

Brain structural trajectories in youth at familial risk for schizophrenia or bipolar disorder according to development of psychosis spectrum symptoms

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Background: The evaluation of child and adolescent offspring of patients with schizophrenia (SzO) or bipolar disorder (BpO) may help understand changes taking place in the brain in individuals at heightened risk for disease during a key developmental period. **Methods:** One hundred twenty-eight individuals (33 SzO and 46 BpO, considered jointly as 'Familial High Risk' (FHR), and 49 controls) aged 6–17 years underwent clinical, cognitive and neuroimaging assessment at baseline, 2- and 4-year follow-up. Twenty FHR participants (11 SzO and 9 BpO) developed psychotic spectrum symptoms during follow-up, while 59 FHR participants did not. Magnetic resonance imaging was performed on a 3Tesla scanner; cortical surface reconstruction was applied to measure cortical thickness, surface area and grey matter volume. **Results:** FHR participants who developed psychotic spectrum symptoms over time showed greater time-related mean cortical thinning than those who did not and than controls. By subgroups, this effect was present in both BpO and SzO in the occipital cortex. At baseline, FHR participants who developed psychotic spectrum symptoms over time had smaller total surface area and grey matter volume than those who did not and than controls. Over time, all FHR participants showed less longitudinal decrease in surface area than controls. In those who developed psychotic spectrum symptoms over time, this effect was driven by BpO, while in those who did not, this was due to SzO, who also showed less grey matter volume reduction. **Conclusion:** The emergence of psychotic spectrum symptoms in FHR was indexed by smaller cross-sectional surface area and progressive cortical thinning. Relative preservation of surface area over time may signal different processes according to familial risk. These findings lay the foundation for future studies aimed at stratification of FHR youth. **Keywords:** High-risk studies; schizophrenia; bipolar; psychosis; structural MRI.

Introduction

Over the last three decades, researchers have attempted to characterize changes in the brain taking place prior to onset of psychosis. To this end, researchers have sought to identify samples exhibiting either subthreshold symptoms or a combination of familial and functional criteria (Miller et al., 2003) and have followed them over time, through progression to health or disease. However, despite evidence from animal models (Gomes, Rincón-Cortés, & Grace, 2016) and birth cohort studies (Cannon et al., 2002) suggesting that changes in the brain and behaviour associated with psychosis begin early in the course of neurodevelopment, the majority of studies in individuals considered at increased for psychosis have been performed in adults. The field has only recently begun to look towards childhood and adolescence as a critical period for understanding development of major adult

mental health outcomes. Studies in adolescents at varying degrees of risk for psychosis, identified either following an 'ultrahigh risk' approach (Cannon et al., 2015) or through community-based samples (Jalbrzikowski et al., 2019), have associated psychotic spectrum symptoms with global and regional grey matter volume and cortical thickness reductions. However, all above studies have relied on either cross-sectional designs or limited follow-up periods, which curtails the ability to capture differences in trajectories. This is especially relevant given the dynamic maturational changes that characterize this developmental phase (Horga, Kaur, & Peterson, 2014) and that the preclinical stage for psychosis may be longer during youth (Schultze-Lutter et al., 2015).

Another unanswered question is whether there is such a thing as a common neural signature to 'psychosis'. Comparative studies between patients with schizophrenia or bipolar disorder (Rimol et al., 2012) have revealed shared differences in their brain structural characteristics, such as thinner frontal

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cortices, but also specificities, such as widespread surface area reduction, which has been identified in patients with schizophrenia only. Brain changes associated with disease are hereditary (Van Haren et al., 2012), and the different measures which contribute to brain volume – cortical thickness and surface area – are thought to be driven by different genetic influences (Winkler et al., 2012). While there is considerable genetic overlap in the common variants conferring risk for schizophrenia and bipolar disorder (Purcell et al., 2009), evidence of distinct genetic loci, different polygenic risk scores and greater enrichment of copy number variants (Georgieva et al., 2014) in schizophrenia confirm that a certain degree of specificity remains between conditions.

Longitudinal studies of young offspring of patients with schizophrenia or bipolar disorder have the potential to overcome limitations of previous studies, and are able to shed light on the common premorbid trajectories leading to psychosis, while also highlighting areas of specificity between disorders. In our cohort study, which has recruited offspring aged 6–17 years, so far we have reported reduced global and regional – frontal, parietal and occipital – grey matter volume and surface area, which were specific to offspring of patients with schizophrenia at cross-section (Sugranyes et al., 2015). Over two years, we found greater longitudinal decrease in cortical thickness in the frontal lobe in offspring of patients with bipolar disorder relative to controls. In addition, for older offspring only, we observed greater longitudinal decrease in cortical thickness in offspring of patients with bipolar disorder relative to offspring of patients with schizophrenia, and less decrease in surface area in offspring of patients with schizophrenia relative to controls (Sugranyes, Solé-Padullés, et al., 2017).

Here, we set out to collect data at three time points over a 4-year period, aiming to assess longitudinal changes in measures of brain structure – cortical thickness, surface area and grey matter volume – which would identify children and adolescents at familial high risk (FHR) for bipolar disorder or schizophrenia who experienced psychotic spectrum symptoms over time. This approach aimed at investigating changes taking place in the brain during a period of heightened risk for psychosis, and to examine specificities of these changes between groups at FHR for schizophrenia versus bipolar disorder.

Based on existing literature and in the light of our own findings so far, we hypothesized that smaller surface area and grey matter volume at baseline, and progressive cortical thinning, would characterize FHR who developed psychotic spectrum symptoms over time. When analysing offspring subtypes, we speculated that the deficits in grey matter volume and surface area observed in offspring of patients with schizophrenia (SzO) at baseline would

normalize in those who remained well, while progressive changes in cortical thickness would be especially notable in offspring of patients with bipolar disorder (BpO). As secondary analyses, we set out to examine how these changes were distributed across the brain at a lobar level.

Methods

This is a naturalistic, longitudinal study including assessments at 0, 2 and 4 years. The recruitment and evaluation of the sample have been described in detail elsewhere (Sanchez-Gistau et al., 2015). Recruitment was performed systematically through parents: patients with a diagnosis of schizophrenia or bipolar disorder from adult psychiatry units with offspring aged 6–17 years were identified and invited to participate in the study. The exclusion criteria for proband parents were intellectual disability and drug or medically induced psychosis or mania. Exclusion criteria for offspring included intellectual disability, head injury with loss of consciousness or severe neurological conditions. Community control parents were recruited through advertisements posted in the same geographic area as the patients. The exclusion criteria were the same as for probands, in addition to personal or first-degree family history of schizophrenia or bipolar spectrum disorders. All 6- to 17-year-old offspring of community control parents were invited to participate in the study; exclusion criteria were the same as those for FHR offspring. To decrease selection bias, control parents who stated motivation to participate due to concerns about school performance or emotional or behavioural problems in their offspring were excluded.

Clinical and cognitive assessment

Participants underwent a comprehensive clinical and cognitive assessment at each visit performed by clinically experienced psychiatrists and psychologists. Clinical diagnoses of the index parents were based on the Spanish version of the *Structured Clinical Interview for DSM-IV-TR Axis I Disorders* (First, Spitzer, Gibbon, & Williams, 2002). This interview was also used for clinical assessment of coparents and offspring aged 18 or above. Participants younger than 18 years were assessed by child and adolescent psychiatrists or psychologists using the Spanish version of the *Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version* (Kaufman et al., 1997). Accumulated prevalence of axis I disorders was calculated at each time point. A measurement of general cognitive capacity was estimated using the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests of the *Wechsler Intelligence Scale for Children* (Wechsler, 2003) or the *Wechsler Adult Intelligence Scale* (Wechsler, 2001) (for participants over 16 years). Pubertal development was assessed using a self-report pictorial questionnaire according to Tanner criteria. (Tanner & Whitehouse, 1976). Cannabis use was measured dichotomously using the *Teen-Addiction Severity Index* administered by an interviewer to the participant individually (Kaminer, Bukstein, & Tarter, 1991).

Participants were assessed at each visit with the *Scale of Prodromal Symptoms Scale* (SOPS) within the *Structured Interview for Prodromal Symptoms* (Miller et al., 2003). Reliability for the SOPS has been undertaken by the team members performing clinical assessments (Kappa statistic for both SOPS total score and subscales >0.8). Scores in the SOPS were used to divide the sample between those who had experienced psychotic spectrum symptoms at at least one longitudinal assessment and those who had not. A definition of ‘psychotic spectrum symptoms’ was defined as any SOPS positive or negative rating equal or over 3, and included both individuals experiencing an attenuated psychosis syndrome (American Psychiatric

Association, 2013) and those meeting criteria for a psychotic disorder (schizophrenia spectrum and other psychotic disorders (295.XX, 298.X, 297.1), or bipolar (296.4, 296.5) or depressive disorders (296.2, 296.3) with psychotic features.

The protocol was approved by the local ethics review board. All participants provided written informed consent or assent after receiving a complete description of the study at each time point. For participants under age 18 years, parents gave informed consent and participants provided assent.

Image acquisition and processing

A high-resolution T1-weighted 3-dimensional magnetization prepared rapid sequence was obtained on a 3-T Siemens Magnetom Trio Tim at the Center for Image Diagnosis at the Hospital Clinic of Barcelona, using the following parameters: 240 sagittal slices, 2,300-ms repetition time, 3.01-ms echo time, 1-mm slice thickness, 900-ms inversion time, 394 × 240 field of view, 256 × 256 matrix size and 9° flip angle. To rule out possible underlying pathology, an axial T2 structural image was acquired and subsequently reviewed by a neuroradiologist blinded to group classification. All scans were visually checked for inaccuracies by two trained raters. Editing procedures detailed on the FreeSurferWiki (<http://freesurfer.net/fswiki/Edits>), consisting of adding control points and/or modification of the brain mask, were required in 5% of the sample, with no difference in rates of corrections between groups (chi-square .92, $p = .82$).

After reorientation along the anterior and posterior commissural line, measurements of cortical thickness and surface area were computed using the standard FreeSurfer 5.3.0 pipeline (<http://www.surfer.nmr.mgh.harvard.edu>) (Fischl et al., 2002). The FreeSurfer automated procedure includes motion correction, nonuniform intensity normalization, registration to Montreal Neurological Institute stereotactic space, skull strip, white matter segmentation, definition of pial surface and parcellation of the brain into 34 cortical regions per hemisphere using the Desikan–Killiany brain atlas (Desikan et al., 2006).

Measures of mean hemisphere cortical thickness and total hemisphere surface area and grey matter volume were computed and divided into frontal, temporal, parietal and occipital parcellations; they were then extracted and subjected to between group comparisons.

Statistical analysis

Comparisons were performed between FHR divided according to whether they had experienced developed psychotic spectrum symptoms at at least one visit over the follow-up period (FHR-P and FHR-NP), and controls. For secondary analyses, the FHR group was further subdivided into offspring subgroups according to whether they had developed psychotic spectrum symptoms over time (SzO-P and BpO-P) or not (SzO-NP and BpO-NP).

Statistical analysis: demographic and clinical measures. Statistical analyses of demographic and clinical variables were performed using SPSS 22.0. For demographic variables, chi-square statistics with Yates correction and Fisher's exact test were used to compare percentages of discrete variables. Univariate analyses of variance and Mann-Whitney U or Kruskal-Wallis tests were used to compare continuous variables. Pairwise contrasts were carried out when the 3-group comparison was statistically significant. Clinical variables were assessed with linear mixed models, where family was included as random variable so as to account for relatedness between participants.

Statistical analysis: neuroimaging measures. For global measures of cortical thickness, surface area and grey

matter volume, linear mixed-effects models were used for (a) cross-sectional analysis, where baseline measures of brain structure were included as outcome variables and 'group' as predictor, and (b) for longitudinal analyses, where measures of brain structure at all available time points were included as outcome variable, and 'group', 'time' (computed as time elapsed from baseline scan to each follow-up assessment) and 'group by time interaction' were also included as predictors. For each model, age at baseline and gender were included as covariates in a stepwise procedure, when showing effects at a $p < .20$ threshold. Hemisphere (right/left) and total intracranial volume (only in the case of grey matter volume and surface area) were also included as fixed effect, and subject ID and family membership were added as random variables. The combined results of the two hemispheres are presented throughout the article. Analyses of lobar measures were based on the same models, where false discovery rate (FDR) correction was used to adjust main group and group by time effects. Post hoc pairwise analyses of all contrasts showing significant main effects were also subjected to multiple comparison correction. The same analyses were also run for subcortical structures including the hippocampus, caudate, putamen and pallidum.

Sensitivity analyses were performed using the same methodology as above, by assessing the effects of general cognitive capacity, other psychiatric conditions or cannabis use on the models showing significant effects. In addition, analyses were repeated in youth with no previous exposure to psychotropic medications, and by dividing FHR offspring according to whether they had experienced psychotic spectrum symptoms at any point in time (including baseline).

Results

Demographic and clinical measures

One hundred twenty-eight participants underwent baseline assessment. Table S1 provides information on relatedness between participants, and Figure S1 illustrates a flow chart illustrating retention rates over the three time points and availability of MRI scans at each assessment. Although there were no demographic, diagnostic or cognitive differences, participants who failed to attend all assessments had higher rates of psychotic spectrum symptoms at baseline than those who did not (see Appendix S1).

Reasons for lack of scan included wearing dental braces, claustrophobia or refusal to undergo scanning. Among participants with at least one valid MRI scan during the study period ($N = 33$ SzO, $N = 46$ BpO and $N = 49$ controls), eleven (33.3%) SzO, nine (19.6%) BpO and five (10.2%) controls experienced psychotic spectrum symptoms at at least one longitudinal assessment. Among these individuals, $N = 4$, all within the group of SzO, had experienced clinical psychosis, while the remaining participants had experienced an attenuated psychosis syndrome. Given the small number of controls who developed psychotic spectrum symptoms over time, these were excluded from the imaging analyses.

Table 1, Tables S2 and S3, and Figure S2 illustrate demographic and clinical information of the sample included in neuroimaging analyses. There were no age or sex differences between FHR-P, FHR-NP or controls. FHR-P had lower general cognitive capacity

than controls at baseline and at 4 years (Figure S2). FHR-P, and FHR-NP at 2 years, had a greater history of use of psychotropic medications than controls, and FHR-P only had greater use of cannabis than controls across all time points. Both FHR-P and FHR-NP had higher rates of attention deficit hyperactivity disorders (ADHD) than controls at baseline and 2 years, while (nonbipolar) mood disorders were more prevalent at 2-year follow-up in FHR-P only (Figure S2).

Neuroimaging measures

Cortical thickness. We observed no effect of group on mean hemisphere cortical thickness at baseline. There was an overall effect of time on mean hemisphere cortical thickness ($F = 603.3$, $p < .001$, $\text{Beta} = -.0273$, $\text{CI}: [-.0316 \text{ to } -.0230]$). Examination of longitudinal effects revealed a group by time effect ($F = 3.18$, $p = .042$) consisting of greater time-related loss of cortical thickness in FHR-P than controls ($\text{Beta} = -.0064$, $t = -2.51$, $p = .012$, $\text{CI}: [-.0115 \text{ to } -.0014]$) and than FHR-NP ($\text{Beta} = -.0051$, $t = -2.02$, $p = .044$, $\text{CI}: [-.0101 \text{ to } -.0001]$) (Figure 1). This was observed in the occipital lobe for FHR-P relative to controls and FHR-NP and in the frontal lobe for FHR-P vs controls at near significance (Table S4). By subgroups, BpO-P showed greater decrease in cortical thickness over time relative to controls, to BpO-NP and to both SzO subgroups (Table S5, Figure 2). At a lobar level, these effects in cortical thickness were observed in the temporal and occipital cortices, and frontal lobe at near significance (Table S5).

Surface area. There was an effect of group at baseline ($F = 5.59$, $p = .005$) whereby FHR-P showed smaller surface area than controls ($\text{Beta} = -3122.5$, $t = -3.32$, $p = .001$, $\text{CI}: [-4984.23 \text{ to } -1260-70]$)

and than FHR-NP ($\text{Beta} = -2000.1$, $t = -2.49$, $p = .015$, $\text{CI}: [-3598.9 \text{ to } -401.41]$). At a lobar level, FHR-P showed a near-significant smaller surface area than controls in the frontal, temporal and parietal lobes, and than FHR-NP in the temporal lobes (Table S4). Details on these effects divided by subgroups of FHR are depicted in Figure 2 and Table S6, which illustrate how both SzO-P and SzO-NP showed smaller total surface area than controls, while BpO-P exhibited smaller surface area than both controls and BpO-NP. These effects were observed in the temporal and parietal lobes.

There was an effect of time on surface area ($F = 57.66$, $p < .001$, $\text{Beta} = -153.07$, $\text{CI}: [-289.47 \text{ to } -16.68]$), and examination of group by time effects ($F = 4.16$, $p = .016$) revealed less time-related decrease in surface area in both FHR-P ($\text{Beta} = 208.1$, $t = 2.56$, $p = .011$, $\text{CI}: [48.36 \text{ to } 367.74]$) and FHR-NP ($\text{Beta} = 129.5$, $t = 2.18$, $p = .029$, $\text{CI}: [12.97 \text{ to } 246.01]$) than controls (Figure 1). By offspring subgroups, group by time effects for total surface area were observed in SzO-NP relative to controls, SzO-P and BpO-NP, and in BpO-P relative to controls, BpO-NP and SzO-P (see Table S5 and Figure 2). At a lobar level, effects described for SzO-NP were observed in the parietal lobe and for BpO-P in the frontal lobe (Table S5).

Grey matter volume. There was an effect of group at baseline ($F = 3.76$, $p = .026$) whereby FHR-P showed smaller baseline total grey matter volume than controls (-9558.8 , $t = -2.70$, $p = .008$, $\text{CI}: [-16579.8 \text{ to } -2537.9]$) and than FHR-NP (-7222.6 , $t = -2.2$, $p = .029$, $\text{CI}: [-13672.9 \text{ to } -772.3]$). FHR-P showed less grey matter volume than controls and than FHR-NP in the parietal lobe (Table S4).

There was an effect of time on grey matter volume ($F = 559.6$, $p < .001$, $\text{Beta} = -3993.9$, $\text{CI}: [-4690.7$

Table 1 Demographic and clinical characteristics of the sample

| | FHR-NP <i>N</i> = 59 | FHR-P <i>N</i> = 20 | Controls <i>N</i> = 44 | Statistics | Significant pairwise comparisons |
|--|-------------------------|------------------------|---------------------------|-------------------------|----------------------------------|
| Sex (σ) | 35 (53.8%) | 11 (55.05%) | 19 (43.2%) | Chi = 2.7, $p = .26$ | |
| Age in years (mean, standard deviation) [range] | | | | | |
| Baseline | 11.6 (3.3) [6–17] | 12.5 (2.7) [6–17] | 12.5 (3.5) [7–17] | $F = 1.07$, $p = .35$ | |
| 2 years | 14.2 (3.1) [9–19] | 14.8 (2.9) [8–19] | 15.5 (3.6) [9–20] | $F = 1.52$, $p = .22$ | |
| 4 years | 16.5 (3.5) [10–22] | 16.9 (2.2) [12–19] | 17.3 (3.4) [11–23] | $F = .54$, $p = .58$ | |
| Pubertal Stage, Tanner scale (mean, <i>SD</i>) | | | | | |
| Baseline | 3.0 (1.3) | 3.4 (1.2) | 3.1 (1.3) | $F = .81$, $p = .45$ | |
| 2 years | 3.8 (1.2) | 4.3 (1.0) | 3.9 (1.2) | $F = 1.4$, $p = .25$ | |
| 4 years | 4.4 (.84) | 4.7 (.95) | 4.4 (.80) | $F = .53$, $p = .59$ | |
| General cognitive capacity (marginal mean, <i>SD</i>) ^a | | | | | |
| Baseline | 103.9 (1.8) | 96.6 (3.0) | 106.7 (2.2) | $F = 3.8$, $p = .025$ | FHR-P < Controls |
| 2 years | 107.8 (2.0) | 101.9 (3.1) | 111.3 (2.4) | $F = 2.9$, $p = .06$ | |
| 4 years | 103.9 (2.6) | 95.8 (4.3) | 109.2 (2.8) | $F = 3.4$, $p = .04$ | FHR-P < Controls |
| 'Any' current/previous axis I diagnosis (<i>n</i> , %) ^a | | | | | |
| Baseline | 27 (45.8%) | 10 (50.0%) | 7 (15.9%) | $F = 5.4$, $p = .006$ | FHR-NP, FHR-P > Controls |
| 2 years | 20 (46.5%) | 12 (66.7%) | 7 (23.3%) | $F = 4.19$, $p = .018$ | FHR-P > Controls |
| 4 years | 14 (43.8%) | 8 (80%) | 10 (31.2%) | $F = 2.84$, $p = .065$ | |

^aGeneralized linear mixed models including family membership as random variable.

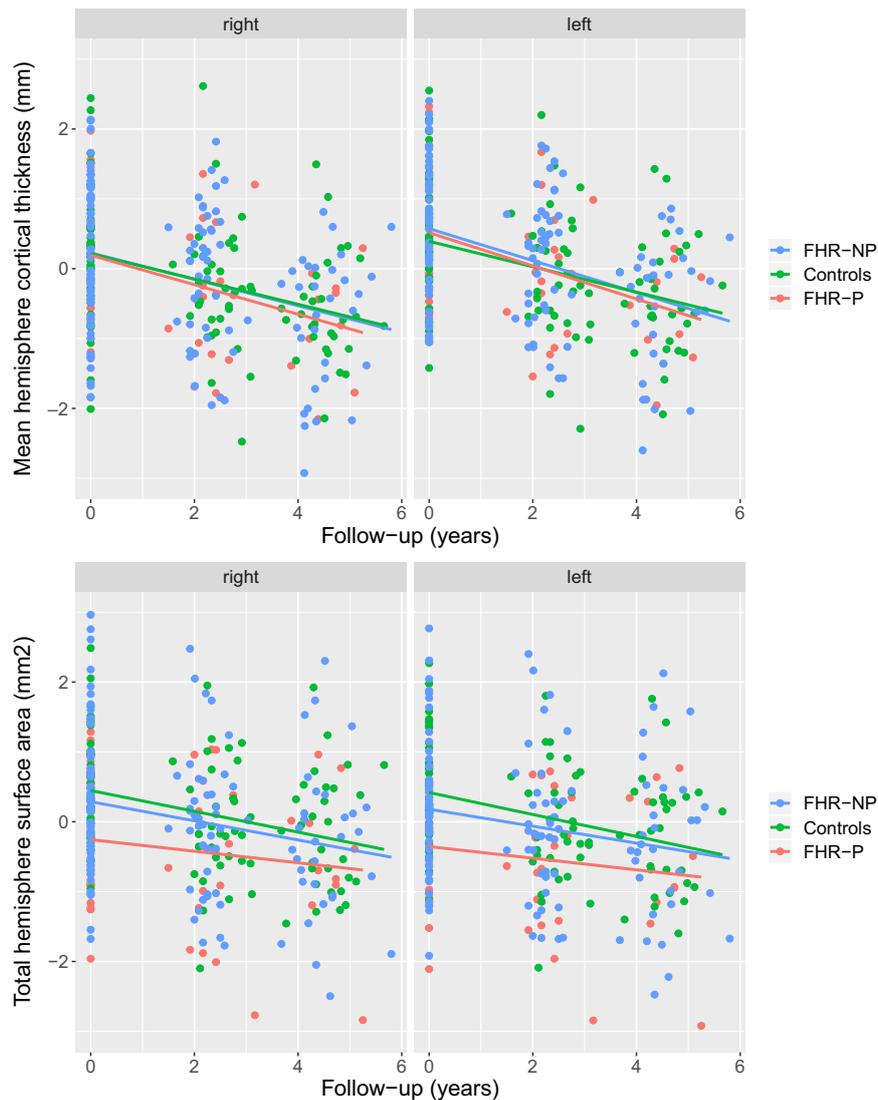


Figure 1 Longitudinal measures of cortical surface area and thickness in familial high-risk offspring according to development of psychotic spectrum symptoms at follow-up

to -3297.1) but no group by time effects for grey matter volume between FHR groups. When subdividing according to offspring subgroup, there was a significant group by time interaction for total grey matter volume, whereby SzO-NP showed less time-related loss of total grey matter volume than controls (Table S5). No group or group by time effects were observed in the hippocampus, caudate, putamen or pallidum (see Appendix S2).

Sensitivity analyses

Results from sensitivity analyses are depicted in Appendix S3. There was no significant effect of potential confounders on any of the above findings, with the following exceptions: in participants with no previous exposure to psychotropic medication, the main effects of FHR group on surface area showed the same direction and similar beta values than with the whole sample (retaining trend-level significance for baseline measures and statistical significance for

group by time effects). For mean total cortical thickness, while the direction of the effects was the same as for the whole group, group by time effects became nonsignificant. Nevertheless, there continued to be a group by time effect for cortical thickness of the occipital lobe and for the frontal lobe – at trend level – within the medication naïve subgroup. While there were no effects of co-occurring ADHD or mood disorders on any of the measures, we did observe that FHR without a history of mood disorders experienced less surface area decrease over time than controls, and FHR with a resolved mood disorder showed less grey matter volume decrease over time than those with a persistent mood disorder and than controls.

Discussion

This study extends previous neuroimaging reports in our familial risk cohort, by identifying longitudinal differences in brain structure according to

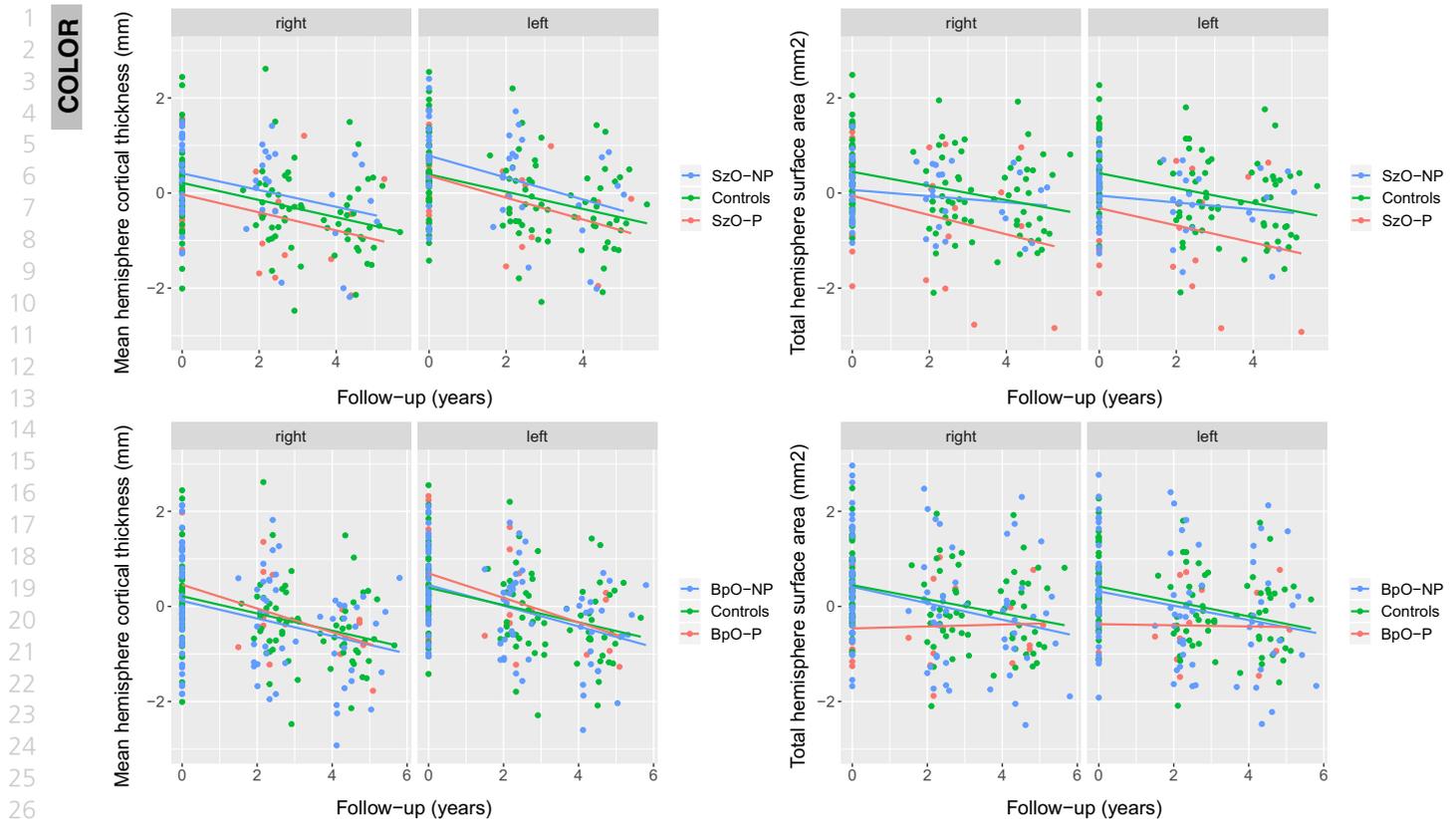


Figure 2 Longitudinal measures of cortical surface area and thickness in offspring of patients with schizophrenia or bipolar disorder according to development of psychotic spectrum symptoms at follow-up

development of psychotic spectrum symptoms over 4-year follow-up. This is possible as the sample grows older, with children entering adolescence and early adulthood, approaching the peak age of onset of psychosis.

In our previous, 2-year follow-up study (Sugranyes, Solé-Padullés, et al., 2017), the only observed changes in cortical thickness consisted of greater cortical thinning in BpO than SzO in older youth. Here, we have continued to observe no differences in cortical thickness at baseline. However, over time, FHR-P experienced greater mean hemisphere and occipital (and near-significant frontal) cortical thinning relative to FHR-NP and to controls. When assessing offspring subgroups, similar effects were found in BpO, in whom there was also a near-significant effect in the temporal lobe, while in SzO, these effects were observed in the occipital cortex only. Our observations provide evidence that cortical thinning associated with illness observed in adult patients (Rimol et al., 2012) and in young adults with ‘ultrahigh’ risk criteria who convert to psychosis (Cannon et al., 2015) could begin progressively during childhood and adolescence, and possibly exhibit early areas of overlap between SzO and BpO in the occipital cortex. Although cortical thinning has been observed in patients with bipolar disorder regardless of the presence of psychotic symptoms (Hibar et al., 2018), in the current sample greater cortical thinning characterized BpO-P, and was

independent of mood diagnosis. To our knowledge, this is the first study so far to assess structural imaging measures in youth at FHR for bipolar disorder experiencing psychotic spectrum symptoms. Cortical thinning has been associated with synaptic pruning, associated glial and vascular changes and/or cell shrinkage (Morrison & Hof, 1997); changes which have been suggested to take place proximally to illness, which could explain the lack of findings in our sample at cross-section, and the progressive differences as individuals grow older, potentially nearer to illness onset. The only area showing greater cortical thinning in SzO-P, the occipital cortex, is among the earliest developing cortical regions (Tamnes et al., 2017). More widespread cortical thinning, extending to anterior regions, may emerge as SzO grow into late adolescence, potentially denoting different timing of cortical maturation between SzO versus BpO.

At baseline, smaller total surface area was specific to FHR-P. When assessing these results by subgroups, we observed that this finding was present in all SzO versus controls, regardless of whether they went on to develop psychotic spectrum symptoms, while in BpO, this was only present in BpO-P. Therefore, our results suggest that for SzO, smaller baseline surface area may be a trait characteristic, which extends our findings at 2 years (Sugranyes, Solé-Padullés, et al., 2017), while for BpO, this may index cases experiencing psychotic spectrum

1 symptoms during follow-up. Comparative studies in
2 adult patients have pointed to specificity of surface
3 area reduction for schizophrenia (Rimol et al., 2012),
4 while a recent meta-analysis has suggested that
5 surface area decrease in bipolar disorder may only
6 be present in patients with psychotic symptoms
7 (Hibar et al., 2018), which coincides with our obser-
8 vations. Our findings also concur with recent data
9 from a community-based study in adolescents which
10 also described cross-sectional frontal and parietal
11 surface area reduction in youth showing psychotic –
12 but not bipolar – spectrum symptoms (Jalbrzikowski
13 et al., 2019), which mirrors the lack of effect of mood
14 diagnoses on our findings at cross-section. Only
15 follow-up of the current sample into adulthood will
16 resolve questions concerning prediction of specific
17 diagnostic outcomes in these youth.

18 Previous reports on changes in surface area in
19 individuals at increased risk for psychosis either for
20 clinical or familial reasons are mixed: another
21 adolescent sample of SzO (Prasad et al., 2010) has
22 described cross-sectional reduction similar to ours,
23 while studies in individuals with ultrahigh risk for
24 psychosis documenting data on surface area are
25 few and provide contradicting results (Takayanagi
26 et al., 2017). Smaller cortical surfaces have also
27 been found to characterize other conditions tradi-
28 tionally considered to be of ‘neurodevelopmental’
29 origin such as ADHD (Ambrosino, de Zeeuw,
30 Wierenga, van Dijk, & Durston, 2017); indeed, we
31 have recently reported a gradient of severity in
32 childhood developmental difficulties (delayed or
33 disrupted acquisition of language, motor, reading/
34 writing skills and elimination disorders), as well as
35 increased rates of ADHD and lower general cogni-
36 tive capacity, between SzO, BpO and controls
37 **7** (Sugranyes, de la Serna, et al., 2017). While these
38 factors appear to aggregate in these individuals, it
39 is noteworthy that neither ADHD nor lower general
40 cognitive capacity significantly changed the current
41 imaging findings and is thus likely to result from a
42 combination of gene – environmental effects impact-
43 ing on both cortical surface and behavioural and
44 cognitive measures.

45 Our findings concerning longitudinal change in
46 surface area were apparently contradictory, as both
47 FHR-P and FHR-NP showed less time-related
48 decrease in total surface area. When assessing
49 offspring subgroups, we observed that the effects
50 in FHR-NP were found in SzO in total surface area
51 and specifically in the parietal lobe. This suggests
52 that our findings at 2 years (Sugranyes, Solé-
53 Padullés, et al., 2017) of less longitudinal decrease
54 in surface area in SzO than in controls were likely
55 driven by those who would not develop psychotic
56 spectrum symptoms at follow-up. These group by
57 time differences in surface area in SzO-NP were
58 coupled with less longitudinal grey matter volume
59 decrease. A different sample of healthy first-degree
60 child and adolescent relatives of patients with

schizophrenia also experienced less time-related
decrease in grey matter volume which normalized
as the sample matured, which the authors inter-
preted as compensatory for early deficits, although
these authors did not provide data for surface area
(Mattai et al., 2011). Therefore, less time-related
decrease in surface area in SzO-NP during adoles-
cence may signal the effect of influences conferring
protection against disease. In contrast, we observed
relative preservation of surface area in BpO-P. In
this case, this change was not coupled with
changes in grey matter volume, and was located
in the frontal lobe, coinciding with one of the
regions of greater cortical thinning associated with
the development of psychotic spectrum symptoms.
Indeed, a number of reports have related cortical
thickness reduction to surface area increase, in
association with developmental changes in sulcal
metrics (Aleman-Gomez, Janssen, & Schnack,
2013). In addition to mechanistic explanations,
there is discussion with regard the genetic link
between surface area and cortical thickness, which
may be stronger earlier in life than during maturity
(Schmitt et al., 2019), and could vary according to
the different genetic background between
schizophrenia and bipolar disorders. A further issue
potentially playing a role in longitudinal change in
cortical surface and grey matter volume concerns
mood disorders. Inclusion of mood disorders in the
models dividing FHR according to psychotic spec-
trum symptoms at follow-up did not significantly
change the results. However, when subdividing FHR
according to history of mood disorders, we observed
that those who had no history of a mood diagnosis
experienced less time-related decrease in surface
area than controls and that those with a mood
diagnosis which had resolved over follow-up showed
less grey matter volume loss than those who con-
tinued to meet criteria for a mood disorder at follow-
up and than controls. Taken together, our observa-
tions help understand previous mixed findings
concerning cortical surface area in samples of
individuals at increased risk for psychosis, and
stress the need for longitudinal studies taking into
account different morphometric measures, familial
background and trajectories of mood symptoms, in
order to fully understand the brain changes leading
to disease.

A number of methodological considerations need
to be taken into account when interpreting the
current findings. First, we acknowledge the small
sample size of the individual offspring groups,
which limited further subdivisions of the sample
(for instance according to pubertal stage or accord-
ing to co-occurring diagnoses). Schizophrenia
patients, particularly, have low fertility rates, which
is a challenge in all offspring studies, especially
when performing systematic recruitment. Second,
we have combined participants experiencing atten-
uated psychotic symptoms with those manifesting

clinical psychotic symptoms, in an attempt to capture the effects of psychosis dimensionally, although this needs to be taken into account when comparing our findings with others following a different approach. Despite strong inter-rater reliability in the SOPS, inter-rater reliability for the K-SADS or SCID-I interview was not determined. Nevertheless, it is worth noting that interviews were performed by a small number of experienced child and adolescent psychiatrists and psychologists, and supervision was provided between team members during a transition period between assessments. Furthermore, all clinical information was collected by experienced clinicians through face-to-face assessments of the offspring and their parents, which grants greater reliability to our data in comparison with other similar studies based on self-reports. A shortcoming of our design is that we have not been able to assess bipolar prodromal symptoms in our sample with a measure designed for this purpose; however, we have presented sub-analyses examining the effect of co-occurring mood disorders, which have also been assessed in the same context with standardized measures. Further, we cannot entirely rule out attrition bias whereby individuals more severely affected could have been less likely to attend follow-up visits; although there were no diagnostic or demographic differences, those who did not attend all assessments had higher rates of psychotic spectrum symptoms at baseline, which may have reduced power to detect differences. The strength of some of the associations decreased when limiting analyses to the medication naïve sample – while we cannot fully exclude that psychotropic medications may have an effect on brain structure, it is likely that those on medication are in fact those either at greatest risk for the disease or those with manifest symptoms, and therefore that the decrease in power may explain most of the reduction of effects. Furthermore, a large portion of cases with medication were stimulants, which have in fact been suggested to have a normalizing effect on brain structural deficits (Nakao, Radua, Rubia, & Mataix-Cols, 2011). Finally, for secondary analyses examining cross-sectional and longitudinal effects of group for each cortical lobe, while corrected for multiple comparisons, our models did not take into account potential correlations between the different lobes.

Conclusions

Our sample provides the opportunity to examine the imprint of familial risk for disease in individuals who carry a combination of both genetic liability and risk markers of disease. The current study provides novel evidence consisting of early cross-sectional surface area and volumetric decrease, and progressive cortical thinning, in FHR who go on to develop psychotic

spectrums at follow-up. Future studies in FHR samples should extend these findings, examining their potential to help stratify FHR individuals according to risk of progression to disease, aiding tailored intervention.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Baseline characteristics of participants according to whether they attended all study assessments.

Appendix S2. Examination of volume of subcortical structures: hippocampus, caudate, putamen and pallidum.

Appendix S3. Sensitivity analyses.

Table S1. Relatedness between participants.

Table S2. Clinical characteristics of the sample.

Table S3. Demographic and clinical characteristics of the sample subdivided by offspring subgroups.

Table S4. Lobar measures of surface area, cortical thickness and grey matter volume for familial high risk participants versus controls.

Table S5. Longitudinal measures of cortical thickness, area and grey matter volume according to offspring subgroups.

Table S6. Baseline measures of cortical thickness, area and grey matter volume according to offspring subgroups.

Figure S1. Flow-chart illustrating participants assessed clinically and availability of scans at each time point.

Figure S2. Clinical characteristics of the sample included in neuroimaging analyses at each time point.

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Key points and relevance

- Offspring of patients with schizophrenia or bipolar disorder show cross-sectional differences in brain structure relative to controls.
- In the current longitudinal study, we demonstrate that high-risk youth who developed psychotic spectrum symptoms over time showed greater cortical thinning than those who did not.
- We found that cortical surface area and grey matter volume reductions at baseline characterized high-risk youth who later developed psychotic spectrum symptoms.
- We documented different trajectories of change in surface area and volume over time between familial risk for schizophrenia versus bipolar disorder.
- Longitudinal changes in brain structure during youth have the potential to distinguish pathways to health and disease in high-risk individuals, which may help design early, tailored interventions.

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