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ORIGINAL ARTICLE

No progressive brain changes during a 1-year follow-up of patients with first-episode psychosis

U. K. Haukvik[1,2]*, C. B. Hartberg[1,3], S. Nerland[1,3], K. N. Jørgensen[1,3], E. H. Lange[1,3], C. Simonsen[1,4], R. Nesvåg[1,3], A. M. Dale[4,5], O. A. Andreassen[1,4], I. Melle[1,4] and I. Agartz[1,3]

[1] *NORMENT K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway*
[2] *Department of Adult Psychiatry, Institute of Clinical Medicine, University of Oslo, Oslo, Norway*
[3] *Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway*
[4] *NORMENT and K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway*
[5] *Department of Neuroscience, University of California San Diego, La Jolla, CA, USA*

Background. First-episode psychosis (FEP) patients show structural brain abnormalities. Whether the changes are progressive or not remain under debate, and the results from longitudinal magnetic resonance imaging (MRI) studies are mixed. We investigated if FEP patients showed a different pattern of regional brain structural change over a 1-year period compared with healthy controls, and if putative changes correlated with clinical characteristics and outcome.

Method. MRIs of 79 FEP patients [SCID-I-verified diagnoses: schizophrenia, psychotic bipolar disorder, or other psychoses, mean age 27.6 (S.D. = 7.7) years, 66% male] and 82 healthy controls [age 29.3 (S.D. = 7.2) years, 66% male] were acquired from the same 1.5 T scanner at baseline and 1-year follow-up as part of the Thematically Organized Psychosis (TOP) study, Oslo, Norway. Scans were automatically processed with the longitudinal stream in FreeSurfer that creates an unbiased within-subject template image. General linear models were used to analyse longitudinal change in a wide range of subcortical volumes and detailed thickness and surface area estimates across the entire cortex, and associations with clinical characteristics.

Results. FEP patients and controls did not differ significantly in annual percentage change in cortical thickness or area in any cortical region, or in any of the subcortical structures after adjustment for multiple comparisons. Within the FEP group, duration of untreated psychosis, age at illness onset, antipsychotic medication use and remission at follow-up were not related to longitudinal brain change.

Conclusions. We found no significant longitudinal brain changes over a 1-year period in FEP patients. Our results do not support early progressive brain changes in psychotic disorders.

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Key words: Bipolar disorder, longitudinal studies, magnetic resonance imaging, schizophrenia.

Introduction

Psychotic disorders such as schizophrenia, schizoaffective disorder and bipolar disorder are severe mental illnesses along a psychosis continuum, with great clinical heterogeneity within each diagnostic group. Recent genetic (Andreassen *et al.* 2013), imaging (Rimol *et al.* 2010, 2012; Haukvik *et al.* 2015), neuropathological (Wang *et al.* 2011) and epidemiological (Lichtenstein *et al.* 2009) studies suggest shared pathophysiological traits along the psychosis continuum, although the exact mechanisms are not known.

There is an ongoing debate as to whether the psychotic disorders are progressive brain disorders or not (Vita *et al.* 2012; Fusar-Poli *et al.* 2013; Zipursky *et al.* 2013). Increasingly sophisticated magnetic resonance imaging (MRI) techniques have facilitated studies of longitudinal brain changes in psychotic disorders. The results are mixed, with some studies showing significant brain volume loss over time in chronic schizophrenia (Veijola *et al.* 2014), first-episode schizophrenia (Andreasen *et al.* 2011), first-episode psychosis (FEP) (Gutiérrez-Galve *et al.* 2015) and the psychosis prodromal state (Cannon *et al.* 2015), whereas other studies report a lack of longitudinal changes (Schaufelberger *et al.* 2011). Some authors argue that antipsychotic medication may cause or moderate the longitudinal changes (Ho *et al.* 2011; Vita *et al.* 2012; Fusar-Poli *et al.* 2013), whereas others report no such associations (Cannon *et al.* 2015). Some studies have analysed changes in *a priori* selected cortical or subcortical regions (Roiz-Santianez *et al.* 2014; Gutiérrez-Galve *et al.* 2015), others in regional gray and white

* Address for correspondence: U. K. Haukvik, M.D., Ph.D., Department of Adult Psychiatry, Institute of Clinical Medicine, University of Oslo, PO Box 1039 Blindern, Oslo 0315, Norway.
(Email: unn.haukvik@medisin.uio.no)

matter or total brain volume (Andreasen *et al.* 2011; Boonstra *et al.* 2011; Veijola *et al.* 2014). Hulshoff Pol & Kahn (2008) reported a 0.5% brain volume reduction in schizophrenia spectrum FEP *v.* 0.2% in controls, and the volume reductions have been associated with poorer clinical outcome in some (Cahn *et al.* 2006; van Haren *et al.* 2008) but not all (Roiz-Santianez *et al.* 2014; Gutiérrez-Galve *et al.* 2015) studies. Meta-analyses have reported progressive changes in FEP and schizophrenia (Vita *et al.* 2012; Fusar-Poli *et al.* 2013). The meta-analyses include subjects across the life span with different brain developmental trajectories and studies with a variety of different image acquisition parameters and scan processing methods.

Patients with FEP display great symptom heterogeneity. Acute symptoms may fluctuate and new affective and psychosis symptoms may emerge. Hence early diagnosis within the psychosis spectrum is challenging, and re-evaluation and change of diagnosis may occur in up to 40% of FEP patients (Salvatore *et al.* 2011, 2013). Previous valuable and important longitudinal studies in FEP have tended to include psychoses within the schizophrenia spectrum and other non-affective psychoses such as brief psychotic disorder and psychosis not otherwise specified (NOS), but not the affective psychoses in bipolar disorder and psychotic depression (for a review, see Morgan *et al.* 2014). This may have led to a bias toward a poor outcome or brain characteristics that are not representative of the broad FEP group. In order to give FEP patients accurate and cautious information of expected illness prognosis, longitudinal studies of brain changes and their association with clinical characteristic in broad FEP samples are crucial.

The aim of the present study was two-fold: (1) to explore if FEP patients showed a different pattern of brain structural change over a 1-year period compared with healthy controls; and (2) to investigate if putative longitudinal brain changes correlated with measures of clinical characteristics and outcome.

We hypothesized: (1) that FEP patients would show greater subcortical volume decline and ventricular volume enlargement, and more pronounced cortical thinning than healthy controls; and (2) that higher percentage longitudinal brain change would correlate with medication use, longer duration of untreated psychosis (DUP), lower age at illness onset and a more severe outcome.

We studied a wide range of distinct surface-based measures of cortical area and thickness across the whole cortical mantle, and volumes of subcortical structures including the ventricles, the basal ganglia (caudate, putamen accumbens, pallidum), the limbic structures (hippocampus, amygdala, thalamus) and the cerebellum to get a comprehensive overview of patterns of longitudinal brain changes, not restricted to *a priori* selected regions.

Method

Subjects

The subject sample consisted of patients with FEP (n = 79) and healthy controls (n = 82) from the on-going multicenter Thematically Organized Psychosis (TOP) Research Study at the University of Oslo and collaborating hospitals in Oslo, Norway. The formal inclusion criteria were: age between 18 and 65 years (but the oldest included FEP patient was 48 years); no head trauma leading to loss of consciousness; and absence of previous or current somatic illness that might affect brain morphology. FEP was defined as patients who had received less than 1 year of adequate treatment for psychotic disorders within the schizophrenia spectrum [n = 44; schizophrenia (DSM-IV 295.1, 295.3, 295.6, 295.9) (n = 37), schizophreniform disorder (DSM-IV 295.4) (n = 2), or schizo-affective disorder (DSM-IV 295.7) (n = 5)], the bipolar spectrum [n = 18; bipolar I disorder (DSM-IV 296.0–7) (n = 15), bipolar II disorder (DSM-IV 296.89) (n = 2), or bipolar disorder NOS (DSM-IV 296.80) (n = 1)], and other psychoses [n = 17; depressive psychosis (n = 5), paranoid psychosis (n = 2), or psychotic disorder NOS (n = 10)]. All patients had a previous or current episode of psychosis defined as a score of 4 or above on the Positive and Negative Syndrome Scale (PANSS) items P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity), P6 (suspiciousness/persecution) and G9 (unusual thought content).

The healthy control subjects were randomly selected from the national population register. They were resident in the same catchment area and were within the same age range as the patients. Baseline scans from the current subject sample have been included in previous larger studies of brain structure differences between schizophrenia, bipolar disorder and healthy controls (Rimol *et al.* 2010, 2012; Haukvik *et al.* 2015).

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and was conducted in accordance with the Helsinki declaration. After complete description of the study to the subjects, written informed consent was obtained from all participating subjects.

Clinical assessments

All patients underwent thorough clinical investigation by specially trained psychologists and physicians at baseline and at 1-year follow-up. At baseline 217 FEP patients underwent MRI scanning. Of the 93 patients who met for a second scanning, 14 subjects were excluded because of poor scan quality or segmentation

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Table 1. *Demographic and clinical characteristics of FEP patients included at baseline and follow-up*

	Baseline only ($n = 138$)		Baseline and follow-up ($n = 79$)		
	Mean (S.D.)	Range	Mean (S.D.)	Range	p[a]
Sex, *n* (%)					0.031
Male	70 (51)		52 (66)		
Female	68 (49)		27 (34)		
Handedness, *n* (%)[b]					N.S.
Right	115 (89)		69 (88)		
Left	13 (10)		9 (12)		
Ambidextrous	1 (1)		0 (0)		
Remission, *n* (%)			46 (58)		N.A.
Age, years	29.4 (9.0)	18–63	27.6 (7.7)	18–47	N.S.
Years of education	12.7 (2.3)	9–18	12.4 (2.2)	7–18	N.S.
Age at illness onset, years	25.5 (8.8)	7–63	23.8 (8.0)	7–44	N.S.
DUP, weeks	78 (136)	0–800	136 (212)	0–1040	0.036
YMRS	5.1 (5.0)	0–22	5.2 (5.8)	0–28	N.S.
CDSS	6.5 (5.0)	0–23	6.2 (4.4)	0–17	N.S.
GAF symptom	45 (13)	26–82	43 (11)	28–76	N.S.
GAF function	46 (12)	24–80	44 (12)	30–80	N.S.
PANSS positive	14.4 (5.2)	7–26	14.9 (5.5)	7–29	N.S.
PANSS negative	14.7 (6.1)	7–39	14.0 (6.0)	7–32	N.S.
Medication, DDD					
FGA	0.4 (0.6)	0.2–2.5	0.2 (0.1)	0.0–0.33	N.S.
SGA	1.4 (1.1)	0.1–9.6	1.0 (0.6)	0.3–3.0	0.031
Antiepileptics	0.7 (0.5)	0.7–2.1	0.8 (0.6)	0.1–2.0	N.S.
Lithium	0.9 (0.3)	0.3–1.3	1.25	N.A.	N.S.

Data are given as mean (S.D.) and range unless otherwise indicated.

FEP, First-episode psychosis; S.D., standard deviation; N.S., not significant; N.A., not applicable; DUP, duration of untreated psychosis; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Function split version; PANSS, Positive and Negative Syndrome Scale; DDD, defined daily dosage; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.

[a] χ^2 Test for categorical variables; *t* test or Mann–Whitney non-parametric test for continuous variables.

[b] $n = 207$.

errors. As such, 79 patients were included in this study. The included patients had longer DUP ($t_{116} = 2.1$, $p = 0.036$), used less second-generation antipsychotics (SGA) at baseline ($t_{159} = -2.2$, $p = 0.031$) and had a smaller proportion of women ($\chi^2_1 = 4.65$, $p = 0.031$). The other demographic and clinical variables at baseline did not differ between follow-up and non-follow-up patients (Table 1).

Clinical diagnoses were assessed using the Structured Clinical Interview for DSM Axis I disorders (SCID-I) module A-E (Spitzer *et al.* 1992) at baseline and follow-up, with an overall agreement for diagnostic categories of 82%, $\kappa = 0.77$ (95% confidence interval 0.60–0.94) between raters. Current psychosocial function was assessed with the Global Assessment of Function scale, split version. Affective state was assessed with the Young Mania Rating Scale and the Calgary Depression Scale for Schizophrenia, and current psychotic symptoms were rated by the PANSS (Kay *et al.* 1987), with high intraclass coefficients (Engh *et al.* 2010). All symptom scales were administered at both time points. Remission at follow-up was defined as no positive symptoms within a week of follow-up assessment as measured by a score of 3 or below on all of the PANSS items P1, P3, P5, P6 and G9. Current use of medication [first-generation antipsychotics (FGA), SGA, lithium, and antiepileptics] was converted into standard defined daily dosages (DDD) in accordance with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (hhtp://www.whocc.no/atcdd).

Healthy controls were interviewed for symptoms of severe mental illness by trained clinical psychologists and examined with the Primary Care Evaluation of Mental Disorders (Spitzer *et al.* 1994) to ensure no current or previous severe psychiatric disorders. Control

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subjects with current or previous somatic illness, or substance misuse disorder including alcohol overuse that could affect brain morphology were excluded.

MRI acquisition and processing

All participants underwent MRI scanning at baseline and follow-up on the same 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions). Two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired at each time point with the Siemens tfl3d1_ns pulse sequence (echo time = 3.93 ms, repetition time = 2730 ms, inversion time = 1000 ms, flip angle = 7°, field of view = 24 cm, voxel size = 1.33 × 0.94 × 1 mm^3, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal:noise ratio. There was no major scanner upgrade during the study period, and patients and controls were scanned interchangeably to avoid the possibility for across-time scanner drifting to confound diagnostic differences. A neuroradiologist evaluated all scans, and subjects with scans showing minor brain pathology were excluded from the study.

The FreeSurfer software (version 5.3.0) (http://surfer.nmr.mgh.harvard.edu/) was used to estimate volumes of subcortical structures (Fischl *et al.* 2002, 2004) and cortical surface area and thickness (Dale *et al.* 1999; Fischl *et al.* 1999); see the online Supplementary material and Haukvik *et al.* (2014, 2015) for details. To extract reliable volume and thickness estimates of longitudinal changes, images were automatically processed with the FreeSurfer longitudinal stream (Reuter *et al.* 2012). Specifically, an unbiased within-subject template space and image are created using robust, inverse consistent registration (Reuter *et al.* 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter *et al.* 2012). Quality control and editing were performed by a trained research assistant supervised by an experienced FreeSurfer user. All volumes were visually inspected for segmentation errors. If found, segmentation errors were corrected using manual editing and/or control points (http://freesurfer.net/fswiki/Tutorials).

Statistical analyses

Statistical analyses were performed by the use of the statistical package SPSS version 20 (IBM, USA), and with the FreeSurfer statistical tools. Demographic and clinical variables were evaluated by *t* tests, non-parametric Mann–Whitney tests and χ^2 analysis as applicable. All statistical tests were two-tailed.

At first, baseline differences in brain structural measures between patients and controls were tested using analysis of covariance (ANCOVA) with the brain as the dependent variable, diagnosis as fixed factor, and age and intracranial volume as covariates for the subcortical measures. Bonferroni correction was applied to adjust for multiple comparisons of 12 subcortical structures (10 bilateral structures – amygdala, hippocampus, thalamus, accumbens, pallidum, caudatus, putamen, cerebellum white matter and cortex, lateral ventricle and lateral inferior ventricle, and in addition the 3rd and 4th ventricles). Diagnostic differences in cortical thickness and area were analysed over 300 000 points across the whole cortical mantle with a general linear model within the FreeSurfer software. A false discovery rate (FDR) of 5% was applied to the α threshold of 0.05 to adjust for multiple comparisons. The analyses were repeated, with inclusion of FEP within schizophrenia spectrum only ($n = 44$) and healthy controls.

Longitudinal percentage change was estimated for each cortical vertex and subcortical structure volume (V) as annual percentage change (PC) from the baseline (time1) scan, where $V_{PC} = [(V_{time2} - V_{time1})/(\text{time2} - \text{time1})]/V_{time1}$. Then, we used a general linear model with diagnosis as a fixed factor and age as covariate to analyse percentage change for each subcortical structure and vertex-wise across the cortical mantle for each cortical measure (area and thickness). The analyses were repeated after exclusion of all subjects with residual values below −2.5 or above 2.5, to investigate the effects of potential outlier observations on the model. We then analysed longitudinal differences between the schizophrenia spectrum disorder patients ($n = 44$) and healthy controls.

Associations between longitudinal brain morphological change and clinical characteristics [DUP, age at illness onset, and the use of antipsychotic medication (FGA and SGA) as DDD] in FEP patients were analysed with non-parametric Spearman correlation analyses because of the lack of normal distribution of the clinical variables (also after the logarithmic transformation procedures). Differences between FEP patients with and without SGA medication and the relationship between clinical outcome (remission at follow-up) and longitudinal brain changes were analysed with multiple ANCOVA models with each brain region as the dependent variable, and remitted FEP *v.* non-remitted FEP patients or SGA users *v.* non-SGA users as fixed factors. Bonferroni correction was applied to adjust for multiple comparisons of 12 subcortical structures to avoid false-positive results. Since the brain structures are not truly independent,

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we present nominally significant uncorrected p values in the Results section. The cortical maps were adjusted for multiple comparisons with the FDR.

Results

Demographic and clinical variables

FEP had fewer years of education ($t_{145} = 4.82$, $p < 0.0001$) and larger scan interval ($t_{159} = -2.65$, $p = 0.009$) compared with healthy controls (Table 2). The SCID-I-verified diagnoses of 18 (23%) FEP subjects changed from baseline to follow-up: five from schizophreniform disorder and four from psychosis NOS to schizophrenia; one from schizophrenia and two from psychotic depression to schizo-affective disorder; two from psychosis NOS and one from bipolar II disorder to psychotic depression; one from brief psychosis to bipolar I disorder; one from psychosis NOS; and one from psychotic depression to bipolar II disorder. Of the patients, 52 used SGA at baseline, 35 were still using at follow-up, 17 had discontinued use, and seven other patients had started using SGA. At follow-up 42 patients used SGA [risperidone ($n = 3$), olanzapine ($n = 14$), aripiprazol ($n = 14$), quetiapine ($n = 10$), ziprazidone ($n = 1$)]. None of the patients received FGA as their primary medication. None of the patients received anticholinergics or central stimulants, one patient received diazepam and one oxazepam daily.

Clinical characteristics at baseline and follow-up are listed in Table 2.

Baseline MRI characteristics

FEP patients had smaller volumes of the right hippocampus ($F_{1,158} = 9.82$, $p = 0.024$) and larger volumes of the 3rd ventricle ($F_{1,158} = 9.48$, $p = 0.024$) compared with healthy controls (online Supplementary Table S1). FEP patients showed regions of cortical thinning and surface area reductions compared with healthy controls, but the differences did not remain significant after FDR correction for multiple comparisons (online Supplementary Fig. S1).

In the schizophrenia spectrum FEP group ($n = 44$), we found the following baseline differences compared with healthy controls: left hemisphere smaller cerebellar cortex ($t_{156} = -3.14$, $p = 0.024$); right hemisphere smaller cerebellar cortex ($t_{156} = -2.97$, $p = 0.036$); and smaller hippocampus ($t_{156} = -2.90$, $p = 0.048$). Schizophrenia spectrum patients had regional reduced cortical thickness and surface area at baseline compared with healthy controls, in concordance with our previous publications (Rimol *et al.* 2010, 2012) (data not shown).

Baseline subcortical volumes and cortical parameters in FEP patients were not significantly related to DUP, age at illness onset, medication use or remission at follow-up. Remission at follow-up was related to larger cortical area at baseline ($p = 0.003$).

Trend-level baseline results are listed in the online Supplementary material.

Longitudinal MRI changes

FEP patients and controls did not differ significantly in regional percentage change in cortical thickness, area or volume, or in any of the subcortical structures after strict FDR and Bonferroni correction, respectively. The variation in percentage longitudinal change was largest for the ventricles, ranging from approximately −20% to +20% of the lateral ventricle volume over a 1-year period, with extreme value outliers at +75% for the left inferior ventricle (Table 3). For the hippocampus the variation in percentage change was narrower, ranging from approximately −5% to +5% volume change over 1 year. Percentage change within all subcortical structures is listed in Table 3. Age at MRI scanning was not related to percentage longitudinal change for FEP patients or healthy controls.

When we repeated the analyses and included only the schizophrenia spectrum FEP, we did not find any significant differences in percentage volume change compared with controls after multiple comparison control (Table 3).

Trend-level longitudinal results are listed in the online Supplementary material.

Longitudinal MRI changes and clinical characteristics

We found no associations that remained significant after adjustment for multiple comparisons between DUP, SGA use, age at illness onset, or remission at follow-up and longitudinal percentage change in any of the subcortical volumes or cortical measures.

Trend-level results are listed in the online Supplementary material.

Discussion

Our main finding was that FEP patients did not show significant longitudinal brain changes over a 1-year period as compared with healthy controls. No significant associations between clinical characteristics, including antipsychotic medication use, and longitudinal brain change were found.

By including affective psychoses (psychotic bipolar disorder and psychotic depression), we studied a FEP group with greater clinical heterogeneity than most of the previous studies (for reviews, see Vita *et al.* 2012; Fusar-Poli *et al.* 2013; Morgan *et al.* 2014). Greater clinical heterogeneity may be related to greater

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Table 2. *Demographic and clinical characteristics of FEP patients and healthy controls*

	Baseline FEP ($n = 79$)		Controls ($n = 82$)		Follow-up FEP		
	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range	p[a]
Sex, *n* (%)							N.S.
Male	52 (66)		54 (66)				
Female	27 (34)		28 (34)				
Handedness, *n* (%)[b]							N.S.
Right	69 (88)		65 (94)				
Left	9 (12)		3 (5)				
Ambidextrous	0 (0)		1 (1)				
Current treatment, *n* (%)[c]							
In-patient	29 (42)						
Out-patient	39 (57)						
No psychiatric health care	1 (1)						
Remission, *n* (%)					46 (58)		N.A.
Age, years	27.6 (7.7)	18–47	29.3 (7.2)	18–48			N.S.
Scan interval, years	1.16 (0.263)	0.71–1.91	1.07 (0.191)	0.79–1.84			0.009
Years of education	12.4 (2.2)	7–18	14.2 (2.4)	9–20			<0.0001
Age at illness onset, years	23.8 (8.0)	7–44					N.A.
DUP, weeks	123 (212)	0–1040					N.A.
YMRS	5.2 (5.8)	0–28			4.4 (5.1)	0–16	N.S.
CDSS	6.2 (4.4)	0–17			4.0 (4.3)	0–22	<0.0001
GAF symptom	43 (11)	28–76			56 (18)	30–95	<0.0001
GAF function	44 (12)	30–80			56 (17)	32–94	<0.0001
PANSS positive	14.9 (5.5)	7–29			12.5 (5.4)	7–30	0.0003
PANSS negative	14.0 (6.0)	7–32			12.9 (5.7)	7–33	N.S.
PANSS general	31.7 (5.8)	18–44			26.6 (8.0)	16–55	<0.0001
PANSS total	60.6 (13.5)	36–91			52.0 (15.4)	36–106	<0.0001
Medication, DDD							
FGA[d]	0.2 (0.1)	0.03–0.33			0.01	N.A.	N.A.
SGA[e]	1.0 (0.6)	0.3–3.0			1.2 (0.8)	0.06–4.0	N.S.
Antiepileptics[f]	0.8 (0.6)	0.1–2.0			1.0 (0.5)	0.1–1.7	N.S.
Lithium[g]	1.25	N.A.			1.2 (0.5)	0.5–1.5	N.A.

Data are given as mean (S.D.) and range unless otherwise indicated.

FEP, First-episode psychosis; S.D., standard deviation; N.S., not significant; N.A., not applicable; DUP, duration of untreated psychosis; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Function split version; PANSS, Positive and Negative Syndrome Scale; DDD, defined daily dosage; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.

[a] χ^2 Test for categorical variables; *t* test or Mann–Whitney non-parametric test for continuous variables.

[b] $n = 147$.

[c] $n = 69$.

[d] $n = 6$ baseline; $n = 1$ follow-up.

[e] $n = 52$ baseline; $n = 42$ follow-up.

[f] $n = 10$ baseline; $n = 10$ follow-up.

[g] $n = 1$ baseline; $n = 4$ follow-up.

diversity of brain characteristics. Dazzan *et al.* (2012) reported that subjects at ultra high-risk for psychosis (UHR) who converted to affective psychoses showed a different pattern of gray matter reduction than UHR subjects who converted to schizophrenia spectrum psychoses. In contrast, Cannon *et al.* (2015) reported that transition from UHR to both affective and schizophrenia spectrum FEP was characterized by common cortical thickness reductions and 3rd ventricle enlargement. Moreover, longitudinal volume reductions specifically in the anterior cingulate cortex have been reported in affective FEP (Koo *et al.* 2008). When we analysed only the schizophrenia spectrum FEP patients, we still did not find any significant longitudinal changes compared with healthy controls. Hence, the lack of longitudinal change cannot be

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Table 3. *Longitudinal percentage change in FEP patients (whole group n = 79), FES patients only (n = 44) and HC participants (n = 82)*

	HC		FEP		FES only		Statistics: uncorrected p[a]	
	Range	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	HC *v.* FEP	HC *v.* FES
Left								
Lateral ventricle	−14.7 to 19.0	1.2 (5.0)	−31.3 to 23.3	1.1 (8.4)	−15.4 to 20.6	1.9 (6.8)	0.912	0.560
Inferior lateral ventricle	−31.1 to 40.6	0.2 (11.2)	−39.5 to 75.3	−0.7 (17.0)	−22.7 to 75.3	2.3 (20.1)	0.665	0.459
Cerebellum white matter	−3.6 to 5.9	0.2 (1.7)	−9.7 to 5.7	0.2 (2.5)	−9.7 to 5.7	0.1 (2.7)	0.982	0.679
Cerebellum cortex	−3.1 to 3.4	−0.5 (1.2)	−6.3 to 4.1	−0.8 (2.1)	−5.0 to 4.1	−0.7 (2.1)	0.155	0.495
Thalamus	−3.1 to 2.4	−0.4 (1.2)	−5.8 to 6.2	−0.5 (1.9)	−3.8 to 6.2	−0.5 (1.7)	0.814	0.849
Caudate	−5.1 to 5.6	−0.7 (1.6)	−6.9 to 8.2	−0.5 (2.2)	−4.9 to 8.2	−0.2 (2.4)	0.561	0.212
Putamen	−5.0 to 7.9	−0.5 (1.8)	−7.0 to 9.7	−0.5 (2.6)	−5.3 to 9.7	−0.4 (2.7)	0.967	0.774
Pallidum	−24.7 to 30.6	0.3 (6.2)	−17.9 to 25.3	0.4 (5.1)	−17.9 to 25.3	1.3 (5.9)	0.912	0.377
Hippocampus	−13.7 to 4.9	0.0 (2.5)	−5.6 to 7.2	−0.3 (2.6)	−5.6 to 7.2	−0.5 (2.7)	0.420	0.269
Amygdala	−18.5 to 14.6	−0.1 (5.2)	−9.3 to 27.9	0.8 (5.9)	−9.3 to 27.9	0.7 (6.6)	0.238	0.385
Accumbens	−13.2 to 15.6	−0.2 (5.7)	−17.9 to 38.3	−1.0 (7.3)	−17.9 to 38.3	−1.4 (8.4)	0.533	0.364
Right								
Lateral ventricle	−16.9 to 20.3	0.9 (5.0)	−34.7 to 21.5	1.0 (8.9)	−27.8 to 20.4	1.8 (7.7)	0.868	0.472
Inferior lateral ventricle	−22.1 to 22.5	−0.9 (8.9)	−34.9 to 76.1	0.3 (13.7)	−21.7 to 76.1	0.8 (14.8)	0.556	0.475
Cerebellum white matter	−5.4 to 5.8	0.10(2.0)	−7.6 to 8.0	0.1 (2.3)	−7.6 to 8.0	0.2 (2.4)	0.948	0.986
Cerebellum cortex	−3.5 to 3.6	−0.4 (1.3)	−6.6 to 3.7	−0.6 (1.9)	−6.6 to 3.7	−0.6 (1.9)	0.413	0.752
Thalamus	−5.6 to 6.1	−0.5 (1.7)	−4.5 to 6.5	−0.6 (1.9)	−4.5 to 3.1	−0.7 (1.7)	0.701	0.535
Caudate	−3.9 to 3.0	−0.4 (1.2)	−5.4 to 3.3	−0.7 (1.8)	−5.4 to 2.9	−0.8 (1.6)	0.205	0.152
Putamen	−4.8 to 3.9	−0.4 (1.5)	−5.7 to 6.1	−0.1 (2.0)	−3.5 to 6.1	−0.1 (1.9)	0.181	0.245
Pallidum	−8.7 t0 7.1	0.1 (2.8)	−10.1 to 12.4	0.6 (4.1)	−4.6 to 12.4	1.8 (3.8)	0.326	0.006
Hippocampus	−5.9 to 4.5	−0.5 (1.7)	−6.7 to 6.0	−0.2 (2.2)	−5.8 to 6.0	−0.1 (2.4)	0.225	0.171
Amygdala	−14.6 to 11.8	0.1 (4.5)	−13.1 to 31.8	1.2 (6.1)	−13.1 to 31.8	1.0 (6.8)	0.209	0.382
Accumbens	−19.8 to 13.0	−1.0 (5.2)	−9.7 to 36.4	1.1 (7.6)	−9.7 to 21.7	1.0 (7.0)	0.049	0.122
Midline								
3rd ventricle	−15.0 to 12.3	−0.6 (4.7)	−24.0 to 27.0	−0.2 (8.8)	−17.3 to 27.0	0.8 (9.1)	0.704	0.252
4th ventricle	−11.7 to 8.1	−1.4 (4.0)	−15.1 to 27.3	0.5 (7.1)	−14.3 to 27.3	0.7 (7.6)	0.055	0.072

FEP, First-episode psychosis; FES, first-episode schizophrenia spectrum; HC, healthy control; S.D., standard deviation.
[a] None of the p values is significant after adjustment for multiple comparisons.

attributed to the inclusion of affective psychoses. The fact that 23% of FEP patients in our cohort changed diagnosis during the follow-up period is in accordance with a previous report of retained psychosis diagnoses in 76.2% (Pope *et al.* 2013), and emphasizes the variability in clinical characteristics and course within this group.

Longitudinal MRI studies face particular methodological difficulties regarding alignment of the baseline and follow-up image. We used the FreeSurfer longitudinal pipeline that co-registrates the baseline and follow-up scan of each individual subject and computes an unbiased within-subject template space and image. By this, the statistical power to detect subtle changes over time has been shown to increase significantly (Reuter *et al.* 2012). We analysed a wide range of brain volumes and cortical parameters, and applied rigorous multiple comparison control accordingly. This is somewhat in contrast to previous studies analysing selected regions of interest (Roiz-Santianez *et al.* 2014; Gutiérrez-Galve *et al.* 2015) or more crude measures such as whole-brain or lobar volumes (for a review, see Vita *et al.* 2012), or studies arguing that less stringent adjustment for multiple tests was required (Andreasen *et al.* 2011; Roiz-Santianez *et al.* 2014). This could explain some of the discrepancies.

Interestingly, by using the exact same FreeSurfer longitudinal pipeline, Cannon *et al.* (2015) found 3rd

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ventricle volume increase and regional frontal cortical thinning in clinical high-risk subjects ($n = 274$) who converted ($n = 35$) to affective or schizophrenia spectrum psychosis. In comparison, we found significantly larger 3rd ventricles in FEP patients at baseline, but no progressive enlargement. This could suggest that some brain changes may occur during transition to psychosis rather than after illness onset. Moreover, we found that patients who were in remission at follow-up had a larger cortical area at baseline. This could reflect subgroups with different illness severity and brain morphological characteristics. These results are intriguing and warrant further investigation.

The pathophysiology of psychotic disorders is heterogeneous, and has been demonstrated to involve, for example, altered dopamine synthesis activity, *N*-methyl-D-aspartate receptor (NMDAr) hypofunction or pro-inflammatory status (for a review, see Kahn & Sommer, 2015). From a functional perspective, FEP with good clinical and functional outcome has been associated with hippocampal volume increase over time (Lappin *et al.* 2014). We cannot exclude the possibility that the lack of positive findings reflects heterogeneity over several domains.

Medication use may affect brain morphology, especially in the basal ganglia that are rich in dopaminergic neurons. We found less longitudinal reduction of caudate volume in FEP patients who were not in remission at follow-up compared with FEP patients in remission, significant at a trend level. This is partly in line with recent findings of less longitudinal caudate volume reduction in FEP patients ($n = 109$) compared with healthy controls ($n = 76$); this finding was, however, independent of clinical outcome among the FEP patients (Roiz-Santianez *et al.* 2014). Longitudinal caudate volume increase in schizophrenia spectrum FEP patients ($n = 211$) has previously been associated with the use of antipsychotic medication (Ho *et al.* 2011). We found no association between longitudinal change and the use of antipsychotics (all non-clozapine SGA) in the caudate or in any other brain region. The directional effects of antipsychotics on basal ganglia volumes may, however, differ not only between FGA and SGA, but also between the different generic compounds within each group (Ebdrup *et al.* 2013). Olanzapine and risperidone (together used by 17 subjects in our sample) have been associated with basal ganglia volume increase or no change, whereas quetiapine (used by 10 subjects in our sample) has been associated with basal ganglia volume decrease or no change (for a review, see Ebdrup *et al.* 2013). Accordingly, associations between longitudinal brain changes and SGA use should be interpreted cautiously.

This study has some notable limitations. Since FEP was defined as less than 1 year of adequate treatment, duration of treatment amongst FEP varied from almost 1 year to just a few weeks at baseline inclusion. Second, the time from baseline to follow-up scanning ranged from 9 months to almost 2 years. If there is a decline around transition to psychosis (Cannon *et al.* 2015) this might be confounded by the different time points in their early psychosis development when each patient was scanned. We used rigorous statistical adjustment for multiple comparisons to avoid false-positive findings. This might have caused type II errors. For completeness, we reported unadjusted p values for the results that were significant at an α-threshold of 0.05 before multiple comparison adjustment in the online Supplementary material. There was a selection bias between the follow-up- and baseline group, with more men with long duration of untreated illness and less SGA treatment in the follow-up group. Finally, several factors may affect brain structure, including birth complications (Haukvik *et al.* 2012, 2014), exposure to childhood trauma (Aas *et al.* 2013), alcohol (Agartz *et al.* 2003), tobacco (Jorgensen *et al.* 2015) and cannabis use (Malchow *et al.* 2013), and exercise (Malchow *et al.* 2015). Detailed investigations of such effects were beyond the scope of this article, but should be investigated in future studies.

Strengths of the current study include the relatively large subject sample, the thorough clinical characterization of participating subjects, inter-rater reliability testing on clinical instruments, SCID-I-verified diagnoses obtained by specially trained psychiatrists, clinical psychologists or physicians, and the use of the same MRI scanner with no major software or hardware upgrades during the study period.

In summary, by analysing longitudinal change in a wide range of specific subcortical volumes and in cortical parameters across the entire cortical mantle without *a priori*-selected regions of interest, we found no significant longitudinal brain changes over a 1-year period in FEP patients. Our results add to the mixed literature on progressive brain changes in psychotic disorders. FEP patients should be informed that they do not necessarily have a progressive brain disorder.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S003329171500210X

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Declaration of Interest

A.M.D. is a founder and holds equity in CorTechs Labs, and also serves on the Scientific Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All other authors report no conflict of interest.

References

Aas M, Haukvik UK, Djurovic S, Bergmann O, Athanasiu L, Tesli MS, Hellvin T, Steen NE, Agartz I, Lorentzen S, Sundet K, Andreassen OA, Melle I (2013). BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **46C**, 181–188.

Agartz I, Shoaf S, Rawlings RR, Momenan R, Hommer DW (2003). CSF monoamine metabolites and MRI brain volumes in alcohol dependence. *Psychiatry Research* **122**, 21–35.

Andreasen NC, Nopoulos P, Magnotta V, Pierson R, Ziebell S, Ho BC (2011). Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. *Biological Psychiatry* **70**, 672–679.

Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, Kendler KS, O'Donovan MC, Rujescu D, Werge T, Sklar P, Roddey JC, Chen CH, McEvoy L, Desikan RS, Djurovic S, Dale AM (2013). Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. *PLoS Genetics* **9**, e1003455.

Boonstra G, Cahn W, Schnack HG, Hulshoff Pol HE, Minderhoud TC, Kahn RS, van Haren NE (2011). Duration of untreated illness in schizophrenia is not associated with 5-year brain volume change. *Schizophrenia Research* **132**, 84–90.

Cahn W, van Haren NE, Hulshoff Pol HE, Schnack HG, Caspers E, Laponder DA, Kahn RS (2006). Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *British Journal of Psychiatry: The Journal of Mental Science* **189**, 381–382.

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R; North American Prodrome Longitudinal Study Consortium (2015). Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biological Psychiatry 77, 147–157.

Dale AM, Fischl B, Sereno MI (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage* **9**, 179–194.

Dazzan P, Soulsby B, Mechelli A, Wood SJ, Velakoulis D, Phillips LJ, Yung AR, Chitnis X, Lin A, Murray RM, McGorry PD, McGuire PK, Pantelis C (2012). Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. *Schizophrenia Bulletin* **38**, 1083–1091.

Ebdrup BH, Norbak H, Borgwardt S, Glenthoj B (2013). Volumetric changes in the basal ganglia after antipsychotic monotherapy: a systematic review. *Current Medicinal Chemistry* **20**, 438–447.

Engh JA, Friis S, Birkenaes AB, Jonsdottir H, Klungsoyr O, Ringen PA, Simonsen C, Vaskinn A, Opjordsmoen S, Andreassen OA (2010). Delusions are associated with poor cognitive insight in schizophrenia. *Schizophrenia Bulletin* **36**, 830–835.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341–355.

Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, Dale AM (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage* **23** (Suppl. 1), S69–S84.

Fischl B, Sereno MI, Dale AM (1999). Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *NeuroImage* **9**, 195–207.

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience and Biobehavioral Reviews* **37**, 1680–1691.

Gutiérrez-Galve L, Chu EM, Leeson VC, Price G, Barnes TR, Joyce EM, Ron MA (2015). A longitudinal study of cortical changes and their cognitive correlates in patients followed up after first-episode psychosis. *Psychological Medicine* **45**, 205–216.

Haukvik UK, McNeil T, Lange EH, Melle I, Dale AM, Andreassen OA, Agartz I (2014). Pre- and perinatal hypoxia associated with hippocampus/amygdala volume in bipolar disorder. *Psychological Medicine* **44**, 975–985.

Haukvik UK, Schaer M, Nesvag R, McNeil T, Hartberg CB, Jonsson EG, Eliez S, Agartz I (2012). Cortical folding in Broca's area relates to obstetric complications in schizophrenia patients and healthy controls. *Psychological Medicine* **42**, 1329–1337.

Haukvik UK, Westlye LT, Morch-Johnsen L, Jorgensen KN, Lange EH, Dale AM, Melle I, Andreassen OA, Agartz I (2015). *In vivo* hippocampal subfield volumes in schizophrenia and bipolar disorder. *Biological Psychiatry* **77**, 581–588.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry* **68**, 128–137.

Hulshoff Pol HE, Kahn RS (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophrenia Bulletin* **34**, 354–366.

Jorgensen KN, Skjaervo I, Morch-Johnsen L, Haukvik UK, Lange EH, Melle I, Andreassen OA, Agartz I (2015). Cigarette smoking is associated with thinner cingulate and insular cortices in patients with severe mental illness. *Journal of Psychiatry and Neuroscience: JPN* **40**, 241–249.

Kahn RS, Sommer IE (2015). The neurobiology and treatment of first-episode schizophrenia. *Molecular Psychiatry* **20**, 84–97.

https://doi.org/10.1017/S003329171500210X Published online by Cambridge University Press

Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Koo MS, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW (2008). A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. *Archives of General Psychiatry* **65**, 746–760.

Lappin JM, Morgan C, Chalavi S, Morgan KD, Reinders AA, Fearon P, Heslin M, Zanelli J, Jones PB, Murray RM, Dazzan P (2014). Bilateral hippocampal increase following first-episode psychosis is associated with good clinical, functional and cognitive outcomes. *Psychological Medicine* **44**, 1279–1291.

Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234–239.

Malchow B, Hasan A, Fusar-Poli P, Schmitt A, Falkai P, Wobrock T (2013). Cannabis abuse and brain morphology in schizophrenia: a review of the available evidence. *European Archives of Psychiatry and Clinical Neuroscience* **263**, 3–13.

Malchow B, Keeser D, Keller K, Hasan A, Rauchmann BS, Kimura H, Schneider-Axmann T, Dechent P, Gruber O, Ertl-Wagner B, Honer WG, Hillmer-Vogel U, Schmitt A, Wobrock T, Niklas A, Falkai P (2015). Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. *Schizophrenia Research*. Published online 23 January 2015. doi:10.1016/j.schres.2015.01.005.

Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, Onyejiaka A, Croudace T, Jones PB, Murray RM, Fearon P, Doody GA, Dazzan P (2014). Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. *Psychological Medicine* **44**, 2713–2726.

Pope MA, Joober R, Malla AK (2013). Diagnostic stability of first-episode psychotic disorders and persistence of comorbid psychiatric disorders over 1 year. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie* **58**, 588–594.

Reuter M, Rosas HD, Fischl B (2010). Highly accurate inverse consistent registration: a robust approach. *NeuroImage* **53**, 1181–1196.

Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012). Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage* **61**, 1402–1418.

Rimol LM, Hartberg CB, Nesvag R, Fennema-Notestine C, Hagler Jr. DJ, Pung CJ, Jennings RG, Haukvik UK, Lange E, Nakstad PH, Melle I, Andreassen OA, Dale AM, Agartz I (2010). Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biological Psychiatry* **68**, 41–50.

Rimol LM, Nesvag R, Hagler Jr. DJ, Bergmann O, Fennema-Notestine C, Hartberg CB, Haukvik UK, Lange E, Pung CJ, Server A, Melle I, Andreassen OA, Agartz I, Dale AM (2012). Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biological Psychiatry* **71**, 552–560.

Roiz-Santianez R, Ayesa-Arriola R, Tordesillas-Gutierrez D, Ortiz-Garcia de la Foz V, Perez-Iglesias R, Pazos A, Sanchez E, Crespo-Facorro B (2014). Three-year longitudinal population-based volumetric MRI study in first-episode schizophrenia spectrum patients. *Psychological Medicine* **44**, 1591–1604.

Salvatore P, Baldessarini RJ, Khalsa HM, Amore M, Di Vittorio C, Ferraro G, Maggini C, Tohen M (2013). Predicting diagnostic change among patients diagnosed with first-episode DSM-IV-TR major depressive disorder with psychotic features. *Journal of Clinical Psychiatry* **74**, 723–731; quiz 731.

Salvatore P, Baldessarini RJ, Tohen M, Khalsa HM, Sanchez-Toledo JP, Zarate CA Jr, Vieta E, Maggini C (2011). McLean–Harvard International First-Episode Project: two-year stability of ICD-10 diagnoses in 500 first-episode psychotic disorder patients. *Journal of Clinical Psychiatry* **72**, 183–193.

Schaufelberger MS, Lappin JM, Duran FL, Rosa PG, Uchida RR, Santos LC, Murray RM, McGuire PK, Scazufca M, Menezes PR, Busatto GF (2011). Lack of progression of brain abnormalities in first-episode psychosis: a longitudinal magnetic resonance imaging study. *Psychological Medicine* **41**, 1677–1689.

Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy 3rd FV, Hahn SR, Brody D, Johnson JG (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA: The Journal of the American Medical Association* **272**, 1749–1756.

Spitzer RL, Williams JBW, Gibbon M, First MB (1992). The Structural Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry* **49**, 624–629.

van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, Rais M, Kahn RS (2008). Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biological Psychiatry* **63**, 106–113.

Veijola J, Guo JY, Moilanen JS, Jaaskelainen E, Miettunen J, Kyllonen M, Haapea M, Huhtaniska S, Alaraisanen A, Maki P, Kiviniemi V, Nikkinen J, Starck T, Remes JJ, Tanskanen P, Tervonen O, Wink AM, Kehagia A, Suckling J, Kobayashi H, Barnett JH, Barnes A, Koponen HJ, Jones PB, Isohanni M, Murray GK (2014). Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. *PLOS ONE* **9**, e101689.

Vita A, De Peri L, Deste G, Sacchetti E (2012). Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Translational Psychiatry* **2**, e190.

Wang AY, Lohmann KM, Yang CK, Zimmerman EI, Pantazopoulos H, Herring N, Berretta S, Heckers S, Konradi C (2011). Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathologica* **122**, 615–626.

Zipursky RB, Reilly TJ, Murray RM (2013). The myth of schizophrenia as a progressive brain disease. *Schizophrenia Bulletin* **39**, 1363–1372.