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ORIGINAL PAPER

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Dorsolateral prefrontal and superior temporal volume deficits in first-episode psychoses that evolve into schizophrenia

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Abstract Regions with a likely involvement in schizophrenia may differ between patients with first-episodes of psychosis respectively with and without evolution into schizophrenia following the initial episode. We have used magnetic resonance imaging (MRI) to assess the volumes of dorsolateral prefrontal (DLPF) and superior temporal gyrus (STG) in a group of 37 first-episode psychotic patients. After an initial MRI study performed by the time of the first episode, the subjects were followed for two years. After this period 22 cases were diagnosed with schizophrenia, while the other 15 did not show clinical evidence for this illness. A Talairach-based tool was used for segmentation and volumetry of the MRI scans. A group of 44 healthy controls was used for comparison and, using lineal regression, to control for the normal effects of age and intracranial volume on the regional parameters of the patients. By the time of their first episode, patients with schizophrenia had significantly less grey matter in the right DLPF and STG regions as compared to both controls and FE without schizophrenia. Nevertheless, these parameters could not predict final diagnosis in a discriminant analysis model. Our findings indicate that subtle structural defects are already found by the time of the first psychotic break in schizophrenia, although clinical implications for these differences seem unclear.

Key words schizophreniform · schizophrenia · magnetic resonance · prefrontal · superior temporal gyrus

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Introduction

Structural alterations of the prefrontal (PF) region and superior temporal gyrus (STG) are well known findings in schizophrenia (Shenton et al. 2001). First episodes (FE) of psychosis with evolution to schizophrenia might show at the index episode significant differences in these regions as compared to other FE without evolution to schizophrenia. This possibility is suggested by previous studies and might have theoretical as well as prognostic implications. Among those studies, Hirayasu et al. (2001) showed that FE patients with schizophrenia but not affective psychosis showed a significant decrease in prefrontal grey matter (GM) in comparison to healthy controls. In the same line, Salokangas et al. (2002) reported decreased prefrontal volumes in FE schizophrenia as compared to healthy controls and psychotic depression. Moreover, hypofrontality was found in FE schizophrenia males but not in schizophreniform psychosis without evolution to schizophrenia (Molina et al. 2005a).

In the present work, we used magnetic resonance imaging (MRI) to compare the volumes of DLPF and STG regions amongst patients with a first psychotic episode respectively with and without evolution to schizophrenia in the following two years and a group of healthy controls. We expected that strucutrural differences, probably of small magnitude, could be evident by the time of the first psychotic episode between patients with schizophrenia and the other two groups.

Participants and methods

Thirty-seven people (22 males) suffering from a first psychotic episode were enrolled in the study; all of them right-handed. These patients participated in a longitudinal study of first-break schizophrenia. They are part of a group of 48 first episodes, from which follow-up information was available only for the 37 here included, as 11 cases were lost during follow-up. To be included in the protocol, the patients had to show a first psychotic episode with symptoms lasting longer than one week, not attributable to organic or toxic causes, and not related to another axis I disorder. The absence of marked stressors, according to Diagnostic and Statistical Manual, fourth edition (DSM-IV), and clearly related to the episode was also required for inclusion. These criteria were aimed at avoiding the inclusion of patients with transient psychotic symptoms. The imaging studies took place within two weeks following enrolment.

After inclusion, all patients were followed for two years on an outpatient basis with monthly visits, to confirm or rule out a diagnosis of schizophrenia at the end of this period. After this follow-up period, two experienced psychiatrists (VM and JS), blind to the results of the MRI scans, diagnosed each patient and decided if the index episode was a first break of schizophrenia or, instead, a single psychotic episode that did not evolve into schizophrenia. For this final diagnosis they used all the available follow-up information (including total duration of significant symptoms), a semi-structured interview (SCID, Clinical Version) (First et al. 1997) and the information provided by the families and clinical personnel. For diagnostic purposes, the duration of symptoms was calculated covering the period before and after initiation of treatment.

According to the final diagnosis, the 37 patients were divided into two groups. The schizophrenia group (SzFE from here on) included 22 patients (14 males, 20 with paranoid schizophrenia, and 2 with undifferentiated schizophrenia according to DSM-IV criteria; age 23.0 ± 3.5 yr). The remaining 15 patients (8 males) formed the group of non-schizophrenic patients (NonSzFE from here on) that included 13 cases of schizophreniform psychosis and two cases of brief psychotic disorder (with a symptom duration of 3 weeks), likewise per DSM-IV criteria. Age in this group was 30.4 ± 8.5 y. This diagnosis meant that their psychotic episodes were shorter than required to be qualified as schizophrenia, did not show any other psychotic episode during follow-up and did not met schizophrenia criteria, including enduring negative symptoms, at the end of this period. The duration of the disease in the group of non-schizophrenics was shorter than 3 months in all cases. Patients in this group had shown psychotic symptoms for a period ranging between 3 and 12 weeks prior the MRI exam (mean 5 ± 7 weeks). During the weeks prior to inclusion they were untreated. The PANSS (Kay et al. 1987) scores did not differ between SzFE and NonSzFE patients by the time of inclusion (positive NonSzFE 19.5 ± 6.0, SzFE 20.6 ± 6.2; negative NonSzFE 12 ± 6.5, SzFE15.9 ± 6.5; general NonSzFE 35.8 ± 8.0, SzFE 39.5 ± 10.8).

Forty-four controls were also included (23 males, age 29.4 ± 9.0). They were recruited among hospital staff and through advertisments and received a small pay for their cooperation. To match the patient group, they had to have a lower than college education level and never received any psychiatric or neurological diagnosis or treatment. Psychiatric diagnoses were ruled out in this group with a semi-strucutured interview (SCID, controls version). Neither significant differences in age, nor in parental socioeconomic status (Hollingshead and Frederick 1953) (controls 2.1 ± 1.7, NonSzFE 2.1 ± 1.8, SzFE 2.2 ± 1.8), nor in years of education (controls 12.8 ± 4.9, NonSzFE patients 10.9 ± 5.9, SzFE patients 11.8 ± 7.0) were detected between any group pairs.

All patients were antipsychotic-naïve prior to the current episode; they were treated solely during one week prior to the MRI study. This was a practical means of enrolling a sample representative of the usual presentation of schizophrenia, avoiding a selection bias related to the ability of acute psychosis patients to cooperate during neuroimaging procedures. All patients received the same treatment during that period (haloperidol 10 mg qd, liquid formulation). In order to prevent dystonic reactions anticholinergic medication was administered during the days before scanning. Nursing personnel verified proper treatment compliance.

Patients in the SzFE group were maintained on antipsychotic treatment (ripseridone) for the entire follow-up period. In the NonSzFE group, the antipsychotic treatment was continued for a period of 6 to 12 months following initial study, on the basis of clinical criteria. After remission, treatment was mantained to prevent relapse, and the length of that period was decided on an individual basis. None of the non- schizophrenia patients presented enduring negative symptoms, disorganization or persistent behavioral alterations at the end of the follow-up period (i. e., more than one year after completing the treatment). The period of complete remission of these symptoms was greater than one year in all cases.

Exclusion criteria for patients and controls at intake were: mental retardation, neurological illness, MRI findings judged clinically relevant (from a neurological point of view) by a radiologist blinded to diagnosis, history of head injury with loss of consciousness, substance abuse criteria during the last 3 years (except for caffeine or nicotine), or any current treatment with known CNS action. Urinalyses were used in all cases to rule out a substance abuse as a cause for the psychotic episode.

After receiving full information, an informed consent form was signed by the patients and a first degree relative. The independent ethics committee endorsed the study.

Imaging method

MRI acquisition

Magnetic resonance imaging studies were acquired on a Philips Gyroscan 1.5T scanner using a T1-weighted 3D gradient echo sequence with the following parameters: matrix size 256 × 256, pixel size 0.9 × 0.9 mm (FOV 256 mm), flip angle 30°, echo time 4.6 ms, slice thickness ranging from 1.1 to 1.5 mm. T2-weighted sequences were also acquired for verification of CSF segmentations and for other clinical purposes (Turbo-Spin Echo, turbo factor 15, echo time 120 ms, matrix size 256 × 256, slice thickness 5.5 mm).

Segmentation and ROI definition

To obtain volume measurements of the main brain lobes, we used a method for semi-automated segmentation of the brain based on the Talairach reference system, similar to the method described previously (Andreasen et al. 1996; Kates et al. 1999). This method has been also used in similar studies measuring longitudinal volume changes in brain regions (Ho et al. 2003). Basically, we used a two step procedure (Desco et al. 2001). The first step involved editing the MRI to remove skull and extracranial tissue, and an initial segmentation of cerebral tissues into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). In a second stage, we applied the Talairach reference system (Talairach and Tournoux 1988) to define regions of interest (ROIs) and to obtain volume data. MR images were processed using locally developed software that incorporates a variety of image processing and quantification tools (Desco et al. 2001). We have used the same method in previous studies (Molina et al. 2003a, 2002, 2003b, 2004, 2005b).

The initial segmentation of cerebral tissues was performed using an automated method, currently included as a standard processing tool in the SPM (Statistical Parametric Mapping) program (Ashburner and Friston 1997), which classifies all MRI pixels into 4 tissue types: GM, WM, CSF, and "other tissues." The algorithm also removes the effect of radiofrequency field inhomogeneities (Ashburner and Friston 2000). This segmentation was checked for inconsistencies and manually corrected whenever necessary by an experienced radiologist blinded to the diagnosis.

In the second stage, the edited MRI (without extracranial tissue) was used to build the Talairach grid, and the ROIs were obtained by superimposing the 3D tissue masks corresponding to WM, GM, and CSF onto each subject's Talairach reference grid, where the regions of

interest were defined as sets of cells. On this MRI with the Talairach grid, volumes for each tissue type were measured by totalling the data from the grid cells associated with each ROI (Desco et al. 2001). Basically, Talairach normalization (Talairach and Tournoux 1988) consists of a piecewise linear transformation and tessellation of each brain into a grid of 1.056 cells. The image processing software is able to automatically calculate the 3D grid upon manual selection of the anterior and posterior commissures (AC and PC) and the mid-sagittal plane, on MR images where scalp and cerebellum were previously removed. Once the grid was calculated and adjusted to each particular brain, the regions of interest were defined as sets of cells, according to the Talairach atlas.

The validity of the Talairach-based procedure as a suitable automated segmentation tool in schizophrenia research has been previously proven (Andreasen et al. 1996; Kates et al. 1999). All manual procedures involved were performed by a single operator, thus avoiding any potential inter-rater variability and other operator-dependent errors. Repeatability of the tissue segmentation and quantification procedure was 99% for total volumes of gray and white tissue (Gispert et al. 2004).

The ROIs included dorsolateral prefrontal (DLPF) and STG regions, defined as the set of cells included in these regions according to the Talairach atlas (Talairach and Tournoux 1988). Measurements were made considering only the GM tissue contained within relevant cells in these regions. Both hemispheres were measured separately.

Statistics

Since age and total cranial size are known factors affecting regional cerebral volumes, their effect was removed by using the residuals from the regression models obtained from a group of healthy individuals (n = 44 in the present study), following the procedure of Pfefferbaum et al. (1992). After this correction, volume variables are expressed as deviations from the expected volumes in healthy individuals of the same age as the patient. Thus, negative residuals represent a quantitative measurement of volume deficit and vice versa. The regression parameters used for this transformation were obtained from a previous study (Molina et al. 2003b).

A multivariate general linear model (analysis of covariance) was used to compare those residuals with group (controls, NonSzFE patients, SzFE patients) and gender as factors. SPSS statistical software (10^{th} release) was used. The post hoc tests were performed only between the SzFE and controls and between SzFE and NonSzFE patients, in order to avoid redundant comparisons (i.e., we did not compare NonSzFE and controls, as both groups had been compared with SzFE patients according to the study hypothesis).

In order to analyze the capacity of differences to predict the final diagnosis of the patients, we included in a discriminant analysis the variables found to show significant between-groups differences. Our objective was to know if we could predict the evolution to schizophrenia from the MRI study obtained at the index episode. Thus, only data from SzFE and NonSzFE patients were introduced in the discriminant analysis model.

Results

All anatomic values were normally distributed in the three groups (Kolmogorov-Smirnoff test).

The test for between subject effects revealed a significant effect of group in the right DLPF and STG regions (Table 1). No significant interactions between gender and group were detected for these or for any other variable. In pair-wise comparisons, SzFE had significanly less gray matter volumes than healthy controls in the following regions right: DLPF (difference between means –1.82 standard error 0.85, 95% CI –3.52 to –0.13, p = 0.03) and right STG (difference in the means –0.48, se 0.20, 95% CI –0.89 to –0.06, p = 0.02).

In a similar fashion, SzFE showed less gray matter than NonSzFE in right DLPF (difference in the means –2.27 se 1.08, 95% CI –4.42 to –0.11, p = 0.03), and right STG (difference in the means –0.57, se 0.26, 95% CI –1.08 to –0.03, p = 0.03).

In the discriminant analysis right DLPF and right GTS, the regions with significant between-groups differences, could not predict the final diagnosis (Wilk's $\lambda = 0.96$, df = 2, p = 0.25). These parameters could not discriminate either between male (Wilk's $\lambda = 0.93$, df = 2, p = 0.54) or between female (Wilk's $\lambda = 0.88$, df = 2, p = 0.44) first episodes with or without a final diagnosis of schizophrenia

Discussion

Our main finding is that at the time of their first psychotic break, patients with poor prognosis (i. e., with a later diagnosis of schizophrenia) showed less right DLPF and STG volumes as compared to both controls and first psychotic episodes without evolution to schizophrenia. Nevertheless, this effect was quantitatively small and could not predict (from a statistical point of view) final diagnosis of the patients.

We are not aware of previous studies comparing regional volumes of first episodes depending on their evolution in the following years. However, other groups have compared regional volumes of first psychotic episodes respectively with schizophrenia and affective

Table 1 Volumes of each region included in the study for the three groups. We show the "raw" values (in cc) and the residuals calculated using the data of the helathy controls. * regions with statistically significant differences (p < 0.05) between the FE with schizophrenia patients and the other two groups. The statistical significance was assessed using the residuals resulting from controlling for the normal effects of age and intracranial volume (see Methods)

Males : females	Controls (n = 44) 23:21		SzFE patients (n = 22) 14: 8		NonSzFEpatients (= 15) 8:7		Type III square sum; F (p value)
	Raw values	residuals	Raw values	residuals	Raw values	residuals	
Left DLPF	30.80 (4.99)	0	33.01 (4.71)	0.29 (4.02)	32.62 (5.74)	2.11 (4.39)	53.09; 2.04 (0.13)
Right DLPF*	32.31 (5.13)	0	32.79 (4.26)	–1.84 (3.27)	32.40 (4.76)	0.42 (2.78)	59.09; 2.93 (0.05)
Left STG	11.14 (1.67)	0	12.05 (1.41)	–0.09 (0.85)	11.23 (2.00)	–0.13 (1.13)	0.33; 0.26 (0.77)
Right STG*	11.18 (1.45)	0	11.38 (1.27)	–0.43 (0.89)	11.14 (1.63)	0.10 (0.87)	3.94: 3.41 (0.03)

first episodes of psychoses. This is a somewhat similar approach to ours as it includes first episodes with poor and good prognosis. Among these studies, Salokangas et al. (2002) reported decreased prefrontal volumes in FE schizophrenia as compared to healthy controls and psychotic depression. Similar results were reported by Hirayasu et al. (2001), who showed that first episode patients with schizophrenia had a significant decrease in prefrontal GM as compared to controls. In this study the comparison group was composed of bipolar patients, which is different than in our case, and the decrement of GM in schizophrenia was left-sided. The lower PF volume in our SzFe patients is also coherent with other previous comparisons. Nopoulos et al. (1995) noted that first episode patients with schizophrenia had a significant decrement in frontal lobe tissue compared with normal subjects. Similar results were reported in FE of the disorganized type by Ohnuma et al. (1997), and a grey matter reduction in FE schizophrenia as compared to controls was found by Lim et al. (1996) and Fannon et al. (2000).

Nevertheless, lower prefrontal volume in FE of schizophrenia as compared to controls was not found by other groups (Bilder et al. 1994; Cahn et al. 2002; Crespo-Facorro et al. 2000b; DeLisi et al. 1991; Gilbert et al. 2001; Lawrie et al. 1999; Lieberman et al. 2001; Szeszko et al. 1999; Whitworth et al. 1998). That discrepancy might relate to methodological issues in image acquisition and proccesing or data analysis, although it may also relate to a significantly decreased volume in some but not all FE patients. Some progressive loss of frontal tissue may precede the first episode in high-risk subjects (Pantelis et al. 2003). Then, it seems plausible that only the patients with greater volume loss predating the initial psychotic break would show by that time a significant volume deficit. Therefore, depending on the proportion of patients with a higher frontal loss prior to illness onset, different cohorts might show or not a significantly lower PF volume. This possibility would be coherent with the small magnitude of the differences in our study, its poor predictive capacity and the dispersion of the individual data (Fig. 1).

A decreased volume of posterior STG has been shown in first episodes of schizophrenia as compared to controls and affective psychoses (Hirayasu et al. 1998). In addition, similar reductions have been reported for the left planum temporale, as well as for the bilateral sum of both Heschl's gyri (Hirayasu et al. 2000). In these studies left planum temporale was 15 % smaller in patients. Another group found a decrease in the volume of left planum temporale in patients with a first psychotic break including diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder (Sumich et al. 2002). In this study, left planum temporale was 22 % smaller in FE schizophrenia patients as compared to controls. A reduction of STG volume is also found in our study, although differences were only significant in the right side and its size was smaller. These discrepacies may be contributed by two methodological differences. First, in those studies regions were manually delineated, being not entirely coincident with those in the present study. Second, the statistical approach was different, as relative volumes were compared between groups while we used age and intracranial volume correction by regression.

Other structures not included in our measurements can also serve as a prognostic marker as to which patients suffering a first schizophreniform episode will later develop schizophrenia. Among these, a reduced volume of the thalamus (Buchsbaum et al. 1996; Gilbert et al. 2001; Gur et al. 1998) and insula (Crespo-Facorro et al. 2000a) have been described in patients with schizophrenia of short duration. The volume of these regions cannot be reliably quantified with our method, and this constitutes a limitation of our study. Furthermore, we used transformed values to discard the between-groups differences that were due to age or intracranial volume. This transformation, being essentially an advantage, may make the comparison with the results of other groups difficult.

Among the advantages of our study is the inclusion of a group of non-affective psychotic patients with good prognosis, with a prospective follow-up time long enough to reasonably rule out the diagnosis of schizo-

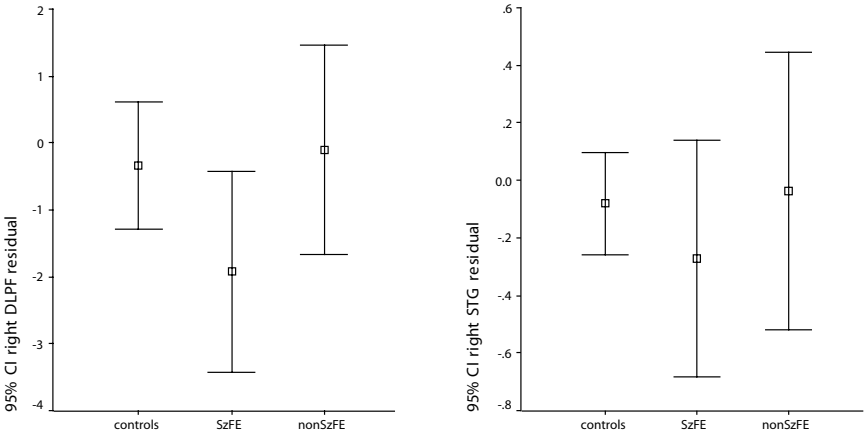

Fig. 1 Error bars of the residuals in the regions with significant between-group differences (*DLPF* dorsolateral prefrontal; *STG* superior temporal gyrus; *SzFe* first episodes of schizophrenia (n = 22); *NonSzFE* frist episodes without schizophrenia (n = 15))

phrenia. Patients of this type have not usually been included in neuroimaging studies, reinforcing the interest of this study despite the relatively small sample size.

In conclusion, a group of poor prognosis, first-episode patients showed an statistically significant lower volume in PF and STG regions as compared to healthy controls and FE with better outcome. Although the magnitude and prognositc capacity of these differences were small, its theoretical implications may be relevant for a better comprehension of the cerebral substrates of schizophrenia.

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