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Identification of two clusters within schizophrenia with different structural, functional and clinical characteristics

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ABSTRACT

Background: Several biologically distinct subgroups may coexist within schizophrenia, which may hamper the necessary replicability to translate research findings into clinical practice.
Methods: Cortical thickness, curvature and area values and subcortical volumes of 203 subjects (121 schizophrenia patients, out of which 64 were first episodes), 60 healthy controls and 22 bipolar patients were used to identify clusters using principal components and canonical discriminant analyses. Regional glucose metabolism using positron emission tomography, P300 event related potential, baseline clinical data and percentage of improvement with treatment were used to validate possible clusters based on MRI data.
Results: All the controls, the bipolar patients and most of the schizophrenia patients were grouped in a cluster (cluster A). A group of 24 schizophrenia patients (12 first episodes), characterized by large intrinsic curvature values, was identified (cluster B). These patients, but not those in cluster A, showed reduced thalamic and cingulate glucose metabolism in comparison to controls, as well as a worsening of negative symptoms at follow-up. Patients in cluster A showed a significant putaminal metabolic increase, which was not observed for those in cluster B. P300 amplitude was reduced in patients of both clusters, in comparison to controls.
Conclusions: Results of this study support the existence of a biologically distinct group within the schizophrenia syndrome, characterized by increased cortical curvature values, reduced thalamic and cingulate metabolism, lack of the expected increased putaminal metabolism with antipsychotics and persistent negative symptoms.

1. Introduction

More than 8000 genetic variants may contribute to the risk of suffering from schizophrenia (Ripke et al., 2013) and recent research supports schizophrenia subtypes characterized by both specific clinical presentation and clusters of genetic variants (Arnedo et al., 2014). Considering the likely effect of genetic variation upon brain structure (Papiol et al., 2005), distinct groups within schizophrenia might be characterized by specific patterns of cerebral alterations.

A possible approach to identify such groups is attempting data-driven (a priori independently of diagnosis) cluster segregation, starting from plausible cerebral variables: i) previously associated to schizophrenia as a group but not unanimously replicated across samples, ii) not primarily related to confounders, such as treatment or chronicity, iii) with likely genetic influence, iv) associated to neurodevelopment and v) likely related to relevant clinical and biological variables.

Cortical thickness may prove useful to this purpose, since cortical thinning has been reported in first-episode (FE) and chronic schizophrenia patients (Crespo-Facorro et al., 2011) (although not unanimously (van Haren et al., 2011)) and in antipsychotic naïve patients (Venkatasubramanian et al., 2008). Cortical thickness is highly heritable (Goldman et al., 2009), with a complex relation with genetic background in schizophrenia (Blasi et al., 2013) and early experience (Whittle et al., 2014). Moreover, cortical thickness increases during normal neurodevelopment (Schmitt et al., 2014) and v) has been associated to treatment response (Szeszko et al., 2012) and cognition (Cassidy et al., 2014) in FE patients.

Abbreviations: CNS, central nervous system; DLPF, dorsolateral prefrontal cortex; EOG, electrooculogram; FE, first-episode; Fig, figure; G1, group 1; G2, group 2; G3, Group 3; HC, healthy controls; LDF, linear discriminant function; MRI, magnetic resonance imaging; PCA, principal component analysis; PET, positron emission tomography; ROI, regions of interest; SNP, single nucleotide polymorphism; Sz A, schizophrenia patients cluster A; Sz B, schizophrenia patients cluster B; Sz, schizophrenia.

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Cortical curvature measures cortical folding and may reflect different neurobiological underpinnings (Ronan et al., 2011). It may contribute to the proposed clustering since higher (Falkai et al., 2007), normal (Fornito et al., 2008) and reduced (Cachia et al., 2008) gyrification indexes have been reported in schizophrenia and FE patients have shown altered gyrification (Harris et al., 2004). Furthermore, gyrification has genetic underpinnings (Piao et al., 2004) and cerebral gyrification takes place largely in the third trimester (White and Hilgetag, 2008), thus, altered gyrification may result from developmental events in this period. Finally, gyrification is associated to formation of proper cortico-cortical connections (Van Essen, 1997).

The present study has reanalyzed data from previous samples assessing cortical thickness and curvature in order to blindly investigate clustering of schizophrenia patients. Regional cortical area was also included in analyses, since it may convey different information than other structural data in schizophrenia (Rimol et al., 2012). In addition, subcortical volumes were included, given the caudate and thalamic volume association with poor-prognosis schizophrenia (Molina et al., 2010b). Regional cortical volumes were not included since they are largely explained by the corresponding area and thickness. In order to validate clusters, other data were collected, including clinical (baseline symptoms and variation with treatment) and biological (glucose metabolic rate, P300 amplitude and latency) parameters. Chronic bipolar subjects were introduced into the analyses to discard clusters being primarily related to chronicity and/or treatment. Therefore, rather than directly comparing anatomical values depending on clinical diagnosis (schizophrenia, bipolar, healthy controls), our approach was looking for biologically distinct clusters, not considering diagnosis a priori as the primary classifying factor. According to our hypothesis, clusters identified on basis of structural alteration would be expected to be treatment-independent, associated to clinical outcome and/or presentation and associated to other relevant biological markers in order to be considered as valid.

2. Methods and materials

2.1. Sample description

Sample included 203 subjects: 121 schizophrenia (Sz) (DSM-IV criteria) patients (64 patients were FE), 22 chronic bipolar patients and 60 healthy controls (HC). Patients were recruited during a psychotic relapse (chronic patients) or first psychotic episode (FE), following their admission to a psychiatric short-term unit. After release they were treated and followed in an outpatient clinic.

MRI data were collected over a 15-year period, in the context of several research projects (identification of cerebral correlates of treatment-resistance (Molina et al., 2003b), early stages (Molina et al., 2003a) of schizophrenia, differences between major psychoses (Molina et al., 2010a) and effects of antipsychotics on brain structure (Molina et al., 2005a)).

Eighteen chronic Sz patients had been treated prior to inclusion with typical antipsychotics, and 39 with atypical antipsychotics. They were included at the time of psychotic relapse. Eighteen bipolar patients were receiving atypical antipsychotics. FE patients had received antipsychotic treatment for less than three days prior to MRI.

Additional data used to validate the hypothesized clusters included:

- Resting metabolic glucose rates in DLPF, orbital, parietal, occipital and temporal lobes, cingulate, hippocampus, caudate, thalamus and pallidum were measured with F_{18}-FDG PET during an attention test, in 64 Sz patients (41 FE) and 34 HC.
- P300 amplitude and latency were measured in 52 Sz patients and 24 HC.
- Clinical status at inclusion was assessed using Positive/Negative Symptoms scale in Schizophrenia (Kay et al., 1987).
- Improvement percentage in 91 Sz patients (40 FE) after 6 months follow-up.

Exclusion criteria included history of substance dependence, any current comorbid Axis I diagnosis or psychoactive treatment, serious head trauma or any neurological or systemic disorder with known effects on CNS.

After complete description of the study to the subjects, written informed consent was obtained. Full comprehension of the procedures was checked during the consent procedure. The research boards of the Hospitals of Salamanca and Doce de Octubre endorsed the study.

The hospital ethical committee approved the study. All techniques and procedures were conducted in accordance with the ethical standards of the Helsinki Declaration.

2.2. Imaging data collection

2.2.1. MRI

Detailed description of MRI acquisition is available elsewhere (Molina et al., 2003b, 2005a, 2010a). In summary, 3D SPGR T1 MRI studies were acquired using a 1.5 system (159 cases using Philips Gyroscan and 44 using General Electrics 1.5 scanner). For each subject, a 3D T1 acquisition was obtained with following parameters: TR = 7.5 ms, TE = 3.5 ms, Flip angle: 8°, 0.78 × 0.78, FOV = 240 mm × 240 mm, matrix size = 256 × 256, in 70–150 slices (thickness between 1.5 mm and 3 mm).

Given their relevance in schizophrenia, the following regions were included in the initial clustering analysis (left and right separately): caudal anterior cingulate, caudal middle frontal, cuneus, inferior parietal, medial orbitofrontal, parahippocampal, pars orbitalis, pars triangularis, precentral, rostral anterior cingulate, rostral middle frontal, superior frontal, superior temporal and insula. For each of these regions, thickness, area and curvature were calculated using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). In addition, subcortical volumes (pallidum, thalamus, caudate and hippocampus) were assessed.

2.2.2. PET acquisition and analyses

Detailed description of acquisition and quantification is available elsewhere (Rimol et al., 2012; Van Essen, 1997). In summary, PET studies were obtained in SIEMENS Exact 47 tomography, 20 min after injecting 370 MBq of 18FDG in resting condition. Image values were proportionally normalized to global count rate for each PET. To perform metabolic measurements of different brain structures, a two-step procedure was adopted to co-register MRI and PET, hence, defining regions of interest (ROI) onto each subject's Talairach co-ordinate system. ROI activity was calculated as the portion of tissue mask contained in the set of grid-cells defining the ROI.

2.2.3. P300

Details are given elsewhere (Molina et al., 2005b). A standard oddball paradigm was used and subjects were instructed to mentally count the number of target tones. Electroencephalograms were recorded from 16 scalp sites, according to 10/20 International System and analyses on P300 were performed on Pz site after correction of EOG

Fig. 1. Scatter plots of the distribution of the values of the first principal component for curvature, thickness, area and subcortical volume, respectively. Subjects are identified by color code. Outliers are marked in red. In the lower row, Scatter plots for the three PCs of the total set of MRI markers, showing different symbols for the final cluster and the type of observation. In the three dimensional scatter plot for these PCs, in subpanel e, the two clusters have been identified with different symbols, showing that patients identified primarily on the basis of higher mean curvature also showed globally smaller thickness and area. Moreover, in subpanel f, the observations have also been represented with different symbols for healthy controls, Sz cases and BP cases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)