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# Straight gyrus morphology in first-episode schizophrenia-spectrum patients

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ABSTRACT

Previous studies on the straight gyrus have shown inconsistent results in first-episode schizophrenia. In the present study, straight gyrus morphometry in first-episode schizophrenia-spectrum patients was investigated by using a region-of-interest methodology. 141 schizophrenia-spectrum patients and 81 healthy subjects were studied. Magnetic resonance imaging brain scans (1.5 T) were obtained and images were analyzed by using BRAINS2. The main resulting measurements were straight gyrus gray matter volume and cortical surface area. Patients with schizophrenia-spectrum disorders did not significantly differ from controls in the straight gyrus morphometric variables evaluated ($p>0.115$). There was neither significant group-by-side ($p>0.199$) or group-by-gender interaction ($p>0.096$). Clinical variables were not significantly related with straight gyrus morphology. Our results, based on a large and representative sample, do not confirm the presence of significant straight gyrus morphometric anomalies in schizophrenia-spectrum disorders, after controlling for potential confounding variables.



## 1. Introduction

Brain structural abnormalities are already present in early phases of the illness and therefore are primary to the development of schizophrenia (Crespo-Facorro et al., 2009; Vita et al., 2006; Wright et al., 2000). Convergent evidence suggests that the pathological process in schizophrenia predominantly affects the frontotemporolimbic–paralimbic regions (Shenton et al., 2001; Suzuki et al., 2002). 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 (Müeller-Preuss et al., 1980).

Previous regions of interest (ROI) studies on the SG have shown inconsistent results in schizophrenia. Our group observed a significant deficit in surface area in the right straight gyrus in first-episode male schizophrenia ($N=23$), failing to find differences in the left side (Crespo-Facorro et al., 2000). In chronic schizophrenia, it has been reported that there are a bilateral volume reduction of SG (Suzuki et al., 2005) and a significant reduction only in the right SG (Chemerinski et al., 2002). But other studies have failed to find SG volume abnormalities (Szendi et al., 2006; Takayanagi et al., 2010). Significant differences in SG laterality in schizophrenia (the tendency towards

*Abbreviations:* ANCOVA, analysis of covariance; ANOVA, analysis of variance; DPP, duration of prodromic period; DUI, duration of untreated illness; DUP, duration of untreated psychosis; ICV, intracranial volume; MRI, magnetic resonance imaging; NSNA, nonschizophrenic non-affective; OS, olfactory sulcus; ROI, region of interest; SG, straight gyrus; VBM, voxel-based morphometry.

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left dominance in healthy volunteers compared to a right dominance in patients) have been reported (Szendi et al., 2006).

For a more thorough investigation of this issue, the present work attempts: (1) to extend previous MRI studies by rigorously exploring the morphometry of the SG in minimally treated first-episode schizophrenia-spectrum patients; (2) to investigate the effect of gender and hemisphere on SG morphology; and (3) to study the relationship between SG morphological variables and clinical variables. We hypothesized that first-episode schizophrenia-spectrum patients would have smaller SG gray matter volume and cortical surface area compared to healthy control subjects and that SG morphometric anomalies may be more prominent in males. To address these questions, we explored a large and heterogeneous sample of patients with a first-episode of schizophrenia-spectrum disorders who are representative of an epidemiological catchment area with both MRI data and detailed information on clinical characteristics.

## 2. Method

### 2.1. Study setting and financial support

Data for the present investigation were obtained from a large epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Santander, Spain. Conforming to international standards for research ethics, this program was approved by the local institutional review board. The referrals to the PAFIP came from the inpatient unit and emergency room at the University Hospital Marques de Valdecilla, community mental health services and other community health care workers in Cantabria. There were no biases in the way patients were referred and the age-corrected (15–50) incidence rate for schizophrenia-spectrum disorder was of 1.38 per 10,000. A more detailed description of our program has been previously reported (Pelayo-Teran et al., 2008).

### 2.2. Subjects

From February 2001 to December 2007 all referrals to PAFIP were screened for patients who met the following criteria: 1) age 15–60 years; 2) living in the catchment area; 3) experiencing their first episode of psychosis; 4) no prior treatment with antipsychotic medication or, if previously treated, a total life time 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 for any of the following reasons: 1) meeting DSM-IV criteria for drug dependence (except nicotine dependence), 2) meeting DSM-IV criteria for mental retardation, and 3) having a history of neurological disease or head injury. The diagnoses were confirmed according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV (SCID –I) (First et al., 2001) by an expert psychiatrist 6 months on from the initial contact. Those patients with DSM-IV based diagnoses of mental retardation or substance dependence (except nicotine dependence) were excluded.

A total of 248 patients who were included in PAFIP were invited to undergo a MRI scan. Of those 248, 75 individuals refused to participate, 17 individuals were unable to complete the scan, 14 provided poor quality images for segmention, and 1 scan was of insufficiently good quality to properly visualise the SG. Therefore, a final set of 141 patients with a high quality baseline MRI scan was analyzed in this study. No differences in main sociodemographic and clinical characteristics were found when patients with and without MRI were compared (data not shown).

At 6 months after enrolment in the study, their Axis I diagnoses were: schizophrenia (N = 81; 57.4%), schizophreniform disorder (N = 36; 25.5%), schizoaffective disorder (N = 3; 2.1%), brief reactive psychosis (N = 13; 9.2%) and not otherwise specified psychosis (N = 8; 5.7%).

A group of 83 healthy volunteers were recruited from the community through advertisements. Two of them were classified as outliers (defined as having an SG gray matter volume 3 SD above or below the mean) and were excluded from the analyses. Therefore, a final set of 81 healthy volunteers with a high quality baseline MRI scan was analyzed in this study They had no current or past history of psychiatric, mental retardation, 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). They were selected in order for the patients to have a similar distribution in age, gender, laterality index, drug history and years of education. 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 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 same trained psychiatrist (BC-F) completed the clinical evaluation of patients at the time of entry into the study. Handedness was assessed by the Edinburgh Inventory (Oldfield 1971).

Duration of untreated illness (DUI) was defined as the time from the first unspecific symptom (reduced concentration or attention, reduced drive and motivation, anergia, depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, deterioration in role functioning and irritability) to psychosis (for such a symptom to be considered, there should be no return to previous stable level of functioning) to initiation of adequate antipsychotic drug treatment. Duration of untreated psychosis (DUP) was defined as the time from the first continuous (present most of the time) psychotic symptom (hallucination, delusion, thought disorder or inappropriate bizarre behavior in which the symptoms are not apparently due to organic cause. A rating of 4 or above on any of the SAPS symptom items for at least 1 week is warranted) to initiation of adequate antipsychotic drug treatment. Duration of prodromic 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 when the emergence of the first continuous (present most of the time) psychotic symptom occurred.

Patients went through a pharmacological protocol and were randomly assigned to treatment with risperidone (N = 24, 17.0%), olanzapine (N = 24, 17.0%), quetiapine (N = 24, 17.0%), ziprasidone (N = 26, 18.4%), aripiprazole (N = 21, 14.9%) or haloperidol (n = 22, 15.6%). At the time of the scan all patients were on antipsychotic treatment. Only three patients had been minimally treated prior to randomizing to antipsychotic treatments: one patient had been on haloperidol for 4 weeks, one patient on quetiapine for one week, and one patient on risperidone for 4 weeks.

### 2.4. MRI acquisition and image processing

All multi-modal MRI scans were obtained at the University Hospital of Cantabria using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). Three-dimensional T1-weighted images and two-dimensional PD and T2 sequences were