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ORIGINAL ARTICLE

A longitudinal study of cortical changes and their cognitive correlates in patients followed up after first-episode psychosis

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Background. Loss of cortical volume in frontotemporal regions occurs in patients with first-episode psychosis (FEP) and longitudinal studies have reported progressive brain volume changes at different stages of the disease, even if cognitive deficits remain stable over time. We investigated cortical changes in patients over the 2 years following their FEP and their associations with clinical and cognitive measures.

Method. Twenty-seven patients after their FEP (20 with schizophrenia, seven with schizo-affective disorder) and 25 healthy controls matched for age and gender participated in this study. Magnetic resonance imaging (MRI) was performed on a 1.5-T scanner both at baseline and after 2 years. Area and thickness of the cortex were measured using surface-based morphometry (SBM). Patients also underwent neuropsychological testing at these two time points.

Results. Progressive cortical thinning in the superior and inferior frontal and, to a lesser extent, superior temporal cortex was observed in patients. Cortical area remained constant. Cortical thinning was associated with duration of treatment at a trend level and was predicted by baseline measures of IQ and working memory. Cortical thinning occurred in the absence of clinical or cognitive deterioration.

Conclusions. The clinical implications of these cortical changes remain uncertain, but patients with less cognitive reserve may be more vulnerable to developing cortical abnormalities when exposed to medication or other disease-related biological factors.

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Key words: Cognitive impairment, cortical area, cortical thickness, first-episode psychosis, follow-up, magnetic resonance imaging, surface-based morphometry.

Introduction

Cortical development is influenced by both genetic and environmental factors (Giedd *et al.* 2007). In schizophrenia, cortical abnormalities may already be present in early life and prenatally (Murray & Lewis, 1987). Longitudinal studies of patients after their first-episode of psychosis (FEP) have suggested that there are progressive cortical changes. This seems to occur throughout the illness (van Haren *et al.* 2011), but is especially prominent during the early years following psychosis onset (van Haren *et al.* 2012). Loss of cortical volume in patients with FEP has been well described in frontal and temporal regions (Ellison-Wright *et al.* 2008) and systematic reviews of longitudinal voxel-based morphometry (VBM) studies have reported progressive loss of grey matter volume in frontal and temporal regions in patients after their first episode in both adult-onset (Hulshoff Pol & Kahn, 2008) and childhood-onset schizophrenia (Arango *et al.* 2008).

Post-mortem studies have shown that neuropathological changes in patients with schizophrenia are more pronounced in the dorsolateral prefrontal cortex than in other cortical regions (Selemon, 2001) and the loss of brain tissue could be due to a reduction in oligodendrogial cells (Uranova *et al.* 2004). Chronic exposure of macaque monkeys to haloperidol or olanzapine was associated with a 10–18% reduction in glial cells in parietal grey matter (Konopaske *et al.* 2007). It remains to be determined whether these progressive brain

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changes in humans reflect pathology specific to schizophrenia (Brans *et al.* 2008) or whether they may be determined by environmental factors such as antipsychotic medication (Ho *et al.* 2011; Vernon *et al.* 2011), cannabis consumption (Rais *et al.* 2008; Martin-Santos *et al.* 2010) or a combination of both.

Cognitive deficits are also present in patients with FEP (Joyce *et al.* 2005), but in contrast to those findings of cortical volume loss over time, longitudinal studies (Leeson *et al.* 2011) suggest that cognitive deficits remain stable over time. A correlation between progressive cortical volume loss and cognitive impairment throughout the illness has been found in some studies (Andreasen *et al.* 2011; Asami *et al.* 2012) but not in others (van Haren *et al.* 2008; Arango *et al.* 2012).

The area and thickness of the cortex are both high heritability but are determined by different genetic mechanisms (Panizzon *et al.* 2009) and may respond differently to developmental or environmental insults (Du *et al.* 2007; Voets *et al.* 2008). It would therefore seem appropriate to measure the area and thickness of the cortex separately while investigating the possible effects of developmental and environmental factors on the cortical changes of schizophrenia. Surface-based morphometry (SBM) methods such as Freesurfer (Fischl & Dale, 2000) are well suited for this purpose and are also capable of detecting longitudinal changes in cortical parameters with small variability of within-subjects measurements at each time point (Reuter *et al.* 2012).

Longitudinal studies using SBM in patients with schizophrenia have reported widespread cortical thinning without concomitant cortical area reductions (Cobia *et al.* 2012), with most extensive loss in the frontal and temporal regions (van Haren *et al.* 2011; Cobia *et al.* 2012). Long-term antipsychotic treatment has been correlated with thinning of the frontal and cingulate cortex whereas poor social outcome was found to correlate with thinning of the middle temporal cortex (van Haren *et al.* 2011), but others failed to find such correlations (Cobia *et al.* 2012; Roiz-Santianez *et al.* 2012). Goghari *et al.* (2013) recently reported an increase in prefrontal cortical thickness in FEP patients after short-term treatment with atypical antipsychotics.

Using SBM in a cross-sectional study of FEP patients, we have previously reported reductions in cortical area in the superior temporal gyrus without changes in cortical thickness (Gutiérrez-Galve *et al.* 2010). These cortical changes were associated with premorbid and current IQ.

We report here an exploratory longitudinal study using SBM (Freesurfer) of patients followed up 2 years after their first psychotic episode. The sample of patients included in this longitudinal study overlaps with that of our cross-sectional study (Gutiérrez-Galve *et al.* 2010). We hypothesized that progressive reductions in cortical thickness would be more prominent than those in cortical area in patients compared to healthy controls. We also explored the relationship between cortical changes and changes in symptoms and cognition over the same time points. To our knowledge this is the first longitudinal study to explore the association between changes in area and cortical thickness and cognitive measures in patients with FEP.

Method

Subjects

The patients presented with a psychotic illness for the first time, and had received no more than 12 weeks of antipsychotic medication. As part of the West London Longitudinal First-Episode Psychosis Study (Huddy *et al.* 2007), diagnostic assessments were conducted at presentation and approximately 1 year later. Diagnosis was ascertained using the diagnostic module of the Diagnostic Interview for Psychosis (DIP-DM; Jablensky *et al.* 2000). Two nurses trained by an experienced psychiatrist (T.R.E.B.) conducted the interviews.

At recruitment, the patients were between 16 and 43 years of age. Twenty-seven FEP patients (17 males) were followed up for 23.8 months after the initial magnetic resonance imaging (MRI) and neuropsychological assessment; at baseline, 24 patients were prescribed antipsychotics (23 atypical, one typical) and at follow-up 18 patients (17 atypical, one typical). Of the 27 patients, 20 had a diagnosis of schizophrenia and seven of schizo-affective disorder. Twenty-five healthy participants (14 males) matched for age and gender who were followed up after a mean of 20.5 months after the initial MRI and neuropsychological assessment served as controls. Sixteen patients and 15 controls who participated in this study had also been included in our previous cross-sectional study (Gutiérrez-Galve *et al.* 2010). Exclusion criteria for all participants were the presence of a medical or neurological illness, including head injury leading to unconsciousness. Controls with prior or family history of psychiatric illness were excluded.

Ethical permission was obtained from the local Ethics Committees. Participants gave written informed consent according to the Declaration of Helsinki.

Demographic details are given in Table 1.

Procedures

Clinical and neuropsychological assessment, MRI acquisition and processing have been described previously (Gutiérrez-Galve *et al.* 2010). Clinical and neuropsychological assessment and MRI were performed at baseline and follow-up. The maximum

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Table 1. *Demographic and total brain volume measures in patients and controls*

	Patients ($n=27$)		Controls ($n=25$)		Comparison
	Baseline	Follow-up	Baseline	Follow-up	Baseline P *v.* C
Age (years)	25.9 (6.5) [16.4–42.8]	27.8 (6.5) [17.8–44.5]	26.8 (7.1) [16.4–44.7]	28.5 (7.1) [17.7–46.8]	$t_{50}=0.52$, $p=0.607$
Male gender, *n* (%)	17 (63.0)	N.A.	14 (56.0)	N.A.	$\chi^2_1=0.22$, $p=0.609$
Left-handed, *n* (%)	3 (11.1)	N.A.	3 (12.0)	N.A.	$\chi^2_1=0.01$, $p=0.920$
Follow-up (months)	N.A.	23.8 (6.2) [12.6–39.0]	N.A.	20.5 (3.0) [16.1–30.0]	$t_{50}=-2.42$, $p=0.042$
Total brain volume (mm^3)	1 522 788 (138105.4)	1 522 584 (131282.1)	1 454 995 (187972.2)	1 453 049 (191393.7)	$p=0.086$
Current IQ	98.1 (16.5) [63–130]	N.A.	110.3 (12.8) [81–137]	N.A.	$t_{50}=2.86$, $p=0.006$

N.A., Not applicable.
Data shown are mean (standard deviation) [range] with *p* values of differences between patients (P) and controls (C).

interval between clinical and neuropsychological assessment and MRI on both occasions was 1 month.

Clinical measures

These included the Scales for the Assessment of Negative and Positive Symptoms (SANS and SAPS; Andreasen, 1983, 1984), the Young Mania Rating Scale (YMRS; Young *et al.* 1978), the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960), age of onset and duration of untreated psychosis (DUP; Perkins *et al.* 2000), alcohol and drug use scales (Drake *et al.* 1990), handedness (Annett, 1970) and social function. Duration of treatment was calculated as the number of days patients were prescribed antipsychotic medication from the first time, as ascertained from their clinical notes.

Neuropsychological measures

We used the National Adult Reading Test (NART; Nelson & Willson, 1991) to measure premorbid IQ, the short Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III; Wechsler, 1997) to measure current IQ, the Cambridge Neuropsychological Test Automated Battery (CANTAB: working memory span, working memory manipulation and Stockings of Cambridge; Sahakian & Owen, 1992) to measure executive function, and the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1995) to measure verbal memory. Cognitive measures were assessed at baseline and follow-up in patients.

Image processing

Freesurfer 4.5.0 (http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing) was used to generate longitudinal maps of surface area and cortical thickness (Dale *et al.* 1999; Fischl *et al.* 1999). The longitudinal process is designed to be unbiased at all time points and a template volume is created instead of initializing the template with information from a specific time point. Using the processed results from the unbiased template, the random variation in the processing procedure is reduced and the robustness and sensitivity of the overall longitudinal analysis is improved (Reuter & Fischl, 2011; Reuter *et al.* 2012).

Total brain volume was estimated using Freesurfer (Buckner *et al.* 2004). Cortical parameters were measured by L.G.-G., blind to participant status.

Analysis of cortical parameters

Twenty-two cortical parcellations in each hemisphere were selected from the Desikan template (Desikan *et al.* 2006): nine frontal (superior, rostral middle, caudal middle, pars opercularis, pars triangularis,

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pars orbitalis, frontal pole, lateral and medial orbitofrontal), eight temporal (transverse, superior, middle, inferior, temporal pole, fusiform, entorhinal and parahippocampal), three parietal (superior, inferior and precuneus), three occipital (lateral, cuneus and lingual) and four cingulate (rostral anterior, caudal anterior, posterior and isthmus). The average cortical thickness, total surface area and total volume of the cortex for frontal, temporal, parietal, occipital and cingulate regions in each hemisphere were calculated from the individual parcellations at baseline and follow-up. The following comparisons were made for each region: (1) follow-up *versus* baseline in patients; (2) follow-up *versus* baseline in controls; (3) patients *versus* controls at baseline and (4) patients *versus* controls at follow-up.

Statistical analysis

Baseline and follow-up cortical parameter measures were used for patients and controls. In patients, baseline and follow-up cognitive measures were used to explore associations between cortical parameters and cognitive measures, and baseline cognitive measures were used to predict cortical changes. The statistical package Stata version 10 (Stata Corporation, USA) was used for analyses. Age, gender, duration of follow-up and handedness were compared using t and χ^2 tests.

Linear regression models were used to estimate longitudinal differences for the clinical and cognitive measures in patients.

Linear mixed models were used to estimate longitudinal differences in whole brain cortical parameters (average cortical thickness, total surface area and total volume) of the parcellations in each of the five brain regions, with side (right/left) and assessment time (baseline/follow-up) as within-subject factors, and diagnosis (control/patient) and gender as between-subject factors. Differences in whole brain cortical parameters and total brain volume were estimated with two-way interactions (diagnosis by assessment time). When significant interactions were present, the same model was repeated separately for each brain region. When significant interactions were present for one region, the model was repeated for the parcellations within that region with three-way interactions (parcellation by diagnosis by assessment time).

Linear mixed models were also used to explore whether changes in cortical parameters were associated with changes in clinical and cognitive variables over time in patients. Two-way interactions were included (clinical variable by assessment time, cognitive score by assessment time). When significant interactions were present for whole brain cortical parameters, the model was repeated for each brain region and for the parcellations within that brain region if these were significant. Age, gender and duration of follow-up were covariates in all models.

As in previous studies (Kuperberg *et al.* 2003; Gutiérrez-Galve *et al.* 2010), we did not control for whole brain volume, as this is a schizophrenia-related variable that would have obscured possible group differences. Adjustment for multiple comparisons was performed for each model using false discovery rate (FDR; Genovese *et al.* 2002) correction and the level of significance was set at 0.05.

To determine whether cognitive functions at baseline predicted changes in cortical parameters at follow-up in patients, linear regression analyses were performed with cortical parameters as the dependent variable. All neuropsychological measures were entered as potential predictors using stepwise entry criteria set at $p=0.10$.

Results

Table 1 shows that there were no differences in age, gender, handedness, time to follow-up or total brain volume between patients and controls. Current IQ differed significantly between patients and controls ($p=0.006$). Total brain volume between patients and controls was greater at follow-up than at baseline at trend level (mean differences between baseline and follow-up by diagnosis $=-6251.8\ mm^3$, $p=0.086$).

Table 2 shows that positive and negative symptoms improved significantly over time ($p<0.05$). There were few significant differences between baseline and follow-up in the cognitive measures. Only verbal learning changed significantly ($p=0.018$) and this was seen in the direction of improvement. In a *post-hoc* analysis, symptoms of depression were not associated with cognitive measures over time (see online Supplementary Table S1).

The analyses were repeated without the schizoaffective subgroup ($n=20$) and the results remained unchanged.

Cortical thickness

Whole brain

The difference in average cortical thickness across all regions between patients and controls was greater at follow-up than at baseline (mean differences between baseline and follow-up by diagnosis $=-0.03402$ mm, $p=0.010$). In patients, average whole-brain cortical thickness was reduced at baseline at a trend level of significance (patients–controls, mean $=-0.05126$ mm, $p=0.072$) and was significantly reduced at follow-up [patients–controls, mean $=-0.08528$ mm, 95% confidence interval (CI) -0.14167 to -0.02887, $p=0.003$].

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Table 2. *Clinical and cognitive measures in patients*

	Baseline	Follow-up	Comparison
Age at onset of psychosis (years)	24.4 (7.1) [12–42] 27	N.A.	N.A.
DUP (weeks)	45.0 (82.2) [0–360] 27	N.A.	N.A.
Duration of treatment (days)	157.6 (223.6) [0–1113] 27	599.2 (296.7) [65–1211] 27	$t_{53}=0.12$, $p=0.907$
Social function	113.0 (9.7) [97.4–131.2] 27	114.7 (9.3) [99.3–129.6] 27	$t_{53}=0.92$, $p=0.362$
SANS	4.3 (5.3) [0–17] 27	2.6 (4.0) [0–14] 27	$t_{53}=-2.44$, $p=0.018$
SAPS	8.6 (4.9) [0–18] 27	2.0 (2.9) [0–9] 27	$t_{53}=-2.25$, $p=0.029$
HAMD	11.6 (10.0) [0–34] 27	4.6 (5.7) [0–19] 27	$t_{53}=-1.25$, $p=0.216$
YMRS	7 (10.6) [0–36] 27	1.0 (3.2) [0–12] 27	$t_{53}=-0.54$, $p=0.592$
Premorbid IQ	103.6 (11.2) [77–120] 27	N.A.	N.A.
Current IQ	98.1 (16.5) [63–130] 27	103.7 (20.6) [67–149] 27	$t_{53}=1.42$, $p=0.162$
Working memory span	6.1 (1.5) [3–9] 26	6.6 (1.3) [5–9] 26	$t_{51}=0.44$, $p=0.660$
Planning	8.0 (2.5) [2–12] 27	8.4 (2.4) [3–12] 26	$t_{52}=-0.56$, $p=0.577$
Working memory manipulation	32.3 (17.7) [0–64] 27	28.2(21.8) [0–66] 27	$t_{53}=-0.73$, $p=0.471$
RAVLT	42.5 (8.2) [27–58] 27	46.1 (11.7) [25–69] 27	$t_{53}=2.45$, $p=0.018$

DUP, Duration of untreated psychosis; SANS, Scales for the Assessment of Negative Symptoms; SAPS, Scales for the Assessment of Positive Symptoms; HAMD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale; RAVLT, Rey Auditory Verbal Learning Test; N.A., not applicable.

Data shown are mean (standard deviation) [range] n tested with p values of differences between baseline and follow-up in patients.

Regional cortical parameters in patients and controls unadjusted by age or gender are given in Table 3.

Frontal cortex

The difference in cortical thickness between the groups was greater at follow-up than at baseline (mean differences between baseline and follow-up by diagnosis = −0.05065 mm, $p=0.008$). Cortical thickness did not differ between the groups at baseline (patients–controls, mean = −0.05561 mm, $p=0.112$) but it was reduced in patients at follow-up (patients–controls, mean = −0.10626 mm, 95% CI −0.17588 to −0.03665, $p=0.003$). This difference was accounted for by thickness reduction in the superior frontal (−0.08569 mm, 95% CI −0.16547 to −0.00593, $p=0.035$), pars opercularis (−0.13267 mm, 95% CI −0.21067 to −0.05466, $p=0.001$) and pars triangularis (−0.13297 mm, 95% CI −0.21254 to −0.05341, $p=0.001$) parcellations (see Fig. 1).

The rate of cortical thinning over time was faster in patients (cortical thinning in patients–controls = −0.00255 mm/month, 95% CI −0.00413 to −0.00096, $p=0.002$, with cortical thinning of −0.00190 mm/month, 95% CI −0.00298 to −0.00081, $p=0.001$ in patients).

Temporal cortex

The difference in cortical thickness between groups was greater at follow-up than at baseline at trend level of significance (mean differences between baseline and follow-up by diagnosis = −0.04391, $p=0.052$). Cortical thickness did not differ between groups at baseline (patients–controls, mean = −0.04281 mm, $p=0.251$) but was reduced in patients at follow-up (patients–controls, mean = −0.08671 mm, 95% CI −0.16117 to −0.01227, $p=0.022$). Cortical thinning in the superior temporal (−0.15801 mm, 95% CI −0.24930 to −0.06672, $p=0.001$) parcellation in the patient group accounted for the difference.

The rate of thinning over time was faster in patients (cortical thinning in patients–controls = −0.00197 mm/month, 95% CI −0.00390 to −0.00003, $p=0.046$, with a thickness reduction of −0.00235 mm/month, 95% CI −0.00364 to −0.00105, $p<0.001$ in patients).

No significant differences between the groups were seen in the thickness of the parietal, occipital or cingulate cortex.

Cortical area

There were no differences in cortical area between groups at baseline or follow-up (mean differences between baseline and follow-up by diagnosis = −324.76 mm^2, $p=0.648$), indicating that the cortical area had remained unchanged in both groups during the follow-up.

We performed a *post-hoc* analysis in the patient group, looking for changes in cortical area in those parcellations (superior frontal, pars opercularis, pars triangularis and superior temporal) showing longitudinal

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Table 3. *Regional cortical parameters in patients and controls unadjusted by age or gender*

Region of cortex		Thickness (mm)[a]				Area (mm^2)[b]				Volume (mm^3)[b]			
		Patients		Controls		Patients		Controls		Patients		Controls	
		B	Fu	B	Fu	B	Fu	B	Fu	B	Fu	B	Fu
Frontal	L	2.88 (0.16)	2.83 (0.13)	2.92 (0.14)	2.92 (0.15)	19732.9 (2285.7)	19653.4 (2459.8)	20619.2 (2229.5)	20657.3 (2354.5)	67733.1 (9127.5)	65018.7 (8868.9)	65639.8 (6288.4)	66479.1 (6756.3)
	R	2.89 (0.15)	2.84 (0.14)	2.95 (0.13)	2.95 (0.14)	19897.7 (2548.9)	19645.2 (2571.2)	20884.2 (2346.9)	20797.5 (2422.6)	65323.8 (9599.7)	65199.8 (9149.8)	65707.5 (6063.2)	66462 (6754.3)
Temporal	L	2.97 (0.12)	2.93 (0.15)	2.99 (0.16)	3.00 (0.16)	13148.6 (1651.7)	13098.5 (1628.8)	14187.6 (2086.2)	14283.5 (2125)	48098.5 (6703.1)	47598.7 (6630.4)	48469.6 (6673.7)	48756.3 (6797)
	R	3.00 (0.13)	2.94 (0.17)	3.06 (0.14)	3.04 (0.15)	13018.9 (1456.1)	12987.5 (1471.9)	14052.8 (1757)	14095.6 (1795.5)	47911.3 (5635.9)	47470.2 (5659.7)	48048.8 (5723.5)	47783 (6135.3)
Parietal	L	2.46 (0.15)	2.43 (0.14)	2.50 (0.12)	2.49 (0.12)	12731.7 (1224.7)	12532.8 (1220. 8)	12699.7 (1384.5)	12682.6 (1424.1)	34216.6 (4645.9)	33512.2 (4603.1)	34351.5 (3545.6)	34226.1 (3631.1)
	R	2.49 (0.16)	2.44 (0.14)	2.52 (0.12)	2.52 (0.12)	12996.7 (1098.2)	12669.5 (1058.3)	13776.4 (1732)	13752 (1781.3)	34349.7 (4086.1)	33865.4 (3780.1)	35762.5 (4761.8)	35565.1 (4912.5)
Occipital	L	2.15 (0.14)	2.13 (0.13)	2.19 (0.09)	2.19 (0.09)	8965.7 (1083.5)	8927.1 (1107.1)	8770.6 (1334.5)	8804.6 (1316.1)	20894.1 (2984.5)	20532.5 (2980.1)	21041.2 (3211.9)	21085.9 (3175)
	R	2.18 (0.13)	2.15 (0.12)	2.23 (0.10)	2.22 (0.09)	8685.7 (1245.3)	8603.4 (1250.2)	8474 (1198.8)	8512.5 (1195.2)	20650 (3647.3)	20170 (3530.9)	20687.4 (2650.3)	20618 (2687.9)
Cingulate	L	3.12 (0.20)	3.07 (0.20)	3.18 (0.17)	3.17 (0.19)	3026.8 (512.6)	3006.1 (494.2)	2920.9 (440.1)	2913.8 (443.1)	9732.7 (1745.8)	9502.3 (1674.4)	9527.8 (1527.4)	9485.3 (1515.3)
	R	3.10 (0.19)	3.04 (0.20)	3.14 (0.21)	3.13 (0.20)	3023.2 (516.1)	3025.7 (526.8)	2953.8 (474.1)	2968.2 (476.8)	9612.8 (1650.9)	9386 (1625.3)	9620.4 (1622.5)	9568.8 (1578.5)

B, Baseline; Fu, follow-up; L, left; R, right.

[a] Values given are mean (standard deviation).

[b] Values given are mean (standard deviation) of the sums of six parcellations each.

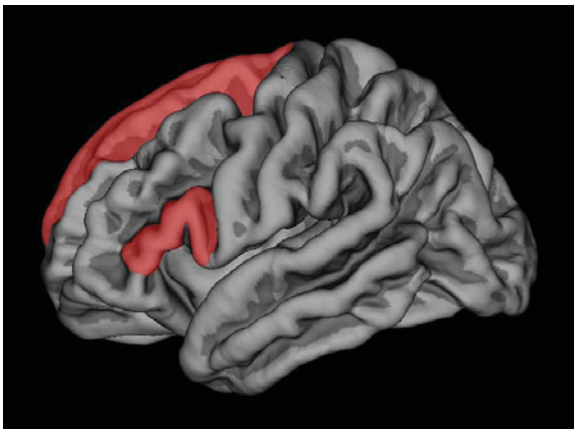

Fig. 1. Parcellations where cortical thickness was significantly different between patients and controls followed up for 2 years: superior frontal, pars opercularis and pars triangularis.

reductions in cortical thickness. The cortical area in the superior frontal parcellation was smaller in patients than in controls at both baseline and follow-up but there was no change in area over time (follow-up–baseline mean by diagnosis = –1.99 mm^2, $p=0.801$; baseline: patients–controls, mean = –269.98 mm^2, $p=0.045$; follow-up: patients–controls, mean = –271.97 mm^2, $p=0.040$) (see Supplementary Table S2).

There were no differences in cortical volume between groups at baseline or follow-up (mean differences between baseline and follow-up by diagnosis = –3864.54 mm^3, $p=0.193$).

Associations with duration of treatment

The association of duration of antipsychotic treatment with average cortical thickness was stronger at follow-up than at baseline (cortical thinning over time = −0.00012 mm/day of treatment, 95% CI −0.00022 to −0.00002, $p=0.020$, with a thickness reduction of −0.00009 mm/day, 95% CI −0.00018 to −0.000001, $p=0.048$ at follow-up).

The association of frontal cortical thickness with duration of treatment was stronger at follow-up than at baseline (cortical thinning over time = −0.00019 mm/day of treatment, 95% CI −0.00033 to −0.00005, $p=0.007$, with thinning of −0.00010 mm/day, 95% CI −0.00018 to −0.000001, $p=0.050$ at follow-up). This was accounted for by thinning in the superior frontal (−0.00014 mm/day, 95% CI −0.00025 to −0.00002, $p=0.020$) and caudal middle frontal (−0.00015 mm/day, 95% CI −0.00027 to −0.00002, $p=0.019$) parcellations.

The association of duration of treatment with frontal cortical volume was stronger at follow-up than at baseline (cortical volume changes over time = −5.05 mm^3/day of treatment, 95% CI −9.41 to −0.68, $p=0.023$, with a volume reduction of −4.09 mm^3/day, 95% CI −7.11 to −1.07, $p=0.008$ at follow-up).

Associations with cognitive variables

Premorbid IQ was associated with total cortical area at baseline and follow-up ($p<0.05$) and the strength of this association was similar on both occasions (over time mean difference in cortical area per IQ point = 0.94 mm^2, $p=0.958$). This was explained by the association with frontal area (baseline: increase of 82.75 mm^2, 95% CI 13.30–152.20, $p=0.020$ per IQ point; follow-up: increase of 89.86 mm^2, 95% CI 20.26–159.44, $p=0.011$ per IQ point).

Premorbid IQ was associated with total cortical volume at baseline and follow-up ($p<0.05$) and the strength of this association was similar on both occasions (over time mean difference in cortical area per IQ point 57.08 mm^3, $p=0.442$). This was explained by the association with frontal (baseline: increase of 280.59 mm^3, 95% CI 34.19–526.98, $p=0.026$ per IQ point; follow-up: increase of 293.44 mm^3, 95% CI 47.67–539.22, $p=0.019$ per IQ point) and parietal volume (baseline: increase of 158.47 mm^3, 95% CI 38.36–278.59, $p=0.010$ per IQ point; follow-up: increase of 168.25 mm^3, 95% CI 49.29–287.21, $p=0.006$ per IQ point).

No associations were found between changes in clinical or cognitive variables and cortical parameters over time (see Supplementary Tables S3–S5).

Prediction of cortical parameters from cognitive performance at baseline

Premorbid and current IQ at baseline predicted reduction in the thickness of the parietal cortex (premorbid IQ: $r^2_{adj}=0.292$, $t=2.47$, $p=0.022$; current IQ: $r^2_{adj}=0.183$, $t=2.59$, $p=0.016$) at follow-up. Working memory span at baseline predicted thickness reductions of the frontal ($r^2_{adj}=0.182$, $t=2.23$, $p=0.045$) and parietal ($r^2_{adj}=0.247$, $t=2.54$, $p=0.019$) cortices at follow-up.

We performed a *post-hoc* analysis to examine the associations between duration of treatment, frontal cortical thickness and premorbid IQ. A binary variable was created with one group of patients with IQ lower than the median score of 103 ($n=13$) and another of patients with IQ higher than or equal to the median score ($n=14$). The association of frontal cortical thickness with duration of treatment was stronger in the group of patients with lower premorbid IQ (three-way interaction $p=0.052$, with cortical thinning of −0.00039 mm/day, 95% CI −0.00062 to −0.00016, $p=0.004$; see Fig. 2).

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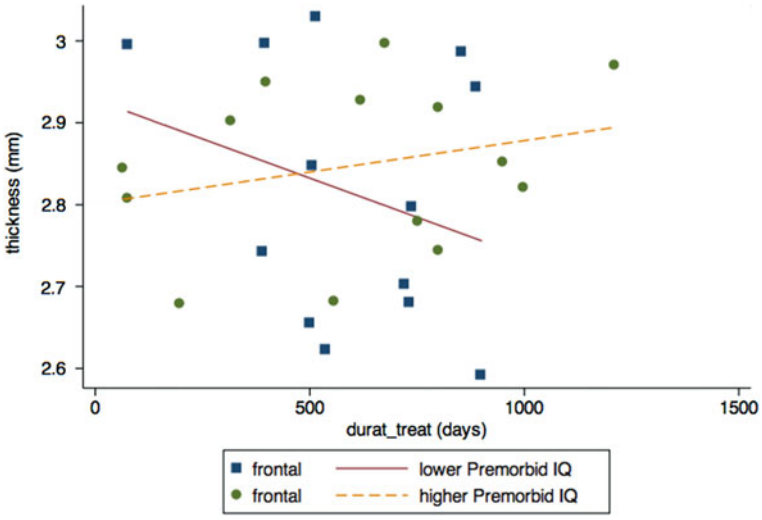

Fig. 2. Scatter plot of the association between duration of treatment and frontal cortical thickness in patients with lower and higher premorbid IQ.

Discussion

The main finding of this study was the thinning of the frontal (superior frontal, pars opercularis, pars triangularis) and, to a lesser extent, superior temporal cortex in patients with FEP followed up for 2 years. By contrast, there were no changes in cortical area over the same period, although in the regions where cortical thinning occurred, reductions in the cortical area were already detectable at baseline in the patient group. We included patients with schizo-affective disorder and schizophrenia in our sample as recent evidence suggests that there are no distinguishing features in the brain structure (Ivleva *et al.* 2013) or cognitive performance (Reilly & Sweeney, 2014) between these two groups. Our findings remained unchanged when patients with schizo-affective disorder were excluded.

Our findings are in keeping with those of others that have reported progressive frontal and temporal cortical thinning in patients with childhood-onset (Thompson *et al.* 2001; Vidal *et al.* 2006) and adult-onset schizophrenia (van Haren *et al.* 2011; Cobia *et al.* 2012) using SBM. The distribution of cortical thinning in our patients involving the superior and inferior frontal gyrus and, to a lesser extent, the superior temporal cortex is also in keeping with the findings of others in chronic (Kuperberg *et al.* 2003) and FEP patients (Narr *et al.* 2005; Wisco *et al.* 2007; Minatogawa-Chang *et al.* 2009; Schultz *et al.* 2010). We have also reported cortical thinning in the inferior frontal gyrus in patients with temporal lobe epilepsy and interictal psychosis (Gutiérrez-Galve *et al.* 2012).

Longitudinal studies using VBM have also found loss of frontotemporal grey matter in patients with first-episode early-onset (Arango *et al.* 2012) and adult-onset (van Haren *et al.* 2008) schizophrenia followed up over time. In our study, cortical thinning was not large enough to translate into group differences in cortical volume, although progressive loss of cortical volume may have been detected in a larger sample. Our findings are similar to those of Cobia *et al.* (2012), who reported thinning of the frontotemporal cortex in 20 patients with adult-onset schizophrenia followed up for 2 years in the absence of changes in cortical area.

Our earlier observations in an overlapping cohort of patients with FEP (Gutiérrez-Galve *et al.* 2010) and those of Rais *et al.* (2012) in a medication-naive cohort suggest that reductions in cortical area without cortical thinning may be present at or before disease onset, whereas cortical thinning may become more prominent over time, pointing to mechanisms operating later in the disease (van Haren *et al.* 2008; Sun *et al.* 2009). The pathological processes underlying these progressive cortical changes have not been fully elucidated, although reduction of the interneuronal neuropil through exaggerated physiological pruning (Boksa, 2012) has been put forward as a possible mechanism.

A study looking at the heritability of grey matter volume in schizophrenia (Owens *et al.* 2012) has reported a small or non-significant heritability for the grey matter of the superior, middle and inferior frontal cortex, suggesting that cortical changes in these regions are not an endophenotype for schizophrenia and that grey matter loss may be due to illness-related

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biological changes including, *inter alia*, exposure to medication and substance abuse.

A recent meta-analysis has reported a correlation between reduction in grey matter volume and cumulative exposure to antipsychotic treatment in patients with schizophrenia (Fusar-Poli *et al.* 2013). A systematic review (Moncrieff & Leo, 2010) has reported loss of frontal cortical grey matter in 14 out of 26 longitudinal MRI studies of medicated patients whereas grey matter loss was only present in five out of 21 studies of medication-naive patients. van Haren *et al.* (2011) have also reported an association between antipsychotic exposure and progressive cortical thinning, particularly in those on typical antipsychotics. Our results also suggest that cortical thinning in those frontal areas of low grey matter heritability (superior and middle frontal gyri) may be due in part to medication exposure, even if most of our patients had only received atypical antipsychotics. However, it should be noted that our measure of exposure to medication was based on duration of treatment, as we did not consider that the available dosage information was accurate enough to explore the association between dose of medication and cortical thinning over time.

The clinical relevance of cortical thinning remains uncertain. Progressive cortical thinning was not associated with the severity of clinical symptoms in our patients, in keeping with the findings of some studies (Cobia *et al.* 2012; Roiz-Santianez *et al.* 2012), but not others (van Haren *et al.* 2011). Similarly, the cognitive performance of our patients did not deteriorate over time despite progressive cortical thinning. A similar finding has also been reported by Cobia *et al.* (2012) in a small group of patients who remained stable clinically and cognitively over a 2-year follow-up. We did find, however, that cortical thinning was predicted by low premorbid IQ and poor working memory present at the time of the first assessment.

Functional imaging studies (Murray *et al.* 2010) have suggested that cognitive function in the early stages of schizophrenia may be preserved in the presence of cortical abnormalities by engaging alternative or additional neural networks, a phenomenon that may reflect cognitive reserve (Barnett *et al.* 2006). More extensive longitudinal studies are required to determine whether these compensatory mechanisms eventually become ineffective.

Our finding that the relationship between duration of treatment and frontal cortex thinning was greater in those with lower premorbid IQ is intriguing. One possible explanation is that patients with lower cognitive reserve (i.e. premorbid IQ) are more vulnerable to medication effects on grey matter. Another is that measures of medication duration or cumulative dose are a proxy for illness severity, which is also reflected in the premorbid IQ (Khandaker *et al.* 2011) and the severity of cortical changes.

Our findings have to be considered as exploratory, given the small sample size of our study, although SBM is sensitive enough to reliably detect longitudinal changes in cortical parameters in small samples (Reuter *et al.* 2012). It is also relevant to mention that we were not able to replicate fully the results of our earlier cross-sectional study performed in an overlapping sample of patients with FEP (Gutiérrez-Galve *et al.* 2010), as only subtle reductions in cortical area were present in the study reported here whereas in our cross-sectional study widespread area reductions were present in the frontotemporal cortex. It remains likely that we may be able to replicate our previous findings fully in a larger patient sample. Another limitation is that we did not have suitable data to explore whether cannabis consumption may have also been related to cortical changes in our patients (Rais *et al.* 2008). Finally, the duration of follow-up was variable in patients and healthy controls, although linear mixed models used in this study cover overdispersion bias (Breslow & Clayton, 1993).

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714001433.

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Declaration of Interest

None.

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