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ORIGINAL ARTICLE

No progression of the alterations in the cortical thickness of individuals with schizophrenia-spectrum disorder: a three-year longitudinal magnetic resonance imaging study of first-episode patients

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Background. Cortical thickness measurement offers an index of brain development processes. In healthy individuals, cortical thickness is reduced with increasing age and is related to cognitive decline. Cortical thinning has been reported in schizophrenia. Whether cortical thickness changes differently over time in patients and its impact on outcome remain unanswered.

Method. Data were examined from 109 patients and 76 healthy controls drawn from the Santander Longitudinal Study of first-episode schizophrenia for whom adequate structural magnetic resonance imaging (MRI) data were available ($n = 555$ scans). Clinical and cognitive assessments and MRIs were acquired at three regular time points during a 3-year follow-up period. We investigated likely progressive cortical thickness changes in schizophrenia during the first 3 years after initiating antipsychotic treatment. The effects of cortical thickness changes on cognitive and clinical variables were also examined along with the impact of potential confounding factors.

Results. There were significant diagnoses × scan time interaction main effects for total cortical thickness ($F_{1,309.1} = 4.60$, $p = 0.033$) and frontal cortical thickness ($F_{1,310.6} = 5.30$, $p = 0.022$), reflecting a lesser thinning over time in patients. Clinical and cognitive outcome was not associated with progressive cortical changes during the early years of the illness.

Conclusions. Cortical thickness abnormalities do not unswervingly progress, at least throughout the first years of the illness. Previous studies have suggested that modifiable factors may partly account for cortical thickness abnormalities. Therefore, the importance of implementing practical actions that may modify those factors and improve them over the course of the illness should be highlighted.

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Key words: Clinical assessment, cortical thickness, first-episode psychosis, longitudinal studies, schizophrenia, structural magnetic resonance imaging.

Introduction

Schizophrenia is a common chronic and disabling brain disorder that is among the world's top 10 causes of long-term disability (Mueser & McGurk, 2004). Imaging and neuropathological investigations have demonstrated brain cortical structural abnormalities that are present at the onset of the disease (Steen *et al.* 2006). These imaging findings, among others, have given support to the prevailing hypothesis that schizophrenia is a disorder of neurodevelopment. Cortical thickness offers important information about brain development processes. In animal studies, the overall thickness of the cortex is reported to be either stable or to lose approximately 2% of its volume with age (Peters & Kemper, 2012), and changes in frontal and temporal thickness are associated with cognitive decline in ageing (Alexander *et al.* 2008). Similarly, in healthy individuals, cortical thickness is reduced with increasing age that mediates, in part, cognitive abilities and general intelligence (Fjell & Walhovd, 2010). Based

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on previous longitudinal magnetic resonance imaging (MRI) studies investigating cortical thickness changes in childhood-onset psychosis (Thompson *et al.* 2001) and chronic patients (van Haren *et al.* 2011; Cobia *et al.* 2012; Nesvag *et al.* 2012), it would be expected that first-episode patients could have a greater cortical thickness reduction over time. Nonetheless, numerous confounding factors can influence brain structures, including antipsychotic medication (Vita *et al.* 2015), stress associated with mental illness (Mondelli *et al.* 2010), smoking and cannabis use (Van Haren *et al.* 2013; Schneider *et al.* 2014), or lifestyle (Lamont *et al.* 2014), although much still remains unclear about these confounding factors. Thus, whether the alterations in cortical thickness may progress differently over time in first-episode schizophrenia patients and the impact of these changes on outcome remain to be properly addressed. We aim: (1) to investigate the pattern of cortical thickness changes over time in a sample of first-episode schizophrenia-spectrum patients compared with healthy control subjects; and (2) to determine whether the cortical thickness changes might substantially influence clinical, cognitive and functional outcome.

Method

Study design

Data for the present investigation were obtained from an ongoing epidemiological and 3-year longitudinal Intervention Programme of First-Episode Psychosis (PAFIP) conducted at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran *et al.* 2008). This programme was approved by the local institutional review board and conformed to international standards for research ethics. Patients meeting the inclusion criteria and their families provided written informed consent prior to inclusion in the PAFIP.

Subjects

Patients included in the PAFIP from February 2001 to December 2007 were invited to participate in this study. To be eligible, they had to fulfil the following inclusion criteria: (1) age 15–60 years; (2) lived in the catchment area; (3) were experiencing their first episode of psychosis; (4) had no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; (5) and met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for schizophrenia, schizophreniform disorder, brief psychotic disorder, schizo-affective disorder or psychosis not otherwise specified. 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.

Individuals who entered the study received extensive clinical and psychopathological assessments and went through an MRI scan. Clinical and MRI assessments were also completed at 1 year and 3 years, as previously described (Roiz-Santianez *et al.* 2014). At baseline, 142 patients and 83 healthy comparison subjects were MRI scanned (Crespo-Facorro *et al.* 2009). For the present longitudinal investigation, only those individuals who completed at least two MRI scans with high-quality images were included. Thus, 109 patients with a schizophrenia spectrum disorder (schizophrenia $n = 79$, 72.5%; schizophreniform disorder, $n = 8$, 7.3%; schizo-affective disorder, $n = 8$, 7.3%; brief psychotic disorder, $n = 6$, 5.5%; psychosis not otherwise specified, $n = 7$, 6.4%, and delusional disorder, $n = 1$, 0.9%) and a control group of 76 healthy subjects were included in the study. The diagnoses were conducted using the Structured Clinical Interview for DSM-IV (SCID-I; First *et al.* 2001) and were confirmed by an experienced psychiatrist 3 years after inclusion for those subjects who attended the 3-year follow-up visit ($n = 102$). Those subjects who did not attend this visit ($n = 7$) had the diagnosis confirmed 6 months from the baseline visit. Our retention rate was 76.8%. Patient attrition was due to a variety of factors: death by suicide ($n = 1$); lost or moved out of the area, ($n = 9$); poor segmentation images ($n = 5$); unable to complete a follow-up MRI scan, ($n = 2$); and refusal to undergo a second (follow-up) MRI examination ($n = 16$). There were no significant differences in a variety of variables [e.g. gender, age at MRI intake, age of onset, intracranial volume, academic level, alcohol, cannabis or tobacco consumption, intelligence quotient (IQ), duration of untreated psychosis (DUP), symptomatology factors, and outcome] between the patients in the attrition group and the patients who decided to continue in the study.

Body weight was determined at baseline, weekly for 3 months, and at 4, 6, 12, 24 and 36 months follow-up (Crespo-Facorro *et al.* 2012).

Healthy comparison subjects were recruited from the community through advertisements. They had no past or present psychiatric, neurological or general medical illness, including substance abuse or significant loss of consciousness, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (Andreasen *et al.* 1992).

Clinical assessment

Clinical symptoms were assessed by using the Brief Psychiatric Rating Scale (BPRS) total (Overall &

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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). We also divided psychopathology into three dimensions of symptoms: positive (scores for hallucinations and delusions); disorganized (scores for formal thought disorder, bizarre behaviour and inappropriate affect); and negative (scores for alogia, affective flattening, apathy and anhedonia) (Grube *et al.* 1998).

Duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such symptom to be considered, there should be no return to previous stable level of functioning) to the date of initiation of an adequate dose of antipsychotic drug taken regularly. DUP was defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment. Duration of untreated 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.

Functionality was evaluated using the global disability item from the Spanish version of the World Health Organization Disability Assessment Schedule (WHO DAS) (Janca *et al.* 1996). Patients were categorized into two groups: good functionality if 1 or lower in the WHO DAS and deficit functionality if 2 or greater in the WHO DAS at 3 years.

Medication assessment

The amount and type of medication being prescribed during the 3-year follow-up period was thoroughly recorded, as previously described (Roiz-Santianez *et al.* 2014). At intake patients were randomly assigned to haloperidol ($n = 19$, 17.4%), olanzapine ($n = 19$, 17.4%), risperidone ($n = 20$, 18.3%), quetiapine ($n = 17$, 15.6%), ziprasidone ($n = 18$, 16.5%) and aripiprazole ($n = 16$, 14.7%). At the 1-year follow-up patients were on haloperidol ($n = 10$, 10.21%), olanzapine ($n = 19$, 19.59%), risperidone ($n = 21$, 22.65%), quetiapine ($n = 16$, 16.49%), ziprasidone ($n = 6$, 6.19%), aripiprazole ($n = 13$, 13.40%), amisulpride ($n = 2$, 2.06%), clozapine ($n = 1$, 1.03%) and risperidone depot ($n = 7$, 7.22%). One patient was not taking antipsychotic medication at the 1-year interview. No reliable information on medication intake was available for one patient at this time point. At the 3-year follow-up the patients were on haloperidol ($n = 4$, 4.82%), olanzapine ($n = 13$, 15.66%), risperidone ($n = 18$, 21.69%), quetiapine ($n = 7$, 8.43%), ziprasidone ($n = 6$, 7.23%), aripiprazole ($n = 10$, 12.05%), amisulpride ($n = 1$, 1.20%), clozapine ($n = 3$, 3.61%) and risperidone depot ($n = 5$, 6.02%). Of the patients, 11 were not taking antipsychotic medication at the 3-year interview. No reliable information on medication intake was available for five patients. Nine patients were treated with mood stabilizers during the follow-up period. Additional information about concomitant medications is available upon request.

Adherence to antipsychotic drugs was assessed by the information obtained from patients and close relatives by the staff (nurse, social worker and psychiatrists) involved in the clinical follow-up. For the present investigation, patients were consensually dichotomized into having a good (defined as patients regularly taking at least 90% of prescribed medication) or a poor adherence (medium or poor compliance) (Crespo-Facorro *et al.* 2012).

Neuropsychological assessments

Cognitive functioning was evaluated at baseline (14 weeks after inclusion), 6 months, 1 year and 3 years after recruitment. For this investigation, differences between baseline and the 3-year follow-up measures of six cognitive domains comprising eight cognitive tests were utilized, with outcome measures in parentheses: (1) verbal memory – Rey Auditory Verbal Learning Test (two measures were obtained: total number of words recalled over learning trials and number of words recalled from the list after delay period); (2) visual memory – Rey Complex Figure Test (long-term recall measure); (3) executive functions – Trail Making Test B (time to complete) and FAS fluency test (number of words in time limit); (4) working memory – Wechsler Adult Intelligence Scale, third edition (WAIS-III) backward digits (total score); (5) speed of processing – WAIS-III digit symbol (standard total score); and (6) attention – Continuous Performance Test Degraded-Stimulus (total number of correct responses) and Brief Test of Attention (total correct responses). The WAIS-III subtest of vocabulary (number of words generated) was used as a covariate to control the effect of pre-morbid IQ.

MRI data acquisition

All MRI scans were obtained at the University Hospital of Cantabria using a 1.5 Tesla General Electric SIGNA System (USA). A MRI protocol [T1, T2 and proton density (PD) sequences] was designed to optimize discrimination between grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The T1-weighted images, using a spoiled grass (SPGR) sequence, were acquired in the coronal plane with the following parameters: echo time (TE) = 5 ms, repetition time (TR) = 24 ms, number of excitations (NEX) = 2, rotation angle = 45 degrees, field of view (FOV) = 26 × 19.5 cm, slice thickness = 1.5 mm and a matrix of 256 × 192. The PD- and

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transverse relaxation time (T2)-weighted images were obtained with the following parameters: 3.0 mm thick coronal slices, TR = 3000 ms, TE = 36 ms (for PD) and 96 ms (for T2), NEX = 1, FOV = 26 × 26 cm, matrix = 256 × 192. The in-plane resolution was 1.016 × 1.016 mm. MRIs of patients and controls were evenly acquired during follow-up time.

Image processing

Processing of the images was performed using BRAINS2 (Magnotta *et al.* 2002). The T1-weighted images were spatially normalized and resampled to 1.0-mm^3 voxels so that the anterior–posterior axis of the brain was realigned parallel to the anterior commissure/posterior commissure line and the interhemispheric fissure aligned on the other two axes. The T2- and PD-weighted images were aligned to the spatially normalized T1-weighted images using an automated image registration program. These images were then subjected to a linear transformation into standardized stereotaxic Talairach atlas space to generate automated measurements of frontal, temporal, parietal and occipital lobes. To further classify tissue volumes into GM, WM and CSF, we used a discriminant analysis method of tissue segmentation based on automated training class selection that utilized data from the T1-weighted, T2-weighted and PD sequences (Harris *et al.* 1999). The discriminant analysis method permits identification of the range of voxel intensity values that characterize GM, WM and CSF. An eight-bit number is assigned to each voxel that indicates its partial volume tissue content (10–70 for CSF, 70–190 for GM and 190–250 for WM). To define the cortical iso-surface to be used in the posterior analyses, a value of pure GM, or 130, was used as a cut-off. This value represents the parametric centre of the GM within the cortex and serves as a useful estimate of its physical centre. This triangulated surface was used as the basis for our calculations of thickness. Cortical thickness was calculated as the minimum distance between the 100% GM triangle surface and the 50/50% GM/WM surface. This measure is an index of cortical thickness. It represents the parametric centre of the cortex or approximately one-half of the cortical thickness. Several studies have been performed to review the reliability and reproducibility of BRAINS (Agartz *et al.* 2001; Okugawa *et al.* 2003).

Statistical analysis

A linear mixed model (LMM) was used to compute cortical thickness changes over the three time points. Subject was treated as a random effect to take into account within-subject correlations in brain volumes. Scan time was included as a repeated measure. A compound symmetry covariance structure for repeated measures was used in this model. The following variables were included as fixed effects used as independent variables or predictors of cortical thickness for different regions of interest: group (dummy coded), gender, age at initial scan and scan time and group × scan time interaction.

A similar LMM was used to examine whether cortical thickness changes in patients might be mediated by functionality (WHO DAS criteria). Here, group was replaced by functionality (good functionality: 51 subjects; deficit functionality: 34 subjects).

In addition, a general linear model (GLM) repeated-measures procedure was conducted for each dependent variable (total, frontal parietal, temporal and occipital cortical thickness) separately, with group (patient, healthy control) as the between-subject variable and time (baseline, 1-year follow-up and 3-year follow-up) as the within-subject variable. The effects of group, time (longitudinal dimension) and time × group (interaction effect) were examined. Age at initial scan was included as a covariate. This GLM procedure does not handle missing data, so only subjects who completed all the three MRI scans (71 patients and 50 healthy subjects) were included in this analysis.

To examine cross-sectional cortical thickness differences between groups at baseline, one-way analysis of covariance was performed. Age at initial MRI and gender were included as covariates.

Relationships between cortical thickness change during the 3-year follow-up period, expressed as percentage change, and clinical improvement (score change between the 3-year and baseline measures of SANS, SAPS, negative, positive and disorganized dimensions total scores) were examined using Spearman rank correlations.

Spearman rank correlations were used to investigate possible statistical relationships between cortical thickness change and cognitive functioning changes during the 3-year follow-up interval.

All statistical analyses were performed with SPSS software version 15 (USA). A two-tailed α level of 0.05 was used for statistical testing. *A priori*, a directional hypothesis was made for the brain measure analyses, thereby lessening the need for Bonferroni corrections. The analyses examining the relationships between the brain measures and clinical and cognitive variables were performed without pre-specified hypotheses, and, therefore, Bonferroni adjustments were applied.

Results

There were no significant differences in the relevant demographic and clinical characteristics between patients ($n = 109$) and healthy subjects ($n = 76$) at intake (all p's > 0.079) (Table 1). No significant differences

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Table 1. *Demographic and clinical characteristics of patients and healthy volunteers*

	Patients ($n = 109$)	Controls ($n = 76$)	Statistics
Males, *n* (%)	66 (60.6)	47 (61.8)	$\chi^2 = 0.03$, $p = 0.859$
Mean age at MRI, years (S.D.)	29.44 (8.21)	27.80 (7.73)	$F = 1.87$, $p = 0.173$
Right-handed, *n* (%)	99 (90.8)	70 (92.1)	$\chi^2 = 0.09$, $p = 0.761$
Mean age at onset, years (S.D.)	28.36 (7.77)	–	–
Mean intracranial volume, ml (S.D.)	1371.72 (137.31)	1380.65 (126.23)	$F = 0.20$, $p = 0.653$
Mean parental socio-economic status (S.D.)[a]	3.67 (0.91)	3.45 (0.73)	$F = 2.30$, $p = 0.085$
Low academic level, *n* (%)[b]	54 (49.5)	27 (36.0)	$\chi^2 = 3.31$, $p = 0.069$
Alcohol users, *n* (%)	66 (60.6)	47 (63.5)	$\chi^2 = 0.16$, $p = 0.686$
Cannabis users, *n* (%)	52 (47.7)	26 (34.7)	$\chi^2 = 3.09$, $p = 0.079$
Tobacco users, *n* (%)	64 (58.7)	43 (57.3)	$\chi^2 = 0.04$, $p = 0.852$
Mean medication time prior to first MRI scan, days (S.D.)	30.6 (24.9)		
Mean DUP, months (S.D.)	11.01 (17.14)	–	–
Median DUP, months	4	–	–
Mean DUI, months (S.D.)	23.64 (27.68)	–	–
Median DUI, months	13	–	–
Mean DPP, months (S.D.)	12.62 (21.22)	–	–
Median DPP, months	5	–	–
Mean baseline symptomatology, total scores (S.D.)			
SANS	6.34 (5.23)	–	–
SAPS	13.65 (4.39)	–	–
BPRS	61.85 (12.68)	–	–
Psychotic dimension	7.33 (2.35)	–	–
Disorganized dimension	6.32 (3.34)	–	–
Negative dimension	4.61 (5.06)	–	–
Mean 3-year follow-up symptomatology, total scores (S.D.)[c]			
SANS	3.65 (5.03)		
SAPS	1.72 (3.43)		
BPRS	30.95 (11.45)		
Psychotic dimension	1.00 (2.00)		
Disorganized dimension	0.72 (1.96)		
Negative dimension	3.21 (4.65)		
Mean cumulative medication intake per year scan-interval (S.D.)[d]	99140.92 (86605.14)		

MRI, Magnetic resonance imaging; S.D., standard deviation; DUP, duration of untreated psychosis; DUI, duration of untreated illness; DPP, duration of untreated prodromic period; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; BPRS, Brief Psychiatric Rating Scale.

[a]Data based on 108 patients.

[b] Data based on 109 patients and 75 healthy controls.

[c] Data based on 94 patients.

[d] Cumulative medication intake are in chlorpromazine equivalents (mg) per year scan-interval.

between the two groups in age and length of interval between MRIs at any of the two follow-up assessments were noted (Table 2).

Cross-sectional findings at baseline revealed a significant cortical thinning in patients in total, frontal, temporal, parietal and occipital cortex (all p's < 0.014).

Scan time effects were significant for all cortical thickness measures, showing progressive cortical thinning over time in all the brain areas (Table 3). The group × scan time interactions indicated the brain regions for which patients differ from healthy control subjects over time. There were significant group × scan time interaction effects for total cortical thickness ($F_{1,309.1} = 4.60$, $p = 0.033$) and frontal cortical thickness ($F_{1,310.6} = 5.30$, $p = 0.022$), reflecting a greater thinning over time in the control group. The rate of change over the 3-year follow-up period in the total mean cortical thickness (expressed as a percentage of baseline cortical thickness) was –2.61% in controls *v.* –0.50% in patients. The change in the frontal lobe cortical thickness was

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Table 2. *Number of subjects, gender, age and average time and range of months between scans*

	Patients				Control subjects			
	Male, *n*	Female, *n*	Mean age, years (S.D.)	Mean scan interval, months (range)	Male, *n*	Female, *n*	Mean age, years (S.D.)	Mean scan interval, months (range)
First scan	66	43	29.44 (8.21)	–	47	29	27.80 (7.73)	–
Second scan[a]	62	35	30.58 (8.33)	12.65 (10.81–17.48)	45	26	29.31 (7.91)	12.61 (11.04–14.72)
Third scan[b]	53	30	33.54 (8.57)	36.76 (34.57–44.94)	30	25	31.32 (7.69)	36.37 (34.26–42.08)

S.D., Standard deviation.

[a] There was no significant difference between the first and second scan interval between patients and control subjects ($F = 0.064$, $p = 0.801$).

[b] There was no significant difference between the first and third scan interval between patients and control subjects ($F = 2.188$, $p = 0.141$).

–3.09% in controls *v.* 0.24% in patients (Fig. 1). Results remained similar when the nine patients treated with mood stabilizers were excluded from the analyses. Our results did not change significantly when cannabis, alcohol and tobacco consumption variables were introduced in the analyses as fixed factors.

Supporting the LMM results, the repeated-measures GLM analysis revealed that there were significant group × time interactions in total cortical thickness ($F_{1,116} = 3.84$, $p = 0.023$) and frontal cortical thickness ($F_{1,117} = 3.22$, $p = 0.042$) (see online Supplementary Table S1).

Correlations between cortical thinning and change in cognitive performance over the 3-year follow-up period among patients are shown in the Supplementary material (online Supplementary Table S2). All correlations were seemingly weak (all r's < 0.34), and after Bonferroni correction, none remained significant.

The analysis of the impact of cortical thickness change and clinical outcome revealed that there was no significant association between cortical thinning and clinical changes at 3 years (see online Supplementary Table S3). Pre-morbid variables (DUP, DUI and DPP) were also not associated with cortical thickness change over time (online Supplementary Table S4). Group × time effects remained similar when only males were analysed. In addition, there were no gender × time (all p's > 0.393) or gender × group interactions (all p's > 0.359) when these factors were included in the analyses as fixed factors.

Patients with good and bad functional outcome (WHO DAS criteria) appeared to have a similar pattern of cortical thickness changes over time (all p's > 0.142).

No significant correlations between variations of body-weight change and cortical thinning during the 3-year follow-up period (all r's > 0.160) were found.

The investigation of the effect of the amount of antipsychotic treatment on brain cortical thinning indicates that there was no significant correlation between cortical thinning and medication intake during the 3-year scan interval (all p's > 0.194). To further study how cortical thickness change may differ according to the amount of antipsychotic treatment, patients were grouped into tertiles of cumulative medication intake: most treatment [358.856 mg chlorpromazine (CPZ) equivalents], intermediate treatment (193.862 mg CPZ equivalents) and least treatment (99.181 mg CPZ equivalents). We conducted an extreme group comparison to contrast cortical thickness change between the most and the least treatment groups. The original LMM was duplicated replacing diagnosis with tertile group membership (most *v.* least treatment) and included a tertile group × scan time interaction time. There were no significant treatment group (all p's > 0.232) or treatment group × time interaction effects (all p's > 0.316).

Finally, we investigated whether cortical thinning might be influenced by antipsychotic medication adherence. No significant effects on adherence were found (all p's > 0.615). Similarly, there were no significant adherence × time interaction effects during the 3-year follow-up period (all p's > 0.236).

Discussion

The main findings of the study were that over a 3-year period: (1) total and frontal cortical thinning was less pronounced during the early course of the illness in patients compared with healthy subjects; (2) cortical thinning during the early years of the illness does not

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Table 3. *Results of best-fit mixed-effects model analyses in a sample of first-episode schizophrenia and healthy subjects*

	Diagnosis		Scan-interval		Group × scan-interval	
Region of interest	b^a (S.E.)	F, p	b^a (S.E.)	F, p	b^a (S.E.)	F, p
Total cortical thickness	−0.1564 (0.0396)	$F_{1,227.1} = 15.57$, $p < 0.001$	−0.0026 (0.0007)	$F_{1,309.6} = 12.79$, $p < 0.001$	0.0020 (0.0010)	$F_{1,309.1} = 4.60$, $p = 0.033$
Frontal cortical thickness	−0.1884 (0.0483)	$F_{1,225.9} = 15.20$, $p < 0.001$	−0.0029 (0.0009)	$F_{1,311.0} = 10.76$, $p = 0.001$	0.0026 (0.0011)	$F_{1,310.6} = 5.30$, $p = 0.022$
Parietal cortical thickness	−0.1046 (0.0391)	$F_{1,226.3} = 7.17$, $p = 0.008$	−0.0022 (0.0007)	$F_{1,305.7} = 8.84$, $p = 0.003$	0.0001 (0.0010)	$F_{1,305.2} = 1.36$, $p = 0.244$
Temporal cortical thickness	−0.1693 (0.0500)	$F_{1,224.2} = 11.45$, $p = 0.001$	−0.0021 (0.0009)	$F_{1,305.8} = 4.85$, $p = 0.028$	0.0008 (0.0012)	$F_{1,305.3} = 0.49$, $p = 0.485$
Occipital cortical thickness	−0.0678 (0.0391)	$F_{1,228.8} = 2.99$, $p = 0.085$	−0.0015 (0.0008)	$F_{1,308.9} = 4.02$, $p = 0.046$	0.0007 (0.0010)	$F_{1,308.4} = 0.55$, $p = 0.459$

S.E., Standard error.
[a] Estimate of regression coefficient.

seem to influence the clinical and cognitive outcome in schizophrenia.

Somewhat contrary to our expectations, total and frontal cortical thinning was less pronounced in patients than in healthy control subjects. Although still significantly different, the decreased cortical thickness found at 3 years appears to be less marked than at baseline. Thus, structural brain alterations observed at the first break are partly reversible during the early course of the illness. Some of the previous structural brain studies in schizophrenia (Keshavan *et al.* 1998; Schaufelberger *et al.* 2011) have demonstrated that brain volume reductions present at illness onset may be restorable. Chronic stress (Blix *et al.* 2013), diet (Sizonenko *et al.* 2013) and cognitive activity (Engvig *et al.* 2010) have been described as modifiable factors that might influence cortical thickness. It has been observed that chronic stress mediates cortical thinning as well as with selective changes of subcortical volumes, with behavioural correlates in the healthy population (Savic, 2013). Recently, Mosconi *et al.* (2014) have shown that the Mediterranean diet may protect against brain tissue loss. Cognitive function has been associated with cortical thickness in fronto-temporal regions (Tuladhar *et al.* 2015) and there are findings of increases in cortical thickness following the practice of cognitive tasks (Haier *et al.* 2009). Lengthy DUP has been associated with reduced cortical volume (Malla *et al.* 2011), and the likely toxic effect of the stress associated with illness symptomatology has been proposed to be underlying these brain anomalies (Andreasen *et al.* 2013). The detailed analysis of thickness changes over time in our study reveals that total (0.50%) and frontal (1.68%) cortical thickness slightly increased over the first follow-up period (from baseline to 1 year) when patients received higher doses of antipsychotic medication. They demonstrated cortical thickness reduction similar to that of healthy controls during the second follow-up period. Nonetheless, we did not find any significant association between cumulative antipsychotic dose and cortical thickness changes at 3 years. A recent longitudinal study investigating the effects of short-term atypical treatment on middle frontal thickness found that patients displayed a significant increase in rostral middle frontal thickness over 8 weeks of treatment compared with controls (Goghari *et al.* 2013). Atypical antipsychotics may induce neuronal plasticity and synaptic remodelling (Horacek *et al.* 2006), which could exert a relative increase in cortical thickness in patients compared with controls by ameliorating the natural age-related cortical thinning observed in healthy individuals. Cortical thinning has been reported to be less pronounced in chronic patients receiving atypical antipsychotics in a longitudinal

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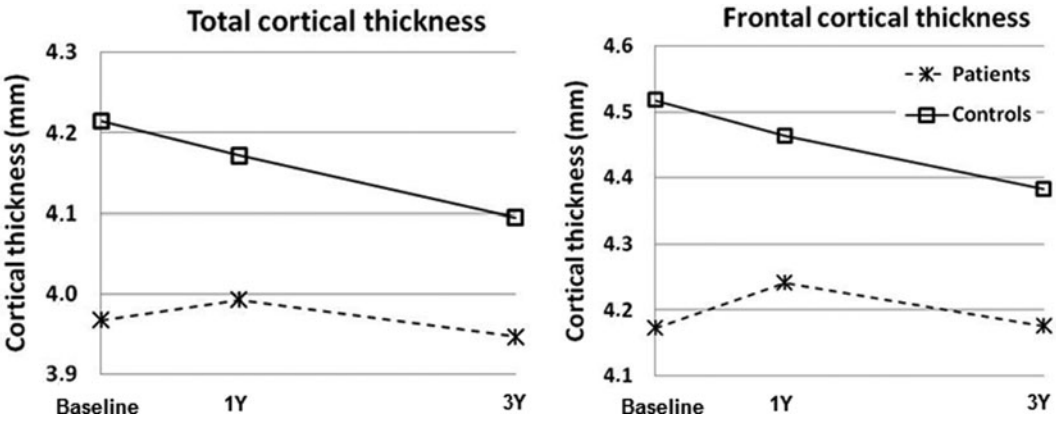

Fig. 1. Changes in total and frontal cortical thickness in patients with schizophrenia and healthy controls during the 3-year follow-up period. 1Y, 1 Year; 3Y, 3 years.

investigation (van Haren *et al.* 2011). In contrast, in a recent study (Roiz-Santianez *et al.* 2012), we found that low doses of haloperidol, risperidone and olanzapine equally affected GM cortical thickness in the medium term (1 year). Previous cross-sectional studies, but not all (Narr *et al.* 2005), found no association between antipsychotic medication and cortical thickness (Kuperberg *et al.* 2003; Nesvag *et al.* 2008). The majority of the patients in our study had been taking only atypical antipsychotics during the follow-up but switched their initially prescribed medication several times during the 3-year follow-up period (Crespo-Facorro *et al.* 2012). Therefore, a valid investigation of the effect of different types of antipsychotics on cortical thickness changes was not viable.

Only three previous studies (van Haren *et al.* 2011; Cobia *et al.* 2012; Nesvag *et al.* 2012) have evaluated cortical thickness longitudinally in chronic schizophrenia, and the results have been inconclusive. Excessive cortical thinning over time in widespread areas on the cortical mantle, most pronounced in frontal and temporal cortex areas, has been described in schizophrenia patients (van Haren *et al.* 2011; Cobia *et al.* 2012). In contrast, Nesvag *et al.* (2012) reported a similar pattern of cortical thinning over time in patients and healthy subjects. The mean duration of illness at baseline among patients was above 11 years in those three studies. Factors commonly associated with illness chronicity, i.e., cognitive and physical inactivity and obesity, may account for these discrepancies between studies. Supporting our results, previous cross-sectional studies have found a similar effect of age on cortical thickness in patients compared with controls (Crespo-Facorro *et al.* 2011; Kubota *et al.* 2011), suggesting that the reduction of cortical thickness in schizophrenia might not be progressive over the course of the illness.

An important question related to brain structural changes over time in schizophrenia is whether they could have a major impact in clinical and cognitive outcome. In the present investigation, we failed to demonstrate a significant association between changes in cortical thickness and clinical outcome. This is in line with the results of some recent longitudinal studies (Ho *et al.* 2003; Cobia *et al.* 2012; Roiz-Santianez *et al.* 2012), but it contradicts the findings of van Haren *et al.* (2011). Most of the previous cross-sectional studies have not found significant correlations between cortical thickness values and the severity of psychopathology (Kuperberg *et al.* 2003; Crespo-Facorro *et al.* 2011; Kubota *et al.* 2011). Also, no evidence of a significant association between cortical thickness changes and cognitive functioning changes over time was found. Some cross-sectional studies have described a link between cognitive impairments and cortical thinning (Cobia *et al.* 2011) and associations of cortical thickness and cognitive domains (Crespo-Facorro *et al.* 2011; Ehrlich *et al.* 2012). However, the only longitudinal study (Cobia *et al.* 2012) examining associations between cortical thickness change and cognitive change scores conducted to date yielded no significant findings.

Our results do not provide support to the current renewal of Kraepelin's concept in the brain imaging literature that suggests a marked progressive brain change in schizophrenia individuals from its earliest stages (DeLisi, 2008). However, our findings are consistent with what is now known about the clinical course of schizophrenia (Zipursky *et al.* 2013) and with our experience in day-to-day clinical practice (Ayesa-Arriola *et al.* 2013). In this line of thinking, cognitive impairments are already present at first episode and thereafter remain static (Rodríguez-Sánchez *et al.* 2013). Therefore, it would have been unexpected that cortical thickness anomalies would progressively increase over time. Likewise, it could be expected that a likely cortical thickness reduction over time is

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associated with an inherent clinical and functional decline following a first episode of psychosis. However, longitudinal studies on schizophrenia have observed that an important percentage of the patients do not suffer a deteriorating course of the illness (Crespo-Facorro *et al.* 2012). The fact that only approximately 55–60% of the patients who had suffered a first episode of psychosis may have functional disability in the long term (Menezes *et al.* 2006) might cast doubt on whether this progressive neuropathological progress may be present in all patients.

A reasonably large sample, uniform follow-up intervals using the same MRI scanner and protocol, and a thorough clinical investigation during the follow-up period add strength to the conclusions drawn from this study. It is important to take into account that there are a large number of scanning and analysis parameters to take into account. Then, it is not possible to apply universal guidance on how to implement brain imaging analyses. Therefore, great caution should be taken into account when comparing the results of brain imaging studies using different software packages (Eggert *et al.* 2012). Several limitations should be taken into account when interpreting these results. First, some subjects were not scanned at all time points. Second, and given the fact that schizophrenia is a life-long disease, a follow-up period of 3 years may be too short to demonstrate subtle changes. Third, structure–function correlations that are usually reported in the literature are between 0.20 and 0.25. Therefore, the use of Bonferroni correction might be considered too strict. Fourth, despite our sample having been treated with low doses of antipsychotics for a short time (mean of 30.6 days) prior to their first MRI scan, this exposure to antipsychotics may influence morphometric characteristics and contribute to the unexpected finding of greater change in healthy comparison subjects relative to patients. Finally, some patients withdrew from their medication, and most of them switched medication during the 3-year follow-up period, which makes the investigation of the effects of different types of antipsychotics an unfeasible study.

In summary, cortical thickness abnormalities that have been consistently observed at the onset of non-affective psychosis may not be unswervingly progressive, at least throughout the first years of the illness. Previous studies have suggested that modifiable factors (i.e. medication, substance abuse, lifestyle and stress) may partly account for cortical thickness abnormalities. Therefore, the importance of implementing practical actions that may modify those factors and improve them over the course of the illness should be highlighted. The percentage of first-episode patients with poor outcomes and with functional recovery remained stable over time, a pattern that would not be expected for a progressive brain disease. Taken together with the clinical and cognitive longitudinal data, our longitudinal imaging findings suggest a more optimistic and inspiring perception of the illness.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715000811

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Declaration of Interest

None.

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