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

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ABSTRACT

Previous evidence indicates that structural brain alterations are already present in the early phases of psychosis. In this study we aim to investigate the relationships among the different diagnoses in the spectrum of non-affective psychosis. A hundred-and-one first-episode psychosis patients (FEP) and 69 healthy volunteers, matched for age, gender, handedness and educational level were analyzed by structural MRI and high-dimensional voxel-based morphometry as implemented in SPM8 software. We obtained three main results: (1) FEP patients showed reduction of grey matter volume (GMV) in the frontal, temporal and occipital lobes, left insula and cerebellum. (2) Age of disease onset was an important factor revealing a gradual decrease of GMV (healthy controls > late onset > intermediate onset > early onset) in the frontal, temporal and occipital lobes, insula and cerebellum. (3) A gradual reduction of GMV related to diagnosis spectrum in the frontal, temporal, parietal and occipital lobes of schizophrenia patients being the most affected. These results suggest that an earlier onset of psychosis is linked to an earlier disease-related disruption of structural brain development, which may be most pronounced in schizophrenia compared to other psychoses.

1. Introduction

Schizophrenia is a complex and chronic brain disorder. Although its precise etiological and pathophysiological underpinnings are still poorly understood, the prevailing explanatory theory posits that disturbances in neurodevelopmental processes (early or late insults) may prompt the onset of the illness during late adolescence or early adulthood (Rapoport and Gogtay, 2011).

In the past decades there has been increasing interest in exploring likely cortical structural anomalies in psychosis patients, as evidenced from magnetic resonance imaging (MRI) studies (Haijma et al., 2013). The potential effect of antipsychotic medication (Dorph-Petersen et al., 2005) and chronicity (Weinberger and McClure, 2002) on gray matter volume (GMV) can be properly controlled when individuals with a first episode of psychosis, who had been minimally treated with antipsychotics (or any other form of treatment), are investigated. Voxel-based morphometry (VBM) studies in first-episode patients have shown that the disorder is associated with relatively small reductions in GMV affecting a number of distributed brain regions (i.e., the frontal, cingulate, temporal and parietal cortices, the striatum, insula, and the thalamus) (Vita et al., 2006; Ellison-Wright et al., 2008). Nonetheless, the most consistent findings have been a reduction in total brain volume and an enlargement of the lateral and third ventricle volumes (Honea et al., 2008; Bora et al., 2011). In addition, reduced cortical thickness has been observed in the frontal, temporal, occipital and parietal regions (Kuperberg et al., 2003; Rimol et al., 2010). This evidence, together with imaging studies in high-risk populations (Koutsouleris et al., 2009; Rimol et al., 2010) and relatives (Boos et al., 2007), supports the hypothesis of an early disruption of brain development in schizophrenia (Murray and Lewis, 1987; Weinberger, 1987).

Previous region of interest (ROI) magnetic resonance imaging (MRI) 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

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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 the 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., 2015) 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 at intake.

Nonetheless ROI 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). 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 from a disturbance of normal brain maturation processes (Koutsouleris et al., 2014). Age of onset has been conceptualized as a proxy measure of the severity of 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 (Matsumoto et al., 2001; Gogtay et al., 2011; Jung et al., 2012).

We aimed to investigate the relationships between structural brain abnormalities and age of illness onset in schizophrenia by means of VBM. To address these questions, we explored a large sample of adult patients with first-episode schizophrenia spectrum disorders and a group of demographically matched healthy controls. Our specific hypothesis included the following: (1) Patients with a diagnostic of schizophrenia would show greater reductions in GMV compared to other schizophrenia-spectrum psychoses .(2) An earlier age of illness onset may determine the presence of marked structural brain anomalies.

2. Methods

2.1. Study setting and financial support

Data for the present investigation were obtained from an ongoing epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran et al., 2008) This program was approved by the local institutional review board conforming to international standards for research ethics. Patients meeting inclusion criteria and their families provided written informed consent to be included in the PAFIP.

2.2. Subjects

Patients included in PAFIP had to meet the following criteria: (1) age 15–60 years; (2) living in the catchment area; (3) experiencing a first episode of psychosis; (4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; and (5) meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, brief psychotic disorder, or schizoaffective disorder. Patients were excluded when meeting DSM-IV criteria for (1) drug dependence (except nicotine dependence), (2) mental retardation, and when having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2001) by an independent psychiatrist 6 months after the initial contact.

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). HCs 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 confirmed by clinical records and family interview. After a detailed description of the study, each subject gave written informed consent to participate.

2.3. Clinical assessment

Clinical symptoms were rated using the Brief Psychiatric Rating Scale total (BPRS) (Overall and Gorman, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The same trained psychiatrist (BC-F) completed the clinical evaluation of patients. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971).

Following disease-related time intervals were retrospectively evaluated: Duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such symptom to be considered, there should be no return to previous stable level of functioning) to the date of initiation an adequate dose of antipsychotic drug taken regularly. Duration of untreated psychosis (DUP) defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug 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.

2.4. Medication assessment

Patients went through a pharmacological protocol and were randomly assigned to treatment with risperidone (n = 17), olanzapine (n = 20), quetiapine (n = 17), ziprasidone (n = 17), aripiprazole (n = 15) or haloperidol (n = 15). Only three patients had been minimally treated prior to randomization of antipsychotic treatments (two in the aripiprazole group and one in the risperidone group). Patients had a baseline structural MRI as soon as they could tolerate the procedure following the initiation of treatment (4.43 weeks).

2.5. MRI data acquisition and image processing

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 × 19.5 cm, slice thickness = 1.5 mm and a matrix of 256 × 192.

Voxel-based morphometry (Ashburner and Friston, 2000) was performed using the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/download/), an extension of the SPM5 software package (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). The VBM preprocessing included the following steps:

First, inspection for scanner artifacts and gross abnormalities for each subject, then, images were segmented into grey matter, white matter and cerebrospinal fluid, in order to improve the quality of segmentation a