, RUJESCU D, RYTEN M, SACHDEV PS, SALAMI A, SATTERTHWAITE TD, SAVITZ J, SAYKIN AJ, SCANLON C, SCHMAAL L, SCHNACK HG, SCHORK AJ, SCHULZ SC, SCHÜR R, SEIDMAN L, SHEN L, SHOEMAKER JM, SIMMONS A, SISODIYA SM, SMITH C, SMOLLER JW, SOARES JC, SPONHEIM SR, SPROOTEN E, STARR JM, STEEN VM, STRAKOWSKI S, STRIKE L, SUSSMANN J, SÄMANN PG, TEUMER A, TOGA AW, TORDESILLAS-GUTIERREZ D, TRABZUNI D, TROST S, TURNER J, VAN DEN HEUVEL M, VAN DER WEE NJ, VAN EIJK K, VAN ERP TG, VAN HAREN NE, VAN 'T ENT D, VAN TOL MJ, VALDÉS HERNÁNDEZ MC, VELTMAN DJ, VERSACE A, VÖLZKE H, WALKER R, WALTER H, WANG L, WARDLAW JM, WEALE ME, WEINER MW, WEN W, WESTLYE LT, WHALLEY HC, WHELAN CD, WHITE T, WINKLER AM, WITTFELD K, WOLDEHAWARIAT G, WOLF C, ZILLES D, ZWIERS MP, THALAMUTHU A, SCHOFIELD PR, FREIMER NB, LAWRENCE NS, DREVETS W; ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE, EPIGEN CONSORTIUM, IMAGEN CONSORTIUM, SAGUENAY YOUTH STUDY (SYS) GROUP. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav.* 2014 Jun;8(2):153-82. doi: 10.1007/s11682-013-9269-5. IF: 4,598 / Q1

7. VÁZQUEZ BOURGON J, MATA I, ROIZ-SANTIÁÑEZ R, AYESA-ARRIOLA R, SUÁREZ PINILLA P, TORDESILLAS GUTIÉRREZ D, VÁZQUEZ BARQUERO JL, CRESPO-FACORRO B. A Disrupted-in-Schizophrenia 1 Gene Variant is Associated with Clinical Symptomatology in Patients with First-Episode Psychosis. *Psychiatry Investig*. 2014 Apr;11(2):186-91.IF: 1,28 / Q3

8. JORGE RE, ACION L, WHITE T, TORDESILLAS-GUTIERREZ D, PIERSON R, CRESPO-FACORRO B, MAGNOTTA VA. White matter abnormalities in veterans with mild traumatic brain injury. *Am J Psychiatry*. 2012 Dec 1;169(12):1284-91. IF: 14,721 / Q1

9. ROIZ-SANTIÁÑEZ R, PÉREZ-IGLESIAS R, ORTÍZ-GARCÍA DE LA FOZ V, TORDESILLAS-GUTIÉRREZ D, MATA I, GONZÁLEZ-MANDLY A, PAZOS A, TABARÉS-SEISDEDOS R, VÁZQUEZ-BARQUERO JL, CRESPO-FACORRO B. One year longitudinal study of the straight gyrus morphometry in first-episode schizophrenia-spectrum patients. *Psychiatry Res-Neuroim*. 2012 Apr 30;202(1):80-3. IF: 3,364 / Q2

10. ROIZ-SANTIÁÑEZ R, TORDESILLAS-GUTIÉRREZ D, ORTÍZ-GARCÍA DE LA FOZ V, AYESA-ARRIOLA R, GUTIÉRREZ A, TABARÉS-SEISDEDOS R, VÁZQUEZ-BARQUERO JL, CRESPO-FACORRO B. Effect of antipsychotic drugs on cortical thickness. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Schizophr Res*. 2012 Oct;141(1):22-8. IF: 4,59 / Q1

11. CRESPO-FACORRO B, ROIZ-SANTIÁÑEZ R, PÉREZ-IGLESIAS R, MATA I, RODRÍGUEZ-SÁNCHEZ JM, TORDESILLAS-GUTIÉRREZ D, ORTÍZ-GARCÍA DE LA FOZ V, TABARÉS-

SEISDEDOS R, SÁNCHEZ E, ANDREASEN N, MAGNOTTA V, VÁZQUEZ-BARQUERO JL. Sex-specific variation of MRI-based cortical morphometry in adult healthy volunteers: The effect on cognitive functioning. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011 Mar 30;35(2):616-23. IF: 2,877 / Q2

12. CRESPO-FACORRO B, ROIZ SANTIAÑEZ R, PEREZ-IGLESIAS R, RODRÍGUEZ-SÁNCHEZ JM, MATA I, TORDESILLAS GUTIERREZ D, SANCHEZ E, TABARES SEISDEDOS R, ANDREASEN N, MAGNOTTA V, VÁZQUEZ-BARQUERO JL. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. *Psychol Med*. 2011 Jul;41(7):1449-60. IF: 5,200 / Q1

13. ROIZ-SANTIÁÑEZ R, PÉREZ-IGLESIAS R, DE LA FOZ VO, TORDESILLAS-GUTIÉRREZ D, MATA I, DE LUCAS EM, PAZOS A, TABARÉS-SEISDEDOS R, VÁZQUEZ-BARQUERO JL, CRESPO-FACORRO B. Straight gyrus morphology in first-episode schizophrenia-spectrum patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011 Jan 15;35(1):84-90. IF: 2,877 / Q2

14. CRESPO-FACORRO B, ROIZ-SANTIÁÑEZ R, QUINTERO C, PÉREZ-IGLESIAS R, TORDESILLAS-GUTIÉRREZ D, MATA I, RODRÍGUEZ-SÁNCHEZ JM, GUTIÉRREZ A, VÁZQUEZ-BARQUERO JL. Insular cortex morphometry in first-episode schizophrenia-spectrum patients: Diagnostic specificity and clinical correlations. *J Psychiatr Res*. 2010;44(5):314-20. IF: 3,723 / Q1

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16. LAIRD AR, ROBINSON JL, MCMILLAN KM, TORDESILLAS-GUTIÉRREZ D, MORAN ST, GONZALES SM, RAY KL, FRANKLIN C, GLAHN DC, FOX PT, LANCASTER JL. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: Validation of the Lancaster transform. *Neuroimage*. 2010 Jun; 51(2):677-83. IF: 5,739 / Q1

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