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Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features

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Abstract

Background—The thickness of the cortical mantle is a sensitive measure for identifying alterations in cortical structure. We aimed to explore whether first episode schizophrenia patients already show a significant cortical thinning and whether cortical thickness anomalies may significantly influence clinical and cognitive features.

Method—We investigated regional changes in cortical thickness in a large and heterogeneous sample of schizophrenia spectrum patients (*n*=142) at their first break of the illness and healthy controls (*n*=83). Magnetic resonance imaging brain scans (1.5 T) were obtained and images were analyzed by using BRAINS2. The contribution of sociodemographic, cognitive and clinical characterictics was investigated.

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Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

Declaration of Interest

Professor Vazquez-Barquero and Professor Crespo-Facorro have received unrestricted research funding from AstraZeneca, Pfizer, Bristol–Myers Squibb, and Johnson & Johnson that were deposited into research accounts at the University of Cantabria. Professor Vazquez-Barquero has received honoraria for his participation as a speaker at educational events from Johnson & Johnson. Professor Crespo-Facorro has received honoraria for his participation as a speaker at educational events from Pfizer, Bristol–Myers Squibb, and Johnson & Johnson and consultant fees from Pfizer. Dr Mata has received honoraria for his participation as a speaker at educational events from Johnson & Johnson. Dr Perez-Iglesias has received honoraria for his participation as a speaker at educational events from Bristol–Myers Squibb-Otsuka. Dr Andreasen has received research funding and advisory board consultation fees from Johnson and Johnson. Professor Tabarés-Seisdedos has received unrestricted research funding from AstraZeneca, Pfizer, Lilly that were deposited into research accounts at the University of Valencia.

Results—Patients showed a significant total cortical thinning (F=17.55, d=−0.62, p<0.001) and there was a diffuse pattern of reduced thickness (encompassing frontal, temporal and parietal cortices) (all p's<0.001, d's>0.53). No significant group × gender interactions were observed (all p's>0.15). There were no significant associations between the clinical and pre-morbid variables and cortical thickness measurements (all r's<0.12). A weak significant negative correlation between attention and total (r=−0.24, p=0.021) and parietal cortical thickness (r=−0.27, p=0.009) was found in patients (thicker cortex was associated with lower attention). Our data revealed a similar pattern of cortical thickness changes related to age in patients and controls.

Conclusions—Cortical thinning is independent of gender, age, age of onset and duration of the illness and does not seem to significantly influence clinical and functional symptomatology. These findings support a primary neuro-development disorder affecting the normal cerebral cortex development in schizophrenia.

Keywords

Brain; cortical thickness; endophenotype; MRI; schizophrenia

Introduction

Imaging and neuropathological evidence indicates that schizophrenia is associated with cortical structural abnormalities. Cortical thickness and surface area offer important information about brain development processes (Rockel *et al*. 1980; Bystron *et al*. 2008) and cortical structure (Kruggel *et al*. 2003; Sowell *et al*. 2003). In schizophrenia, regional gray-matter thinning in frontal, temporal and parietal heteromodal association cortices (White *et al*. 2003; Narr *et al*. 2005a,b; Venkatasubramanian *et al*. 2008) and a differential pattern of cortical thickness asymmetry (Haller *et al*. 2009) have been reported in first episode patients. Marked global and regional (frontal and temporal) thickness reductions have also been observed in chronic samples (Kuperberg *et al*. 2003; Nesvag *et al*. 2008; Goldman *et al*. 2009). A different pattern of cortical thickness abnormalities in sulci and gyri has also been associated with the illness. Cortical thickness anomalies are more prominent in the sulci than in the gyri (White *et al*. 2003; Goghari *et al*. 2007). The differential effects of age, gender, diagnoses, handedness and antipsychotic medication on variation in cortical thickness in schizophrenia have also been explored with inconclusive findings (Narr *et al*. 2005*a*).

It is of interest that variability in cortical thickness has been associated with differences in general intelligence (Gong *et al*. 2005; Shaw *et al*. 2006) and cognitive abilities (Karama *et al*. 2009). In this line of research, reduced cortical thickness is associated with deficits in a wide variety of cognitive functions in rats (Flagstad *et al*. 2005). We hypothesized that neuropsychological deficits in schizophrenia could be linked with the observed pattern of brain changes affecting frontal, temporal and parietal heteromodal association cortices. However, only a few studies have assessed the behavioral significance of morphometric cortical anomalies in first episode schizophrenia (for a review, see Crespo-Facorro *et al*. 2007). The present investigation might shed additional light into the field.

It is yet to be elucidated whether: (1) these cortical anomalies in first episode schizophrenia could be related, at least in part, to the effect of the illness itself, gender, age or handedness; (2) these cortical anomalies may significantly influence clinical and cognitive features of the illness.

Method

Study setting and financial support

Data for the present investigation were obtained from a large epidemiological and 3-year longitudinal intervention programme of first-episode psychosis (PAFIP) conducted at the out-patient clinic and the in-patient unit at the University Hospital Marques de Valdecilla, Santander, Spain. It conformed to international standards for research ethics and was approved by the local institutional review board. A more detailed description of our programme has been previously reported (Pelayo-Terán *et al*. 2008).

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 <6 weeks; (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 ; (3) having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (First *et al*. 2001) carried out by an experienced psychiatrist 6 months from the baseline visit.

A total of 264 first episode patients who were included in PAFIP were invited to undergo a magnetic resonance imaging (MRI) scan. Of those 264 patients, 89 individuals refused to participate, 23 individuals were unable to complete the scan and 10 obtained poor quality images. Therefore, a final set of 142 patients with a high quality baseline MRI scan were analyzed in this study. No differences in main socio-demographic 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*=82, 57.7%), schizophreniform disorder (*n*=36, 25.4%), schizoaffective disorder (*n*=3, 2.1%), brief psychotic disorder (*n*=13, 9.2%) and not otherwise specified psychosis (*n*=8, 5.6%).

A group of 83 healthy volunteers were initially recruited from the community through advertisements. They had no current or past history of mental retardation or of psychiatric, neurological or general medical illnesses, including substance abuse and significant loss of consciousness, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (Andreasen *et al*. 1992). 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, in accordance with local ethics committee.

Clinical and cognitive assessments

Clinical symptoms were rated using the Brief Psychiatric Rating Scale total (Overall & Gorman, 1962), the Scale for the Assessment of Negative Symptoms (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984). We also divided psychopathology into three dimensions of symptoms (psychotic, negative and disorganized).

All study subjects were invited to complete a comprehensive cognitive battery (Gonzalez-Blanch *et al*. 2007). For this investigation, we selected six cognitive tests that comprise five cognitive domains, with outcome measures shown in parentheses: (1) executive functions :

Trail Making Test B (time to complete); (2) working memory: Wechsler Adult Intelligence Scale (WAIS) III – backward digits (total score) ; (3) speed of processing: WAIS III-Digit Symbol (standard total score) ; (4) attention : Continuous Performance Test (CPT) Degraded-Stimulus (total number of correct responses); (5) visual memory: Rey Complex Figure Test (long-term recall measure). The WAIS III subtest of vocabulary (number of words generated) was used as pre-morbid IQ. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971).

Medication assessment

Patients went through a pharmacological protocol and were randomly assigned to treatment with risperidone (*n*=24, 16.9%), olanzapine (*n*=24, 16.9%), quetiapine (*n*=25, 17.6%), ziprasidone (*n*=26, 18.3%), aripiprazole (*n*=21, 14.8%) or haloperidol (*n*=22, 15.5%). Only three patients had been minimally treated prior to randomizing to antipsychotic treatments.

Patients had a baseline structural MRI as soon as they could tolerate the procedure following the initiation of treatment. The mean time between initiation of antipsychotic treatment and baseline MRI scan was 4.42 weeks (range 0.14–18.57).

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, USA). Three-dimensional T1-weighted images, using a spoiled grass sequence were acquired in the coronal plane (see Crespo-Facorro *et al*. 2007 for details).

Processing of the images was done by using BRAINS2 (Andreasen *et al*. 1996; Magnotta *et al*. 2002). The T1 scan was loaded and resample to 1.0 mm^3. The definition of Talairach parameters was accomplished to define how the Talairach grid is warped on to the brain. The T2 and proton density (PD) datasets were aligned to the resampled T1 image. The co-registered T1, T2 and PD image sets were used as input into a tissue classification module, which can handle multispectral data (Harris *et al*. 1999). The segmented image is used to extract a triangle-based polygonal model of an iso-surface, representing the parametric center of the gray-matter tissue class (Magnotta *et al*. 1999). The resulting three-dimensional iso-surface approximates the spatial center of the cortex and is used to provide estimates of values that are direct or indirect quantitative measurements of cerebral cortex.

Measurements

Cortical depth—This measure is the minimum distance between the 100% gray-matter triangle surface and the 50%/50% gray/white matter surface. This measure is an index of cortical thickness ; it represents the parametric center of the cortex or approximately one-half the cortical thickness.

Cortical surface area—This value is the sum of the areas of the triangles making up the surface of the brain.

The methods used to quantify these aspects of surface anatomy have been extensively evaluated and validated (Magnotta *et al*. 1999).

Statistical analysis

All statistical analyses were performed with the SPSS software version 15 (SPSS Inc., USA). Because of the skewed distribution of duration of untreated psychosis (DUP), duration of untreated illness (DUI) and age of onset, a logarithmic transformation was conducted to convert data to normal distribution.

To examine differences in morphological measurements between patients and healthy subjects, a repeated-measures analysis of covariance (ANCOVA) was performed.

For the primary analysis, the between subject factors were group (patients and controls) and gender, and the within subject factor (repeated measures) was side (left or right). Cortical thickness and surface area were used as the dependent variables. Age was used as covariates. The group by side interaction was used to determine differences in asymmetry between groups. All *post-hoc* comparisons were Bonferroni corrected.

As a secondary analysis, we explored the specificity of these cortical anomalies between the different diagnostic groups using as the between subject factor the three diagnostic groups: schizophrenia; schizophreniform; non-schizophrenic non-affective (NSNA) psychosis.

We also analyzed all the morphological measurements in the sample using only right-handed individuals to rule out the effect of handedness.

Cohen's *d* is provided to estimate the magnitude of the differences between groups. A two-tailed α-level of 0.05 was used for statistical testing.

Pearson correlation coefficients were used as an explanatory analysis to assess the relationship between morphological measurements and cognitive and clinical variables. In this correlation analysis, we used a more stringent threshold ($p<0.01$) of statistical significance to dismiss spurious statistically significant claims. Once we identified the variables that were more likely related with cortical thickness, we carried out a multiple regression analysis in order to discriminate the factors that more accurately predict cortical thickness in our sample. As independent variables, we included not only the significant variables from the correlational analysis but also variables that could be potentially confounding factors : gender, age, cannabis consumption and years of education.

Results

Subject characteristics

The comparisons of patients and controls regarding sociodemographic, clinical and cognitive characteristics are presented in Table 1. All were Caucasian. There were no significant differences between patients and controls with regard to age, gender, height, educational level, parental socio-economic status and alcohol or cannabis consumption. When the three diagnostic groups of patients (schizophrenia, schizophreniform and NSNA psychosis) were statistically explored, there were no statistically significant differences in relevant sociodemographic characteristics between the three groups of patients and controls (data are available from the first author upon request).

Global cortical measurements

Table 2 displays the results from the analysis evaluating each cortical measure in patients and healthy subjects. The total intracranial brain volume did not differ between groups (see Table 1).

For total cortical thickness, the two groups showed significant differences with a medium-large effect size ($F=13.54$, $d=-0.62$, $p<0.001$). When specific measures of sulcal and gyral thickness were evaluated, both measures differed between the groups ($F=27.48$, $d=-0.81$, $p<0.001$ and $F=6.55$, $d=-0.47$, $p=0.011$, respectively). Those subjects with psychosis had significantly thinner total, gyri and sulci cortical thickness. Results remained similar after adjusting for age and intracranial volumen.

There were no significant differences between the two groups in cortical surface area (F=0.82, d=0.05, p=0.365).

There were no significant differences between the diagnostic groups in cortical thickness and cortical surface area (all p's>0.132) (data are presented in the supplementary material).

Regional cortical measurements

The cortical measurements were also evaluated for each of the four cerebral lobes (Table 2). The pattern of regional cortical thickness in patients compared with healthy controls revealed a higher significant thinning in frontal, temporal, parietal and occipital cortices (all p's<0.037, d's< −0.38). The marked sulcal thinning extended to all cerebral lobes (all p's<0.001, d's< −0.58), whereas gyral thinning was localized in frontal and temporal regions (F=5.18, d=−0.44, p=0.024, F=10.10, d = −0.53, p=0.002, respectively). No regional differences in cortical surface area were observed.

Intervening variables

We also examined whether these cortical anomalies were mediated by the differential influence of gender, age and handedness.

Factor scores from the ANCOVA did not show main effects of group by gender for any of the cortical thickness variables (all p's > 0.114) (see Table 2). Similarly, no significant group × side interactions were noted for any of the cortical measures.

Significant correlations were found between cortical thickness and age in the two groups, schizophrenia (r = −0. 514; p < 0.0001) and young healthy volunteers (r = −0. 408; p < 0.0001). These correlations suggest that the younger the individual, the thicker the cortical ribbon. Correlations between cortical thickness and age were performed within each gender (see Fig. 1). The analysis of the slopes of the correlations revealed no significant differences in the effect of age in males, patients and controls (r=−0.373 and r=−0.315, respectively). Similarly, female patients and female controls showed a comparable effect of age on cortical thickness (r=−0.721 and r=−0.613, respectively). Decrease in mean cortical thickness with increasing age in the four cerebral lobes was similar in patients and controls (data not shown).

Finally, the analysis of only right-handed individuals (n=125 patients and n=75 controls) revealed a similar significant group effect for cortical thickness and similar lack of significant group by side interactions than when we analyzed the complete sample. Handedness does not seem to affect significantly cortical thickness anomalies found in first episode schizophrenia.

All these analyses of correlation are available from the first author upon request.

Correlations between cortical thickness and clinical and cognitive measures

Correlations between clinical symptoms and cortical thickness measures are shown in Table 3. There were no significant associations between the severity of symptoms at baseline and any of the cortical thickness (all |r's| <0.12 and p's>0.15). No significant associations were seen either between DUP, DUI, duration of prodromic period (DPP) and age of onset and cortical thickness measurements (all |r's| <0.12 and p's>0.15).

Correlations between cortical and cognitive measurements are shown in Table 4. Patients had a weak significant negative correlation between attention and total and parietal cortical thickness (r= −0.24, p=0.021 and r=−0.27, p=0.009, respectively). Only the latter

association remains statistically significant when using a more stringent threshold ($p<0.01$). No other significant associations between cognitive variables and cortical measurements were found.

Based on the previous correlation analysis, CPT scores, age, gender, years of education and cannabis use were entered in a stepwise linear regression model. The final model predicts a part of the variability of parietal cortical thickness ($F=18.02$, $p<0.001$; $R^2= 0.275$). Univariate analysis shows that age (β: −0.507; $p<0.001$), and CPT scores (β=−0.211, $p=0.018$) were significantly associated with parietal cortical thickness.

Discussion

We found that patients with schizophrenia at the first break of the illness already showed a significant cortical thinning compared with young healthy volunteers. There was a diffuse pattern of reduced thickness (encompassing frontal, temporal and parietal heteromodal association cortices) and a marked thinning of sulci. These morphological changes seem to be independent of age, gender, handedness and other intervening variables. Cortical thinning in schizophrenia does not seem to significantly influence clinical and functional symptomatology. Interestingly, the three diagnostic groups of patients show a similar pattern of cortical thickness, suggesting a common neurobiological pattern that might be shared by non-affective psychotic illness.

Cortical thickness and surface area

Although not all studies have found consistent results (Wiegand *et al*. 2004; Haller *et al*. 2009), a significant cortical thinning has been observed in first episode schizophrenia with a childhood and adolescent (White *et al*. 2003) and adult (Narr *et al*. 2005*a*, *b*; Venkatasubramanian *et al*. 2008) onset. These studies suggested that cortical regions most affected may be frontal, temporal and parietal heteromodal association cortices. In addition to frontopolar and cingulate thickness reductions, Narr and colleagues (2005b) observed cortical thinning within the occipital cortex. Venkatasubramanian and colleagues (2008) described that prefrontal thickness deficits seem to be significantly located in the medial orbitofrontal cortices. The small sample size in the negative studies from Wiegand *et al*. (2004) and Haller *et al*. (2009) (n=17 and n=20, respectively) may explain the inconsistency of their results. In chronic schizophrenia, widespread cortical thinning with a distinct reduction in temporal and frontal thickness (Kuperberg *et al*. 2003; Nesvag *et al*. 2008; Goldman *et al*. 2009) and parietal operculum sulcal thinning (Csernansky *et al*. 2008) has been also observed. Due to the demonstrated differential maturation trajectories of the cortical regions (Gogtay *et al*. 2004), insults disrupting later stages of cortical maturation might distinctly affect anterior cortical regions with a lesser impact on posterior cortical regions (Nesvag *et al*. 2008). It may be hypothesized that cellular shrinkage, reduction in dendritric arborization and disruptions in white matter bundles connecting association cortical areas are pathological mechanisms that account for cortical thinning and impaired connectivity and functionality (Morrison & Hof, 1997; Rajkowska, 1997; Selemon *et al*. 1998). The precise description of the relationship between neuropathological abnormalities and the reduction of cortical thickness in schizophrenia is still obscure.

Our finding of a reduction of 5.5% in total cortical thickness is consistent with the results of a previous study on early onset schizophrenia using a similar methodological approach (White *et al*. 2003). Venkatasubramanian and colleagues (2008) also reported a 5.1% thickness reduction in orbitofrontal cortex. The cortical thinning found in chronic patients seems to be of a similar or even lesser magnitude than in first episode patients (Kuperberg *et al*. 2003; Nesvag *et al*. 2008). We hypothesized that cortical thinning found in early stages of the illness is stable and relatively independent of the course of the illness itself.

Previous imaging studies in schizophrenia have shown a differential cortical thickness asymmetry (Hamilton *et al*. 2007). Haller and colleagues (2009) observed that cortical thickness asymmetries but not direct cortical thickness measurements may be distinctively affected in first episode patients. We found herein that both healthy volunteers and first episode patients have a similar pattern of cortical asymmetries (see Table 2).

Differences in structure and connectivity exist between gyri and sulci (Hilgetag & Barbas, 2006) and thicker gyral crowns have been described in healthy controls (White *et al*. 2003). We have consistently demonstrated differences in total cortical thickness of gyri and sulci [4.58 (0.50) mm and 3.74 (0.37) mm, respectively] in healthy volunteers (Crespo-Facorro *et al*. in press). We found herein a widespread and prominent thinning of cortical thickness of sulci. Similar results have also been found in childhood and adolescent schizophrenia compared with healthy volunteers (White *et al*. 2003). Goghari and colleagues (2007) have suggested that sulcal thinning in the superior temporal and cingulate regions may serve as structural endophenotype in schizophrenia.

No lobar or global anomalies in surface area were observed in the present study. In first episode schizophrenia patients, reductions in specific cortical surface area (orbitofrontal, straight gyrus and insular cortex) have been described (Crespo-Facorro *et al*. 2000*a*, *b*). Wiegand and colleagues (2004) did not find significant differences in prefrontal complexity measure (an estimate of cortical surface area) in first episode patients compared with healthy volunteers. We might conclude that during the early phases of schizophrenia there is no evidence of a cortical surface reduction either globally or in lobes, although anomalies in more specific cortical subregions might be present.

Intervening variables

We found a significant effect of age in cortical thickness. However, our data revealed a similar pattern of cortical thickness changes related to age in both groups. In healthy volunteers, males seem to have more pronounced age-related cortical thinning (Good *et al*. 2001) and cortical atrophy (Coffey *et al*. 1998) than females. In schizophrenia, whole brain gray-matter volumes and regional changes in intensity-based gray-matter concentration were shown to occur prematurely in male patients with chronic schizophrenia (Narr *et al*. 2003). Nesvag and colleagues (2008) described differences in the aged-related thickness changes in chronic patients and controls. However, the existence of a distinctive pattern of age-related cortical thickness changes in schizophrenia is still under debate (Weinberger & McClure, 2002). The present study showed no significant effect of schizophrenia in age-related cortical thickness variations. Moreover, we did not find any difference between patients and controls in age-related cortical thickness when males and females were compared independently (see Fig. 1).

We observed that in schizophrenia there is not a significant influence of gender in cortical thickness and surface area. Narr *et al*. (2005b) observed no significant gender differences in cortical thickness across the entire cortex in patients with a first episode of schizophrenia.

Differential cortical thickness asymmetries in schizophrenia have been associated with handedness (Hamilton *et al*. 2007). Although there was no difference in handedness between our groups, we have further investigated the influence of handedness in asymmetries of cortical measures by analyzing only the subsample of right-handed individuals. No significant effects in global or regional cortical measures were associated with handedness.

Clinical and cognitive correlations

No evidence of a significant association between age of onset, DUP, DUI and DPP and cortical measurements was found (Table 3). Some of the previous studies, but not all (Wiegand *et al*. 2004), have also failed to demonstrate significant associations between clinical pre-morbid variables and cortical thickness in schizophrenia (Kuperberg *et al*. 2003; Nesvag *et al*. 2008). In addition, there were no significant associations between clinical features (total scores of the three dimensions) and cortical measurements. Although a small negative correlation between the severity of negative symptomatology and the thickness of left medial orbitofrontal cortex has been observed (Venkatasubramanian *et al*. 2008), most of the previous studies did not consistently find significant correlations between cortical thickness values and psychopathological variables (Kuperberg *et al*. 2003; Wiegand *et al*. 2004; Goldman *et al*. 2009). Wiegand *et al*. (2004) have described that patients who were younger at the time of their first episode have a significant thicker prefrontal cortex, suggesting a relationship between age of onset and cortical thickness in schizophrenia. We did not find any association between the age of onset of the illness and cortical measurements.

We found a significant association between attention and parietal thickness in schizophrenia patients. Previous functional and morphometric imaging studies have shown that deficits in attention were related to abnormalities of the parietal cortex in schizophrenia (Salgado-Pineda *et al*. 2003, 2004; Weiss *et al*. 2007). Gender did not influence the pattern of correlations between cognitive functioning and cortical thickness in patients. Our group has recently observed significant correlations between cognitive functioning and prefrontal and parietal thickness in healthy females, but not in healthy males (Crespo-Facorro *et al*. in press). However, despite this differential pattern of associations between cognition and cortical measurements in patients and controls, no significant differences in semantic memory and executive functioning were found between female patients and controls.

Methodological limitations

There were a few limitations to this study. First, because of the distribution of ages in our sample it was not possible to correctly explore the effect of age in cortical measures. Although a wide range of ages have been included (age ranged from 17.23 to 57.88 years), 75% of the total sample was younger than 33.8 years. Second, although our patients were minimally treated (mean=4.42 weeks) the effect of antipsychotic medication in cortical thickness should not be ruled out. Previous investigations did not report the influence of antipsychotic medications in cortical thickness (Kuperberg *et al*. 2003; Narr *et al*. 2005a, b). Longitudinal studies are warranted to determine changes in the cerebral surface anatomy during the course of the illness and also to determine the effects of different antipsychotic treatments. Finally, it was not possible from our findings to explore the possibility that group differences also exist on a finer microstructural level, including cellular architecture and connectivity.

Conclusions

In the present study, we observed spread differences in cortical thickness between first episode schizophrenia patients and healthy volunteers. The fact that cortical thinning is already present at early phases of the illness and is independent of intervening variables offers evidence for the potential of these changes to be a biological marker of the illness and, in turn, their value as neurodevelopmental endophenotypes should be evaluated. Further studies are warranted to elucidate the influence of different neurobiological mechanisms (cellular shrinkage, reduction in dendritic arborization and disruptions in white matter bundles) associated with reduced cortical thickness in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The study, which was designed and directed by B.C.-F. and J.L.V.-B., conformed to international standards for research ethics and was approved by the local institutional review board. We thank the PAFIP researchers who helped with data collection and especially acknowledge Obdulia Martinez and Mrs Gema Pardo for data collection and Victor Ortiz and David Torrellas for their assistance in imaging analysis. In addition, we acknowledge the participants and their families for enrolling in this study. The present study was performed under the following grant support: Instituto de Salud Carlos III PI020499, PI050427, PI060507; Plan Nacional de Drogas Research Grant 2005-Orden sco/3246/2004; SENY Fundació Research Grant CI 2005–0308007; Fundación Marqués de Valdecilla API07/011.

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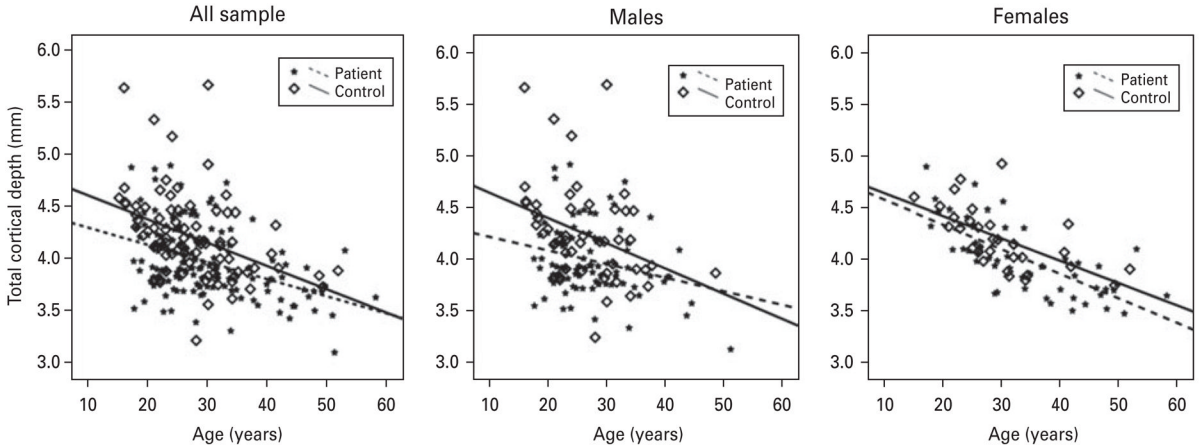

Fig. 1.
Correlations between total cortical thickness and age in patients and healthy volunteers.

Table 1

Demographic and clinical characteristics of patients and healthy volunteers

	Patients (*n*=142)	Controls (*n*=83)	Statistics
Males *n*, (%)	88 (61.97)	52 (62.65)	χ^2=0.01, *p*=0.92
Age at MRI, mean, (S.D.), years	29.73 (8.70)	27.57 (7.57)	*F*=3.55, *p*=0.06
Height, mean (S.D.), cm	169.04 (9.33)	171.29 (8.70)	*F*=3.15, *p*=0.08
Right-handed *n*, (%)[a]	125 (89.93)	75 (91.46)	χ^2=0.14, *p*=0.71
Age at onset, mean, (S.D.), years	28.55 (8.35)	–	–
Intracranial volume, mean (S.D.), ml	1377.34 (136.96)	1384.83 (124.81)	*F*=0.17, *p*=0.68
Parental socio-economic status, mean (S.D.)[b,e]	3.64 (0.91)	3.51 (0.75)	*F*=1.12, *p*=0.29
Low academic level *n*, (%)[f]	72 (50.70)	32 (39.51)	*F*=2.60, *p*=0.11
Alcohol users *n*, (%)[c]	88 (62.97)	50 (63.29)	*F*=0.04, *p*=0.85
Cannabis users *n*, (%)[c]	69 (48.59)	30 (37.50)	*F*=2.55, *p*=0.11
Tobacco users *n*, (%)[c]	81 (57.04)	47 (58.75)	*F*=0.06, *p*=0.81
DUP mean, (S.D.), median, months	12.48 (28.84), 3.00	–	–
DUI mean, (S.D.), median, months[d]	28.61 (48.16), 12.00	–	–
DPP mean, (S.D.) median, months[d]	16.06 (37.51), 4.00	–	–
Symptomatology (total scores)			
SANS	6.31 (5.12)	–	–
SAPS	13.63 (4.33)	–	–
Psychotic dimension	7.46 (2.34)	–	–
Disorganized dimension	6.17 (3.41)	–	–
Negative dimension	4.46 (4.85)	–	–

MRI, Magnetic resonance imaging; DPP, duration of prodromic period [period from the first unspecific symptoms related to psychosis to the first continuous (present most of the time) psychotic symptom]; DUI, duration of untreated illness [time from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to the previous stable level of functioning) to initiation of adequate antipsychotic drug treatment] ; DUP, duration of untreated psychosis [time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment] ; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a] Based on data from 139 patients and 82 volunteers.

[b] Based on data from 141 patients and 80 volunteers.

[c] Based on data from 142 patients and 80 volunteers.

[d] Based on data from 141 patients.

[e] Parental socio-economic status is based on the Hollingshead–Redlich scale.

[f] Low academic level was defined as secondary education or lower.

Table 2

Cortical measurements in 142 schizophrenia spectrum patients and 83 healthy subjects

	Patients (*n*=142)		Control subjects (*n*=83)			Group		Group × side		Group × gender	
	Mean	**S.D.**	**Mean**	**S.D.**	***d***	***F***	***p***	***F***	***p***	***F***	***p***
Surface area	172468.40	18301.85	171563.24	17019.39	0.05	0.82	0.365	3.27	0.072	0.452	0.502
Total cortical thickness	3.98	0.33	4.21	0.42	−0.62	13.54	<0.001	1.27	0.261	1.55	0.214
Gyral cortical thickness	4.36	0.43	4.58	0.50	−0.47	6.55	0.011	2.52	0.114	0.93	0.336
Sulcal cortical thickness	3.47	0.28	3.74	0.37	−0.81	27.48	<0.001	<0.01	0.965	2.04	0.155
Frontal lobe											
Surface area	68811.81	6937.57	68651.16	7263.97	0.02	0.73	0.394	1.21	0.273	<0.01	0.961
Total cortical thickness	4.22	0.39	4.46	0.46	−0.57	10.54	0.001	0.30	0.582	1.65	0.200
Gyral cortical thickness	4.67	0.49	4.90	0.55	−0.44	5.18	0.024	0.17	0.680	0.95	0.331
Sulcal cortical thickness	3.52	0.34	3.82	0.43	−0.77	22.88	<0.001	0.02	0.889	2.52	0.114
Parietal lobe											
Surface area	41630.78	4475.59	41730.44	4273.97	−0.02	<0.01	0.968	0.85	0.358	2.76	0.098
Total cortical thickness	3.71	0.33	3.91	0.39	−0.54	9.80	0.002	0.10	0.758	0.85	0.356
Gyral cortical thickness	4.03	0.45	4.20	0.50	−0.35	3.11	0.079	0.28	0.600	0.48	0.489
Sulcal cortical thickness	3.34	0.30	3.58	0.38	−0.69	18.88	<0.001	0.04	0.841	0.98	0.323
Temporal lobe											
Surface area	37946.39	4960.82	37484.61	4233.36	0.10	1.25	0.266	2.64	0.106	0.42	0.517
Total cortical thickness	4.23	0.42	4.54	0.52	−0.64	15.53	<0.001	0.73	0.394	1.07	0.302
Gyral cortical thickness	4.80	0.56	5.13	0.68	−0.53	10.10	0.002	1.34	0.249	0.62	0.432
Sulcal cortical thickness	3.50	0.34	3.80	0.38	−0.83	28.75	<0.001	0.05	0.832	1.66	0.199
Occipital lobe											
Surface area	19750.02	3856.17	19676.45	3385.58	0.02	0.17	0.677	<0.01	0.961	<0.01	0.939
Total cortical thickness	3.16	0.30	3.30	0.39	−0.38	4.42	0.037	0.51	0.475	0.41	0.521
Gyral cortical thickness	3.00	0.39	3.07	0.46	−0.18	0.63	0.428	0.46	0.497	0.56	0.456
Sulcal cortical thickness	3.37	0.29	3.58	0.42	−0.58	13.21	<0.001	0.30	0.583	0.49	0.484

Covariate : Age.

Surface area is presented as mm^2, and cortical thickness as mm.

Table 3

Correlations between clinical characteristics and cortical thickness measurements

	Total cortical thickness		Frontal cortical thickness		Parietal cortical thickness		Temporal cortical thickness		Occipital cortical thickness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SANS[a]	−0.05	0.54	−0.04	0.66	−0.06	0.50	−0.07	0.44	−0.11	0.21
SAPS[a]	0.04	0.68	0.03	0.73	0.04	0.62	0.03	0.76	0.02	0.85
Psychotic symptoms[a]	0.05	0.59	0.03	0.75	0.06	0.46	0.06	0.49	−0.03	0.74
Disorganized symptoms[a]	0.01	0.88	0.02	0.82	0.01	0.90	−0.01	0.93	0.04	0.64
Negative symptoms[a]	−0.08	0.32	−0.09	0.32	−0.06	0.47	−0.09	0.27	−0.12	0.16
DUP[a]	−0.01	0.95	−0.04	0.68	0.05	0.58	<0.01	0.99	−0.04	0.66
DUI[b]	−0.09	0.30	−0.12	0.15	−0.04	0.62	−0.04	0.63	−0.07	0.44
DPP[b]	−0.09	0.34	−0.11	0.26	−0.08	0.41	−0.07	0.47	−0.11	0.27
Age of onset[a]	−0.03	0.76	−0.03	0.71	−0.07	0.45	0.01	0.88	0.03	0.73

SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; DUP, duration of untreated psychosis ; DUI, duration of untreated illness ; DPP, duration of prodromic period.

[a]Based on data from 142 patients [schizophrenia (*n*=82), schizophreniform disorder (*n*=36), schizoaffective disorder (*n*=3), brief psychotic disorder (*n*=13) and not otherwise specified psychosis (*n*=8).

[b]Based on data from 141 patients [schizophrenia (*n*=82), schizophreniform disorder (*n*=35), schizoaffective disorder (*n*=3), brief psychotic disorder (*n*=13) and not otherwise specified psychosis (*n*=8).

Table 4

Correlations of cognitive variables and cortical thickness in patients

	Total cortical thickness		Frontal cortical thickness		Parietal cortical thickness		Temporal cortical thickness		Occipital cortical thickness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
WAIS-III Vocabulary										
All (*n*=104)	−0.08	0.402	−0.04	0.698	−0.08	0.447	−0.13	0.190	0.02	0.818
Males (*n*=62)	−0.11	0.423	−0.13	0.341	−0.07	0.589	−0.10	0.448	0.04	0.780
Females (*n*=42)	0.12	0.454	0.27	0.092	0.03	0.837	−0.09	0.596	0.13	0.416
WAIS–III Backward Digits										
All (*n*=111)	0.04	0.683	0.04	0.678	0.04	0.675	0.03	0.796	0.03	0.787
Males (*n*=66)	−0.03	0.814	−0.04	0.761	0.01	0.941	−0.03	0.813	−0.08	0.543
Females (*n*=45)	0.15	0.327	0.16	0.309	0.07	0.644	0.09	0.569	0.16	0.293
Rey Complex Figure Test										
All (*n*=108)	−0.08	0.431	−0.12	0.211	−0.07	0.476	0.03	0.755	−0.04	0.706
Males (*n*=65)	−0.11	0.389	−0.20	0.126	−0.07	0.581	<0.01	0.985	−0.04	0.776
Females (*n*=43)	0.12	0.444	0.12	0.442	0.02	0.903	0.21	0.190	0.06	0.707
WAIS-III Digit Symbol										
All (*n*=111)	−0.12	0.234	−0.10	0.312	−0.09	0.329	−0.12	0.228	−0.05	0.635
Males (*n*=66)	−0.20	0.119	−0.19	0.135	−0.18	0.164	−0.15	0.228	−0.17	0.186
Females (*n*=45)	0.01	0.967	0.04	0.825	0.05	0.773	−0.10	0.532	0.17	0.269
Trail Making B Test										
All (*n*=110)	0.05	0.630	0.04	0.663	0.07	0.498	0.01	0.929	0.00	0.999
Males (*n*=66)	0.12	0.365	0.15	0.250	0.13	0.317	0.03	0.824	0.01	0.947
Females (*n*=44)	−0.21	0.188	−0.24	0.127	−0.13	0.427	−0.13	0.429	−0.10	0.533
Continuous Performance Test										
All (*n*=98)	−0.24	0.021	−0.18	0.077	−0.27	0.009	−0.19	0.063	−0.12	0.252
Males (*n*=58)	−0.23	0.093	−0.14	0.322	−0.30	0.024	−0.21	0.115	−0.07	0.625
Females (*n*=40)	−0.22	0.190	−0.19	0.257	−0.22	0.190	−0.16	0.354	−0.15	0.378
Covariates: age, years of education										

WAIS, Wechsler Adult Intelligence Scale.