

One year longitudinal study of the straight gyrus morphometry in first-episode schizophrenia-spectrum patients

1. Introduction

Longitudinal magnetic resonance imaging (MRI) studies have shown that the brain might experience progressive tissue loss after the first psychotic onset of schizophrenia (Ho et al., 2003; Kasai et al., 2003; Lieberman et al., 2005; Nakamura et al., 2007).

The prefrontal cortex is among the major structures that have received the most attention in the search for the neural substrate of schizophrenia (Suzuki et al., 2005); the human prefrontal cortex is, though, a large and highly differentiated brain region. It is conceivable to argue that specific subregions within the frontal cortex might be distinctively involved in the pathophysiology of schizophrenia (Crespo-Facorro et al., 2000). Within the prefrontal cortex, imaging studies have shown a distinction between the straight gyrus (SG) and the orbitofrontal cortex during several cognitive tasks, suggesting that the SG may be part of a circuit that mediates some specific emotional functions in humans (Andreasen et al., 1995). Although the orbitofrontal cortex has been extensively studied in schizophrenia, less attention has been paid to the SG. The SG is situated medially to the olfactory groove (olfactory sulcus) at the ventromedial edge of the frontal lobe, and is considered to be the frontal extension of the anterior cingulate gyrus. Animal studies have reported that the SG is a part of the anterior limbic system and is specifically connected to auditory cortex neurons in the convexity of the superior temporal gyrus (Müller-Preuss et al., 1980). In line with other studies (Szendi et al., 2006; Takayanagi et al., 2010), we have reported that SG morphometry did not significantly differ between healthy subjects and schizophrenia spectrum patients at the onset of psychosis (Roiz-Santiañez et al., 2011). However, studies in chronic schizophrenia patients have revealed SG anomalies (Chemerinski et al., 2002; Suzuki et al., 2005). To the best of our knowledge, no longitudinal studies have investigated the possibility of progressive SG volume loss in first-episode schizophrenia patients using a region-of-interest (ROI) methodology.

The primary aim of this study was, using a highly reliable ROI technique, to examine the progressive gray matter volume change of the SG in first-episode schizophrenia-spectrum patients compared with healthy subjects. The second purpose was to study the relationship between SG volume change and clinical symptoms. We hypothesized that first-episode schizophrenia-spectrum patients would show a larger gray matter volume decrease over time in the SG compared to healthy subjects.

2. Method

2.1. Subjects

Ninety-three first-episode schizophrenia spectrum patients (59 males and 34 females) and seventy healthy subjects (44 males and 26 females) were included in this study. Patients were drawn from a large prospective longitudinal study on first-episode psychosis (PAFIP) conducted at the University Hospital Marques de Valdecilla, Santander, Spain. A detailed description of our program has been previously reported ([Pelayo-Teran et al., 2008](#)). All the participants were included in our previous cross-sectional SG study ([Roiz-Santiañez et al., 2011](#)). Patients and healthy subjects were included in this study only when two MRI scans with an interval of about 1 year (mean=384.60 days, S.D.=33.87) were available. At 6 months after enrollment in the study, their Axis I diagnoses were as follows: schizophrenia (N=53; 57.0%), schizophreniform disorder (N=27; 29.0%), schizoaffective disorder (N=2; 2.2%), brief reactive psychosis (N=6; 6.5%), not otherwise specified psychosis (N=4; 4.3%) and delusional disorder (N=1, 1.1%). Mean age at onset was 28.29 years (S.D.=7.83). The mean duration of psychosis at intake was 11.64months (S.D.=18.08). At baseline, 17 patients were taking a typical antipsychotic (haloperidol) and 76 patients were on atypical antipsychotics (17 olanzapine, 16 risperidone, 14 quetiapine, 17 ziprasidone and 12 aripiprazol). At the 1-year assessment all but two patients were on antipsychotics (haloperidol: 11, olanzapine: 19, risperidone: 18, quetiapine: 16, ziprasidone: 12, risperdal consta: 4, aripiprazole: 11). The mean dose in chlorpromazine equivalents ([Andreasen et al., 2010](#)) was 224.86 mg/day.

2.2. Clinical assessments

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 mean values at baseline were 61.90 (12.38) for the BPRS, 6.28 (5.15) for the SANS and 13.57 (4.36) for the SAPS. At follow up the mean values were 30.58 (8.19) for the BPRS, 4.19 (5.15) for the SANS and 1.31 (2.67) for the SAPS.

2.3. MRI acquisition and Image processing

Subjects were scanned twice on a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI) at the University Hospital of Cantabria. Three-dimensional T1-weighted images and two-dimensional proton density (PD) and T2 sequences were acquired. Imaging parameters have been previously described ([Crespo-Facorrot et al., 2007](#)).

Images were processed using the software BRAINS2 ([Andreasen et al., 1996](#); [Magnotta et al., 2002](#)). In short, T1-weighted images were spatially normalized and resampled to 1.0-mm³ voxels. T2-and PD-weighted images were aligned to the spatially normalized T1-weighted image. In order to classify volumes into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), the data sets were segmented by using the multispectral data and a discriminant analysis method based on automated training class selection ([Harris et al., 1999](#)).

The tissue-classified image was then used to generate a triangle-based iso-surface with a threshold of 130 representing pure gray matter, which corresponds to the parametric center of the cortex and serves as a useful estimate of its physical center (Magnotta et al., 1999). Hand-traced regions of interest (ROIs) were used to surround contiguous areas of the gray-matter triangle isosurface. On each two-dimensional (2D) slice, the cortical surface is visualized as a continuous contour that represents the intersection between the 2D plane and the three-dimensional (3D) triangulated surface.

The SG was manually traced on consecutive transaxial slices as described in Roiz-Santiañez et al. (2011). Briefly, tracing begins on the most inferior slice which contains the SG and moves upward to the most superior slice in which the olfactory sulcus (OS) can be identified. In each transaxial slice, the SG is defined as the portion of the frontal lobe medial to the OS. When the OS is interrupted by another frontal region, an orthogonal line is traced from the anterior extremity of the OS to the medial surface of the hemisphere. A single rater (V O-GF) traced all the ROIs. The rater was blinded to the time (baseline or 1 year) and diagnosis. The reliability study for this method was performed on a set of 10 MRI scans using the original tracing from (Crespo-Facorro et al., 1999) as gold standard. Both the intra-class and inter-class R coefficients for SG gray matter volume measurements were greater than 0.95.

2.4. Statistical analysis

All statistical analyses were performed with the Statistical Program for the Social Sciences (SPSS v 19.0, SPSS Inc., Chicago, 2006). To test the hypothesis that patients and healthy subjects would present different progressive SG volume changes, we performed repeated measures analysis of covariance (repeated measures ANCOVA) for the left and right SG gray matter volume separately. The between-subject factor was the group (patient vs. healthy subject) and the within-subject factor was time (baseline and 1 year). Age and intracranial volume were included as covariates. We have also performed similar analysis of only schizophrenia patients vs. healthy controls. Pearson's product-moment correlation coefficients with age and intracranial volume as covariates were calculated to examine the relationships between percent SG gray matter volume change ($100 \times (\text{Vol}_2 - \text{Vol}_1) / \text{Vol}_1$) and medication dose and clinical variables (total scores of SANS, SAPS and BPRS) both at baseline and 1-year follow-up. Throughout, a two-tailed alpha-level of 0.05 was used for statistical testing.

3. Results

There were no significant differences between groups with regard to age, gender, laterality, intracranial volume, parental socioeconomic status, alcohol or cannabis use (all $P > 0.115$). Inter-scan interval did not differ significantly ($F(1,61) = 0.04$; $P = 0.841$) between patients (mean = 385.06 days, S.D. = 36.98) and healthy subjects (mean = 383.98 days, S.D. = 29.48). These data are available upon request.

The SG gray matter volumes at baseline and follow-up and the percentage of volume change are described in.

There were no significant effects of time ($F(1,159) < 0.001$; $P > 0.33$) or diagnosis group ($F(1,159) < 2.76$; $P > 0.10$) (patients vs. healthy subjects). Neither were there significant significant group-by-time interactions for any of the ROIs analysed ($F(1,159) < 0.12$; $P > 0.72$). No significant differences were found either when males and females were analyzed separately. Similarly, the analysis of only right-handed individuals (87 patients and 65 healthy subjects) did not show significant differences. Analyses conducted with patients on either atypical or typical (haloperidol) antipsychotics as the independent variable did not reveal statistically significant results. It is also of interest that there were no significant differences when diagnosis (schizophrenia, schizophreniform disorder and nonschizophrenic non-affective (NSNA) psychoses patients) was included as the between-subject factor. No significant differences were found between control subjects and schizophrenia patients, (all P 's > 0.196). Interestingly, there were no significant differences when patients with positive symptoms predominance vs. negative symptoms were included as the between-subject factor (all P 's > 0.14). There were no significant correlations between clinical variables (SANS, SAPS and BPRS total scores) at either baseline or 1 year follow-up assessment and the percent change of SG gray matter volumes (all P 's > 0.204). Neither were there significant correlations between clinical improvement and ROI changes over time (all P 's > 0.44). Correlations between SG gray matter volume change and medication dose were very weak (all r 's < 0.23).

4. Discussion

In a large representative sample of schizophrenia-spectrum patients in a first episode of psychosis, we found that during a 1-year period: 1. Patients did not show a different pattern of SG gray matter volume change compared to healthy subjects; 2. SG gray matter volume change was not associated with clinical variables.

To the best of our knowledge, this is the first longitudinal MRI study in first-episode schizophrenia-spectrum patients that investigate the SG morphology using an ROI technique. A similar pattern of SG volume loss between patients and healthy subjects was observed. Moreover, there was no significant effect of time ($F(1,159) < 0.001$; $P > 0.33$). A high volume loss was found in both groups. This might be explained by the fact that the SG is a relatively small structure and the variance of its volume was very high. The SG volume loss found was uncommonly high. The prefrontal cortex has been described as one of the structures with most substantial progressive volume change (Raz et al., 1997) and sub-regions within the prefrontal cortex might show different rates of volume change (DeLisi et al., 1997; Gur et al., 1998). Although contrary to our hypothesis, the results are in accordance with some longitudinal studies that observed similar patterns of brain volume change between patients and healthy subjects (Puri et al., 2001; James et al., 2002; Dickey et al., 2004; James et al., 2004).

Our negative results herein seem to provide further support to the hypothesis that biological mechanisms implicated in the pathophysiology of schizophrenia seem to affect more global structural characteristics such as total brain or lateral ventricular volume (Crespo-Facorro et al., 2009) rather than affecting particular cortical regions in the short term (i.e., straight gyrus, temporal pole).

It has been suggested that atypical antipsychotic medication might attenuate the progressive brain changes in schizophrenia (Cahn et al., 2002). However, when we compared the SG volume change between patients who were most of the time on atypical antipsychotic medication with those on typical antipsychotic medication, we did not observe any significant difference. Additionally, we did not identify significant correlations between SG volume change and length of time taking antipsychotic medication. It is also of note that, in a previous study (Crespo-Facorro et al., 2008), we did not find significant differences in cortical morphological changes after 1 year of treatment in patients with non-affective psychosis treated with either atypical or low doses of typical antipsychotics.

In this study, the SG volume change was not correlated with clinical variables. Our previous SG cross-sectional study (Roiz-Santiañez et al., 2011) also revealed that SG gray matter volume was not correlated with clinical variables by the onset of psychosis. Some longitudinal studies (Gur et al., 1998; Takahashi et al., 2009; Takahashi et al., 2011) have reported gray matter progressive changes associated with clinical symptoms when longer periods of time were investigated. Lengthier studies are warranted to investigate the association between the SG volume change and the severity of symptomatology.

The sample size and a careful control of possible confounding factors (age, sex, handedness and other demographic factors) add strength to the conclusions drawn from this study. However, there were some limitations. First, the diagnostic heterogeneity of the sample might bias our findings. For this reason we have repeated all the statistical analyses leaving out the two patients with schizoaffective disorder and the results were once again similar. Second, we did not investigate morphometric change of other cortical brain regions functionally and structurally related to the SG (i.e., medial, anterior, posterior and lateral orbital gyri). Finally, as indicated previously, another limitation is the relatively short follow-up period. If the patient's illness progresses over a longer time period, we are only studying a very limited period of the illness.

In summary, we have observed a similar pattern of SG gray matter volume change over a 1-year period between first-episode schizophrenia-spectrum patients and healthy subjects. In addition, volume change of the SG does not seem to significantly influence the severity of symptomatology.

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