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Non-linear development of brain morphometry in child and adolescent offspring of individuals with bipolar disorder or schizophrenia

Simon R. Poortman [a,1,*], Nikita Setiaman [a,1], Marjolein E.A. Barendse [a], Hugo G. Schnack [a,b], Manon H.J. Hillegers [a,b], Neeltje E.M. van Haren [a,b]

[a] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht, the Netherlands

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ABSTRACT

Offspring of parents with severe mental illness (e.g., bipolar disorder or schizophrenia) are at increased risk of developing psychopathology. Structural brain alterations have been found in child and adolescent offspring of patients with bipolar disorder and schizophrenia, but the developmental trajectories of brain anatomy in this high-familial-risk population are still unclear. 300 T1-weighted scans were obtained of 187 offspring of at least one parent diagnosed with bipolar disorder (n=80) or schizophrenia (n=53) and offspring of parents without severe mental illness (n=54). The age range was 8 to 23 years old; 113 offspring underwent two scans. Global brain measures and regional cortical thickness and surface area were computed. A generalized additive mixed model was used to capture non-linear age trajectories. Offspring of parents with schizophrenia had smaller total brain volume than offspring of parents with bipolar disorder (d=-0.20, p=0.004) and control offspring (d=-0.22, p=0.005) and lower mean cortical thickness than control offspring (d=-0.23, p<0.001). Offspring of parents with schizophrenia showed differential age trajectories of mean cortical thickness and cerebral white matter volume compared with control offspring (both p's=0.003). Regionally, offspring of parents with schizophrenia had a significantly different trajectory of cortical thickness in the middle temporal gyrus versus control offspring (p<0.001) and bipolar disorder offspring (p=0.001), which was no longer significant after correcting for mean cortical thickness. These findings suggest that particularly familial high risk of schizophrenia is related to reductions and deviating developmental trajectories of global brain structure measures, which were not driven by specific regions.

1. Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are both severe mental illnesses that affect approximately 1% of the world population (GBD 2019 Mental Disorders Collaborators, 2022). Their peak illness onset lies around the age of 20 (Dalsgaard et al., 2020; Kessler et al., 2005; Solmi et al., 2022), and manifestation is often preceded by a transdiagnostic prodrome (Maier et al., 2006; Shah et al., 2020). Adolescence is therefore a critical phase in the development of SZ or BD.

Throughout adolescence, natural maturation of the brain takes place as it undergoes synaptic pruning, a process during which redundant neural connections are eliminated, involving extensive structural and functional reorganization. This process varies in timing and patterns across different brain properties (Blakemore, 2012). While white matter follows linear increases of volume over time, puberty is suggested to affect the development of cortical gray matter volume in a non-linear manner, showing an increase before adolescence and a peak around the age of 12 for the parietal and frontal lobes, at the age of 16 for the temporal lobe and in young adulthood for the occipital lobe (Bethlehem et al., 2022; Giedd et al., 1999; Goddings et al., 2019). The development of cortical thickness, which shows a linear decrease over time, and of cortical surface area, showing a curvilinear pattern of change, are not entirely congruent with cortical volume development and vary across brain regions (Wierenga et al., 2014).

It has been suggested that, based on adult patient studies, SZ and BD (with psychosis) both relate to a continuum of psychotic disorders

* Corresponding author at: Erasmus University Medical Center - Sophia Children's Hospital, Department of Child and Adolescent Psychiatry/Psychology, KP2, Wytemaweg 8, Rotterdam, 3015, CN, the Netherlands.
E-mail address: srpoortman@gmail.com (S.R. Poortman).
[1] Simon R. Poortman and Nikita Setiaman contributed equally to this work.

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(Yamada et al., 2020). SZ and BD have shared anomalies in white matter structure and connectivity (O'Donoghue et al., 2017) and gray matter volume (Arnone et al., 2009; Ellison-Wright and Bullmore, 2010). Additionally, cross-disorder comparison shows that the overlap in patterns of brain abnormalities between SZ and BD is greater (i.e., similar effect sizes) than between either one of these disorders and major depressive disorder (Cheon et al., 2022). Nonetheless, effect sizes in cortical thickness are more pronounced in SZ than in BD (Hibar et al., 2018; van Erp et al., 2018), and fronto-temporal regions and subcortical structures, such as the thalamus, hippocampus and amygdala are more affected in SZ than in BD (Maggioni et al., 2016; Yamada et al., 2020). Comprehending the variability in brain development between SZ or BD may help discriminate between these two disorders that partially share a genetic background and clinical outcome (Lichtenstein et al., 2009).

Illness and treatment effects can complicate the interpretation of the distinction between SZ and BD, and studies in individuals with established illness cannot elucidate the aberrations in the brain before or during illness onset. Studies in child and adolescent offspring at familial high-risk allow for the investigation of pathognomonic risk and resilience factors, which predispose or protect an adolescent to future onset of a psychiatric disorder. Offspring of patients with schizophrenia (SZo) or bipolar disorder (BDo) are at increased risk of developing SZ, BD or other psychopathology (Lau et al., 2018; Mesman et al., 2013; Setiaman et al., 2023; Uher et al., 2023), and are often unmedicated, consequently attenuating potentially confounding effects of psychotropic medication intake. Longitudinal brain imaging studies in this population are imperative to shed light on the neurodevelopmental trajectories related to the risk of or resilience against severe mental illness. Crucially, these trajectories could indicate when potential deviations in high-familial-risk offspring start appearing. If the trajectories consistently show lower or higher levels throughout the studied age range, then the divergence likely begins earlier in childhood. Conversely, if these deviations first become noticeable during adolescence, it would point to synaptic pruning as a mechanism and it would be critical to examining interactions with relevant biological, environmental, or behavioral processes occurring at this time, such as puberty, social interactions, substance use. Early adolescence might also serve as an important period for interventions or preventive strategies essential for managing symptoms or improving long-term outcomes. Transdiagnostic studies on the brain development of offspring at high familial risk of SZ and BD are however sparse.

Thus far, one comparative longitudinal cohort study (The Bipolar and Schizophrenia Young Offspring Study, BASYS) focused on brain development in SZo and BDo. Similar to the pattern found in adult patients (Cheon et al., 2022) and their first degree relatives (De Zwarte et al., 2019), the observed brain deviations are more pronounced in SZo than in BDo. SZo showed reduced global gray matter volume and reduced cortical surface area compared to BDo (Sugranyes et al., 2017b, 2017a, 2015), with larger deviations being associated with presence or severity of (prodromal) psychopathology. Using a longitudinal design (Sugranyes et al., 2021), they found a greater decrease of cortical thickness in offspring with psychopathology than in offspring without psychopathology. Moreover, SZo with psychopathology showed a larger decrease over time of surface area and gray matter volume than SZo without psychopathology. Surprisingly, BDo with psychopathology showed larger increase over time in surface area than BDo without psychopathology. However, these studies used linear modeling methods, and the curvilinear development of structural brain measures in high-familial-risk offspring has not been investigated yet.

In the current study, we compare global and regional structural brain development over time between SZo, BDo, and controls during childhood and adolescence, using a non-linear method to estimate the association between age and structural brain measures in individuals with one or two brain scans. Additionally, we explored whether effects could be explained by either IQ and/or dimensional psychopathology and repeated the analyses with a linear method to allow for comparison with earlier studies.

2. Experimental procedures

2.1. Participants

The Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) is an ongoing prospective cohort study, investigating the development of the brain, genetics, cognitive functioning, and environment, that contribute to risk of and resilience against mental illness (Setiaman et al., 2023). Data from the first two waves is used for the current study. After exclusions for scan quality and other reasons (see Supplemental Table S1 for an overview of scan exclusion reasons per group at each wave), the current sample includes a total of 300 magnetic resonance imaging (MRI) brain scans of 187 child and adolescent offspring (80 BDo, 53 SZo, 54 controls) from 124 families (see Supplemental Table S2 for a comparative breakdown of family sizes across the three groups). At wave 1, 140 individuals aged between 8 and 18 years comprised 54 BDo, 42 SZo and 44 controls. At wave 2, 160 participants aged between 11 and 23 years included 72 BDo, 43 SZo and 45 controls. A total of 113 individuals (46 BDo, 32 SZo and 35 controls) were scanned at both waves, with 2.2 to 5.9 years between assessments (mean=3.9 years; Table 1, see Supplemental Fig. S1 for the age scatter plot; see Supplemental Table S3 for the distribution of scan occurrences in each group). Cohort-wide exclusion criteria were an IQ below 70, a major medical history or history of neurological illness, and for controls only, a first-degree relative with a severe mood or psychotic disorder. Control offspring and their parents could have mild psychopathology (see (Setiaman et al., 2023)) to prevent having a "super-normal" control group, which would unduly magnify potential group effects (Kendler et al., 2019). Participants were considered to be at familial risk if they had at least one first or two second-degree relatives with BD or SZ. Given that the majority of the final sample comprises offspring (180 out of 187 participants, 96%; one was a sibling and six had two second-degree relatives) and for the sake of readability, we decided to use the term "offspring". In the final sample, 8 BDo (from 5 families) had two parents with BD and 3 SZo (from 2 families) had one parent with SZ and one parent with BD; the rest of the high-familial-risk offspring had one parent with BD or SZ. Clinical diagnoses of index parents were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., n.d.). Parents of controls were screened for psychopathology with the MINI-Schedules for Clinical Assessment in Neuropsychiatry (Nienhuis and Giel, 2000), followed by a SCID-I in case of reported psychopathology. At wave 1, 96% of the offspring never used psychotropic medication. At wave 2, this was 83%.

Written informed consent was obtained from participants older than 12 years and from both parents or legal caregivers for participants aged between 8 and 18 years. Parents gave written consent for their own participation as well. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht. Findings on subsets of the current study sample have been published before (Collin et al., 2017; de Leeuw et al., 2017; Poortman et al., 2024; Setiaman et al., 2023; van Haren et al., 2020).

2.2. Structural brain imaging

2.2.1. MRI acquisition and preprocessing

MRI brain scans were obtained on a Philips 3T Achieva or Philips 3T Ingenia CX scanner (Philips Medical Systems, Best, the Netherlands) located at the University Medical Center Utrecht (see Supplemental Tables S4 and S5 for detailed group comparisons regarding the two scanners used). Freesurfer (v6.0) (Fischl, 2012) was used to process and segment the T1-weighted images. The Desikan-Killiany atlas was applied to parcellate the brain into 68 cortical regions of interest (ROIs) (34 per hemisphere) (Desikan et al., 2006). Visual quality control was done by two independent researchers according to the ENIGMA

Table 1
Demographic and clinical characteristics.

	Bipolar Disorder offspring		Schizophrenia offspring		Control offspring		Main group effect				Pairwise (p < .05)	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1		Wave 2		Wave 1	Wave 2
							F	*p*	*F*	*p*		
n	54	72	42	43	44	45						
n Families	40	51	30	30	29	29						
Age at scan, years, mean (SD)	14.12 (2.57)	17.89 (2.56)	13.17 (2.89)	16.68 (2.95)	13.33 (2.16)	16.75 (2.45)	1.95	0.146	3.92	**0.022**		BDo > SZo
Sex, F/M, *n* (% female)	26/28 (48)	35/37 (49)	25/17 (60)	32/11 (74)	20/24 (45)	22/23 (49)		0.380		**0.014**		SZo > BDo & Co
IQ, mean (SD)	106.3 (19.1)	104.6 (14.3)	102.3 (19.0)	100.5 (19.1)	116.6 (12.5)	114.0 (12.9)	7.92	**<0.001**	9.15	**<0.001**	BDo & SZo < Co	BDo & SZo < Co
Scan interval, years, mean (SD)[a]	3.99 (0.69)		3.81 (0.62)		3.70 (0.98)		$F = 1.40$, $p = 0.251$					
DICOM/PARREC, *n* (% DICOM)	41/13 (76)	65/7 (90)	32/10 (76)	41/2 (95)	37/6 (86)	43/2 (96)		0.381		0.560		
DSM-IV diagnosis, *n* (%)	27 (50)	45 (63)	22 (52)	31 (72)	9 (20)	12 (27)		**0.002**		**<0.001**	BDo & SZo > Co	BDo & SZo > Co
K-SADS sum scores, mean (SD)												
Depression	39.57 (9.49)	45.00 (12.12)	39.60 (9.99)	45.37 (11.85)	33.95 (3.73)	36.82 (7.65)	6.92	**0.001**	9.31	**<0.001**	BDo & SZo > Co	BDo & SZo > Co
Mania	10.37 (3.43)	10.89 (3.34)	9.57 (1.25)	10.28 (2.74)	9.07 (0.33)	9.11 (0.38)	4.19	**0.017**	6.19	**0.003**	BDo > Co	BDo > Co
Psychosis[b]	34.72 (2.77)	36.14 (4.11)	35.74 (3.57)	36.53 (3.53)	33.45 (0.87)	33.71 (1.62)	8.04	**<0.001**	9.33	**<0.001**	SZo > Co	BDo & SZo > Co
Psychotropic medication[c], *n* (%)	5 (9)	15 (21)	0 (0)	9 (21)	0 (0)	4 (9)		**0.012**		0.189	NS	

Statistical comparison was performed using Fisher's exact test for categorical and analyses of variance (Tukey's test for pairwise comparisons) for continuous variables. BDo = bipolar disorder offspring, Co = control offspring, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children, NS = not significant, SZo = schizophrenia offspring.
bold = statistically significant ($p \leq 0.05$).
[a] 113 (46 bipolar disorder offspring, 32 schizophrenia offspring and 35 control offspring) of 187 offspring (60%) were scanned at both timepoints.
[b] Data missing for one bipolar disorder offspring at wave 1.
[c] Psychotropic medications include antidepressants, antipsychotics, methylphenidate and mood stabilizers.

procedures (https://enigma.ini.usc.edu). For intracranial volume calculation, a C++ pipeline called IntracranialVolume was used (Caspi et al., 2020) (see Supplemental Methods for the rationale behind this decision, and for a detailed description of the MRI acquisition and (pre) processing procedure).

2.2.2. Structural brain measures

Eight global brain measures (total brain volume, intracranial volume, mean cortical thickness, cortical surface area, cortical gray matter volume, cerebral white matter volume, lateral ventricle volume and third ventricle volume) and seven bilateral subcortical volumes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus) were included. The mean of the left and right cortical thickness and surface area were calculated for each ROI (n=34). See Supplemental Methods for the rationale behind the bilateral approach.

2.3. Statistical analysis

2.3.1. Non-linear age trajectories of the structural brain measures

To evaluate group differences in age trajectories of the brain measures, a generalized additive mixed model (GAMM) analysis was performed using the *mgcv* package (v1.9-1) in R (v4.3.2) (R Core Team, 2022). GAMMs are used to model non-linear relationships between the dependent and predictor variables by adding smooth functions of the covariates (Wood, 2006). As with linear mixed-effects models, GAMMs make use of both the cross-sectional and longitudinal data in a dataset, such that no data has to be excluded, reducing bias and improving power. The interactions between age and group were estimated using the group (ordered) variable in the *by* argument of the smooth term for age. A separate smooth term for age was added to represent the smooth effect of age in the reference level of the ordered group variable (once with controls as the reference level for the comparisons of each of the high-familial risk groups versus controls, and once with BDo as the reference level for the comparison between SZo and BDo). Group, sex, scanner (Philips Achieva/Ingenia), and data format type (as our data was stored in DICOM format as well as PAR/REC after an alteration in our archiving system) were added as fixed effects. Subject ID and family ID were included as nested random effects to account for within-subject and within-family effects, respectively. Based on previous literature (Bethlehem et al., 2022; Mills et al., 2016) and on visual inspection of the raw data, *k* was set at 4 for all analyses. Of the eight global brain measures, analyses for cortical gray matter, cerebral white matter, lateral ventricle, and third ventricle volumes were corrected for total brain volume by adding it as a fixed effect. Regional analyses were once conducted without and with correction for the respective global measure (i.e., mean cortical thickness or cortical surface area) to examine whether any group differences in trajectories were different from the pattern across the whole brain. The formula of the main analysis is as follows: 'gamm(BrainMeasure ~ GroupFactor + Sex + Scanner + DataFormat + s(Age, $k = 4$) + s(Age, by = GroupOrdered, $k = 4$), random = list(FamilyID = ~1, SubjectID = ~1))'.

2.3.2. Linear age trajectories of the structural brain measures

Given that most longitudinal studies on brain development in high-familial-risk populations for SZ or BD thus far have applied linear statistical models (Sugranyes et al., 2021), we repeated our analyses using linear mixed model analyses for a closer comparison with these studies, using *lme4* (v1.1-35.1). To model the linear relationship between the brain measures and the predictors, this model included group, age, the interaction between group and age, sex, scanner and data format type as fixed effects and subject ID and family ID as nested random effects,

resulting in the following formula: 'lmer(BrainMeasure ~ Group + Age + Group x Age + Sex + Scanner + DataFormat + (1| FamilyID/SubjectID))'.

2.3.3. Group effects in the structural brain measure analyses

To examine group differences irrespective of age, the group variable from the GAMM model was used.

2.3.4. Sensitivity analyses

To explore the effects of IQ or symptom severity on our findings, the main analyses on the global brain measures were repeated once with IQ and once with the K-SADS summed scores of depression, mania and psychosis added as fixed effects.

2.3.5. Multiple comparison correction

To correct for multiple comparisons, we applied a Benjamini-Hochberg False Discovery Rate (FDR) correction (q=0.05) (Benjamini and Hochberg, 1995) on the pairwise smoothed age*group comparisons using the *p.adjust* function from the R package *stats*, once for the eight global brain measures, once for the seven subcortical volumes, and once for each of the analyses on the 34 ROIs (i.e., mean of left and right cortical thickness and surface area).

3. Results

3.1. Demographic and clinical characteristics

Table 1 provides an overview of the demographic and clinical characteristics of each group. Since there were group differences in age, sex, IQ and psychopathology, we included these as control variables (age and sex in all models; IQ and psychopathology in sensitivity analyses). See Supplemental Results for attrition bias analysis results.

3.2. Non-linear age trajectories of the structural brain measures

After correction for multiple comparisons, the GAMM analyses revealed a significantly different trajectory with age in cerebral white matter volume (corrected for total brain volume) and mean cortical thickness in SZo compared to controls (edf=2.681, F=4.11, p=0.003 and edf=2.744, F=4.50, p=0.003, respectively) (Fig. 1). With increasing age, cerebral white matter volume increases and mean cortical thickness decreases in all three groups, but after the age of 17 to 18 years, both the cerebral white matter volume increase as well as the mean cortical thickness decrease level off in SZo. Supplemental Fig. S2 shows that confidence intervals do not overlap between roughly 12 and 16 years and after 18 years for white matter and between 15 and 17 years and

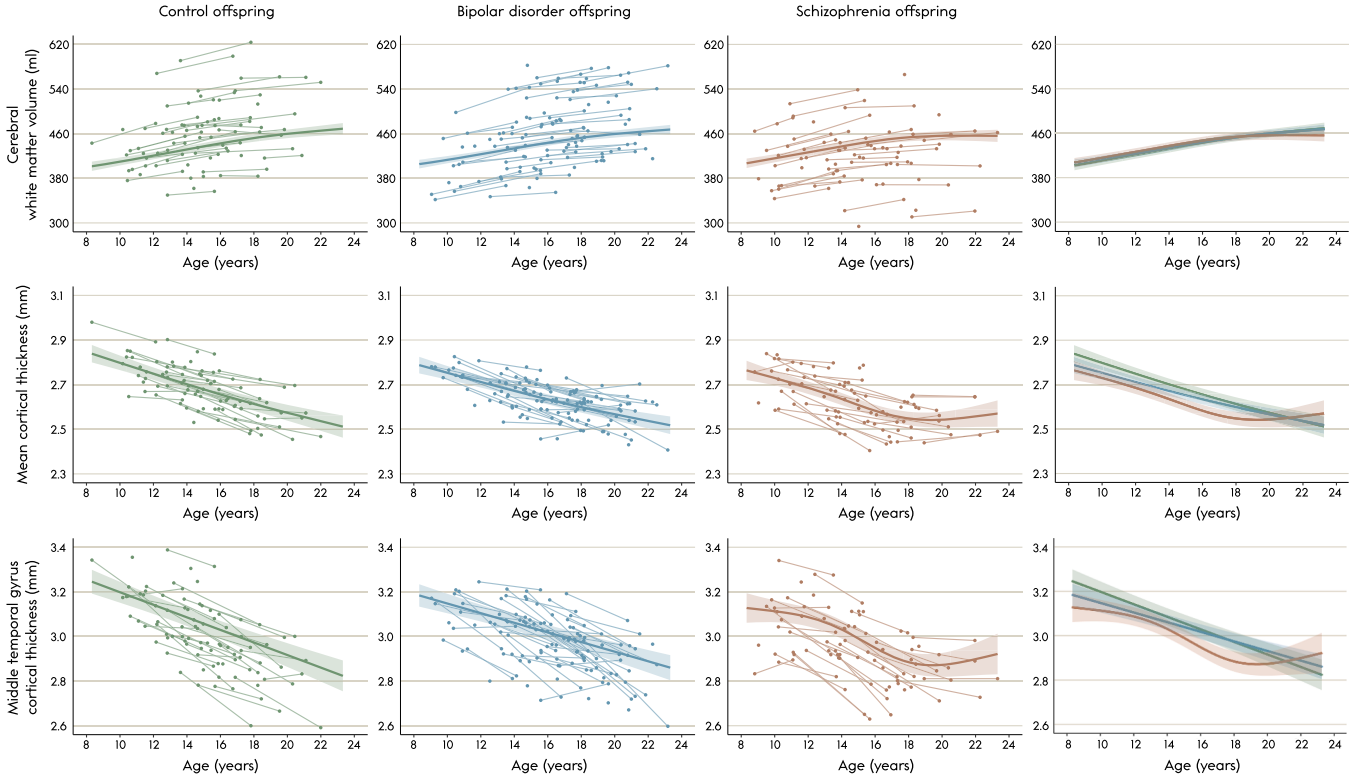

Fig. 1. Age trajectories (in years) of mean cortical thickness, cerebral white matter volume (corrected for total brain volume) and middle temporal gyrus cortical thickness (uncorrected for mean cortical thickness) per group. Generalized additive mixed model (k=4) fits and standard error bands are presented on top of the raw data. The age slopes of schizophrenia offspring differed significantly from those of control offspring for mean cortical thickness (p=0.003) and cerebral white matter volume (p=0.003), and from those of control offspring and bipolar disorder offspring for middle temporal gyrus cortical thickness (p<0.001 and p=0.001) (right-most figures).

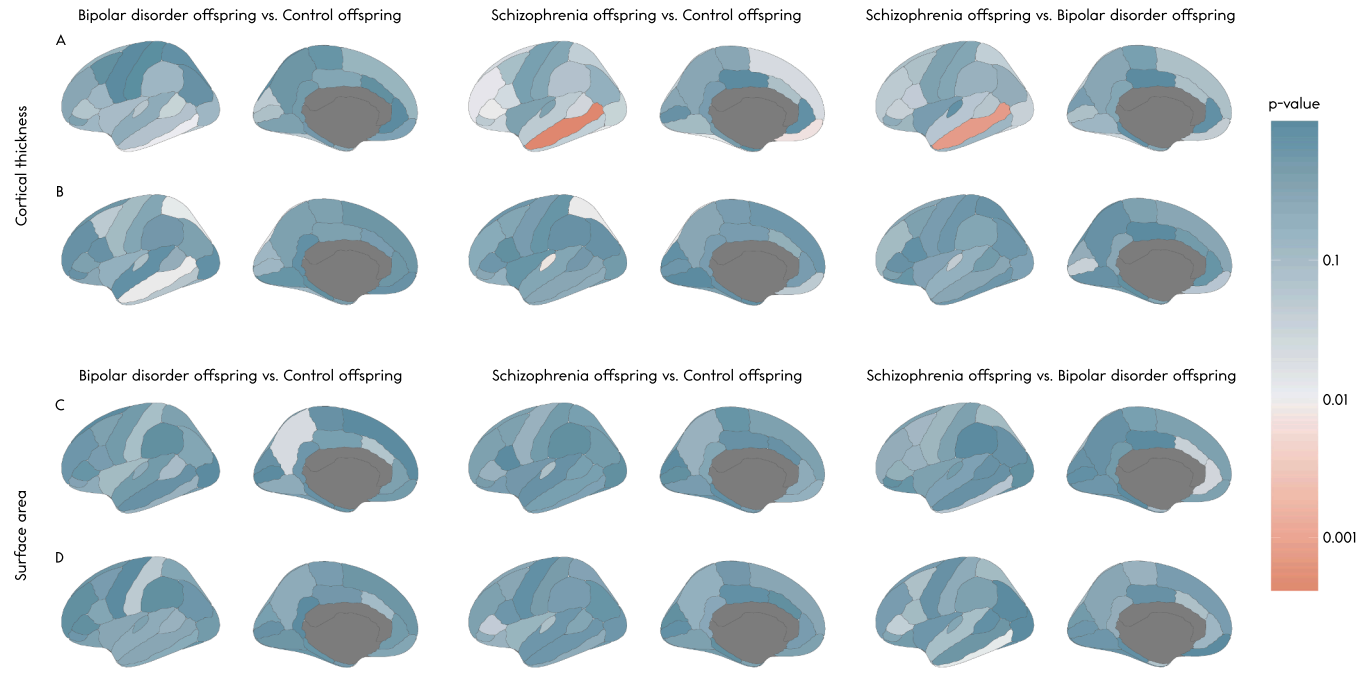

Fig. 2. Brain color maps of regional *p*-values (on a natural-logarithmic scale for visualization purposes) for each age*group pairwise comparison in the generalized additive mixed model analyses (k=4) on cortical thickness, once uncorrected (A) and once corrected (B) for mean cortical thickness, and surface area, once uncorrected (C) and once corrected (D) for cortical surface area. Since models were run on bilateral averages of each cortical region, the maps are plotted on the left hemisphere purely for visualization purposes.

after 20 years for cortical thickness suggesting deviating neurodevelopmental trajectories in the second half of adolescence in SZo compared to controls. The effect of age on the other six global brain measures did not differ significantly between groups (Supplemental Table S6; Supplemental Figs. S3 and S4). Supplemental Table S7 shows the effects of the confounding variables in the analyses on the global brain measures. The effect of age on the subcortical volumes did not differ significantly between groups (Supplemental Table S8).

Regionally, the cortical thickness of the middle temporal gyrus followed a significantly different trajectory with age in SZo compared to controls (edf=2.870, F=6.007, p<0.001) and BDo (edf=2.870, F=5.480, p=0.001) (Fig. 1 and Supplemental Table S9), which was no longer significant after mean cortical thickness was added to the model (Supplemental Table S10). No significant differences were found for regional surface area (Supplemental Tables S11 and S12). Fig. 2 shows the brain color maps of the regional *p*-values for all pairwise age trajectory comparisons.

3.3. Linear age trajectories of the structural brain measures

Linear mixed-effects model analyses on the global brain measures yielded no significant group differences in age slopes (Supplemental Table S13).

3.4. Group effects in the structural brain measure analyses

After correction for multiple comparisons, the GAMM analyses revealed significantly lower total brain volume in SZo compared to controls (d=-0.22, p=0.005) and BDo (d=-0.20, p=0.004), and mean cortical thickness was significantly lower in SZo compared to controls (d=-0.23, p<0.001) (Supplemental Table S6 and Fig. 3). No significant group differences were found on subcortical volumes (Supplemental Table S8).

Regionally, SZo had significantly lower cortical thickness of the pars triangularis and precentral gyrus compared to controls (d=-0.26, p=0.001 and d=-0.28, p<0.001) and BDo (d=-0.24, p<0.001 and d=-0.20, p=0.005), and compared to controls only, lower cortical thickness of the inferior parietal cortex (d=-0.24, p=0.002), lateral occipital cortex (d=-0.26, p=0.001), precuneus (d=-0.21, p=0.005), superior parietal cortex (d=-0.22, p=0.004), superior temporal gyrus (d=-0.28, p<0.001), supramarginal gyrus (d=-0.23, p=0.003) and transverse temporal cortex (d=-0.26, p=0.001) after correction for multiple testing (Supplemental Table S14). None of these regional differences remained significant when mean cortical thickness was controlled for (Supplemental Table S15). No group differences in regional surface area were found (Supplemental Tables S16 and S17). Fig. 4 shows the brain color maps of the regional effect sizes (Cohen's d) for all pairwise group comparisons.

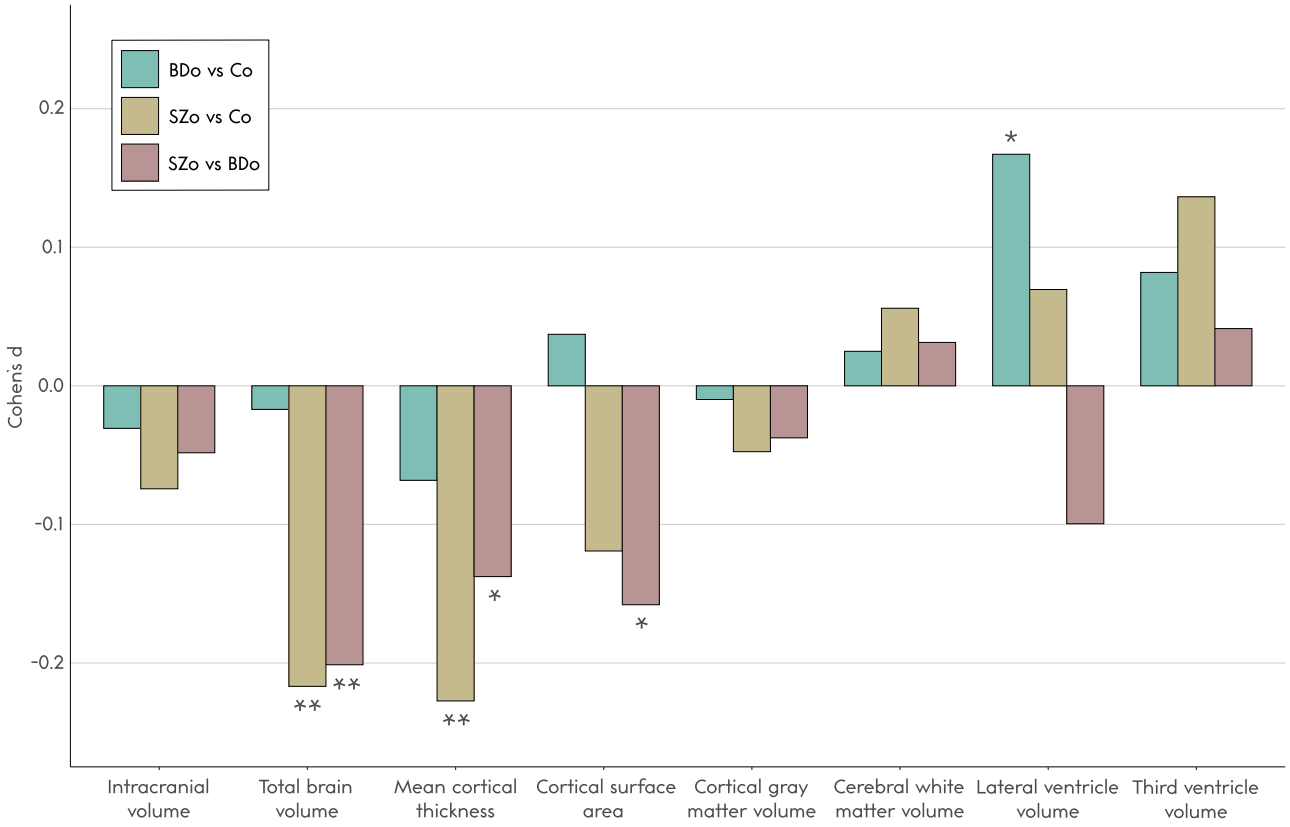

Fig. 3. Cohen's *d* effect sizes comparing offspring of parents with bipolar disorder (BDo) with control offspring (Co) (teal), offspring of parents with schizophrenia (SZo) with Co (gold) and BDo with SZo (light red). A negative Cohen's *d* means first group < second group, and a positive Cohen's *d* means first group > second group. The four right-most measures (cortical gray matter volume, cerebral white matter volume, lateral ventricle volume and third ventricle volume) are corrected for total brain volume. *Nominally significant effect sizes ($p<0.05$, uncorrected); **$q<0.05$, corrected. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. Sensitivity analyses

Repeating the analyses with either IQ or the three K-SADS summed symptom scores added as fixed effects partially changed the nature of our findings. After adding IQ, *p*-values changed marginally and the group comparisons of cerebral white matter volume and mean cortical thickness age trajectories were no longer significant (cerebral white matter volume: *edf*=2.226, *F*=5.46 and *p*=0.003 to *edf*=2.220, *F*=5.09 and *p*=0.004; mean cortical thickness: *edf*=2.744, *F*=4.50 and *p*=0.003 to *edf*=2.681, *F*=4.11 and *p*=0.005) (Supplemental Table S18 and Supplemental Fig. S5; see Supplemental Table S19 for subcortical volumes). When controlling for K-SADS sum scores, these remained significant, and the group comparison of BDo and SZo now reached significance in both measures as well (cerebral white matter volume: *edf*=2.226, *F*=4.47 and *p*=0.008 to *edf*=2.246, *F*=4.56 and *p*=0.007; mean cortical thickness: *edf*=2.744, *F*=3.52 and *p*=0.010 to *edf*=2.730, *F*=3.73 and *p*=0.008). Additionally, the age trajectory of cortical gray matter volume (corrected for total brain volume) was now also significantly different between SZo and controls (*edf*=2.167, *F*=4.23 and *p*=0.013 to *edf*=2.199, *F*=4.57 and *p*=0.009) (Supplemental Table S20 and Supplemental Fig. S6; see Supplemental Table S21 for subcortical volumes).

Regarding group effects irrespective of age, the lower total brain volume in SZo compared to controls and BDo and mean cortical thickness in SZo compared to controls remained significant after adding IQ (Supplemental Table S18), as did the lower mean cortical thickness in SZo compared to controls after controlling for K-SADS sum scores (Supplemental Table S20). Although effect sizes remained highly similar, group differences in total brain volume were no longer significant after adding K-SADS sum scores, in SZo compared to controls (*d*=-0.22, *p*=0.005 to *d*=-0.21, *p*=0.007) and SZo compared to BDo (*d*=-0.20, *p*=0.004 to *d*=-0.20, *p*=0.005) (Supplemental Table S20).

4. Discussion

In this prospective cross-disorder offspring study, we investigated non-linear structural brain development in young individuals at high familial risk of SZ and BD compared to controls. We found that SZo showed differential non-linear age trajectories of mean cortical thickness decrease and cerebral white matter volume increase (corrected for total brain volume) compared to controls. Regionally, SZo had a different non-linear trajectory with age in cortical thickness of the middle temporal gyrus compared to controls and BDo. In SZo, the trajectories level off around the end of adolescence, which is not the case in control offspring. Regardless of age, SZo had a smaller total brain volume than controls and BDo, and a thinner cortex than controls. Moreover, both high-familial-risk offspring groups had a significantly lower IQ and more (severe) psychiatric symptoms, and correction for IQ or symptom severity changed the findings slightly, providing suggestive evidence that IQ and symptom severity explain part of the deviating global structural brain developmental trajectories with age in SZo. Specifically, correction for IQ attenuated the differences in age trajectory between SZo and controls, and correction for symptom severity amplified the age trajectory differences between SZo and controls as well as between SZo and BDo. Total brain volume was no longer significantly smaller in SZo after correction for symptom severity, although effect sizes remained highly similar.

Several other cohort studies have examined brain development in young individuals at high familial risk of BD (FHR-BD) or SZ (FHR-SZ) separately in a longitudinal design. Greater cortical thinning and volume

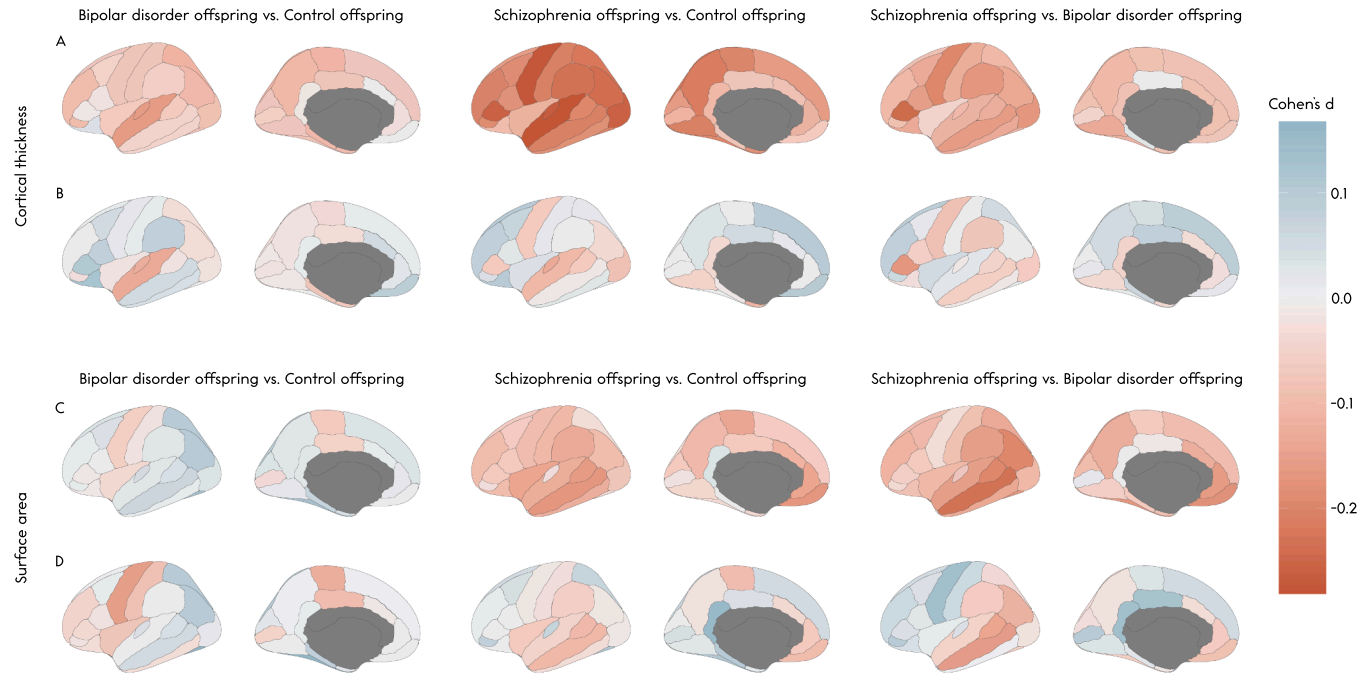

Fig. 4. Brain color maps of regional effect sizes (Cohen's *d*) for each pairwise group comparison in the generalized additive mixed model analyses (k=4) on cortical thickness, once uncorrected (A) and once corrected (B) for mean cortical thickness; and on surface area, once uncorrected (C) and once corrected (D) for cortical surface area. Since models were run on bilateral averages of each cortical region, the maps are plotted on the left hemisphere purely for visualization purposes. Red reflects regions where the first group has thinner cortex or smaller surface area than the second group, and blue-gray reflects regions where the first group has thicker cortex or larger surface area than the second group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

loss over time were found in frontal regions of FHR-BD compared to controls (Papmeyer et al., 2015; Roberts et al., 2022), and cortical thickening of frontal regions and volume loss of the right amygdala were seen in FHR-BD who later developed major depressive disorder (Nickson et al., 2016; Papmeyer et al., 2015), while no changes over time in subcortical volumes were observed (Papmeyer et al., 2016; Roberts et al., 2022). FHR-SZ showed a more pronounced decrease of cortical, frontal, occipital and auditory association cortex surface area (Bhojraj et al., 2011a; Prasad et al., 2010) and of gray matter volume in all four lobes (Prasad et al., 2010) as well as in frontal and temporal regions (Bhojraj et al., 2011b), although relatively preserved surface area over time has been reported as well (Bois et al., 2015). Inconsistent findings have been reported on deviating trajectories of cortical thickness in FHR-SZ, with a maintenance or slight increase over time in lobar cortical thickness compared to decreases in controls (Prasad et al., 2010) as well as excessive decrease over time in global and lobar cortical thickness, independent of subsequent clinical outcome (Bois et al., 2015). Our findings showing no significant group differences in age trajectories of subcortical volumes is congruent with studies in FHR-BD (Papmeyer et al., 2016; Roberts et al., 2022). However, contrary to the studies finding longitudinal effects in cortical thickness of FHR-BD (Papmeyer et al., 2015; Roberts et al., 2022), our analyses revealed no differences in the age trajectories of mean cortical thickness between BDo and controls. Regarding FHR-SZ, our findings are in line with a previous study (Prasad et al., 2010), as our analyses showed a different trajectory of mean cortical thickness in SZo compared to controls; SZo starts off lower than controls, follows a comparable trajectory during middle adolescence and then levels off nearing the end of adolescence, whereas in controls the decrease is more consistent and linear with increasing age. Correspondingly, with an age range similar to ours (10–20 years versus 8–23 years in our study), SZo in the study by Prasad and colleagues showed a lower cortical thickness at baseline in three lobes, which remained stable or increased slightly while it decreased over time in controls (Prasad et al., 2010). Taken together, the findings of these studies indicate different timing of cortical maturation during adolescence particularly in those at familial risk of SZ. Still, a direct comparison between these studies and our study is hard to make due to differences in methodology and sample characteristics. These longitudinal studies thus far investigated the difference between two time points across a wide age range while we fitted non-linear trajectories of brain change against the effect of age. While the former approach may still account for the fact that change between two time points is dependent on the age at assessment as long as it is added to the model, it does not provide information on the age range(s) at which groups might differ from each other, which fitting non-linear age trajectories does. Moreover, when we repeated our analyses with linear regression models, no significant differences between high-familial-risk and control offspring were found, stressing the importance to acknowledge that the brain develops in a non-linear fashion.

Irrespective of age, SZo have a smaller total brain volume than controls and BDo, and a thinner cortex than controls. Regionally, SZo showed a widespread thinner cortex compared to controls and, to a lesser extent, BDo. None of these regional findings remained significant after controlling for mean cortical thickness, suggesting a global effect of familial risk of mental illness on cortical thickness and cortical thinning in SZo. Our finding of a smaller total brain volume in SZo is in line with other cohort studies (Keshavan et al., 1997; Rajarethinam et al., 2007) and large-scale meta-analyses of studies investigating first-degree relatives of patients with SZ (FDR-SZ) and BD (FDR-BD) (de Zwarte et al., 2019). It is important to note, though, that the MRI data from the first wave of the current cohort was included in this meta-analysis. Also, our finding of a thinner cortex and widespread regional cortical thinning in SZo, that is no longer seen after a correction for mean cortical thickness, corroborates previous findings in FDR-SZ (de Zwarte et al., 2022). Similarly, BDo exhibiting no differences in global brain measures compared to controls in our study is congruent with FDR-BD showing no alterations (de Zwarte et al., 2019). These results provide further support for familial risk of SZ being associated with global, rather than

local, structural brain abnormalities.

Throughout the entire age range of all assessments (8–23 years), total brain volume and mean cortical thickness are significantly lower in SZo compared to controls and BDo (Fig. 3 and Supplemental Fig. S3), suggesting that deviations in brain structure were already present before childhood, and may have developed throughout early childhood or sooner. Prior work has indeed demonstrated that, on average, individuals with SZ had a smaller head circumference at birth compared to controls (Cantor-Graae et al., 1998; Kunugi et al., 1996a, 1996b; McNeil, 2000; McNeil et al., 1993), suggesting that brain and/or cranium growth in the prenatal phase is an early indicator of altered neurodevelopment in SZ patients. In contrast, a neuroimaging study in neonates born from at least one parent with SZ showed that they had larger volumes of several global brain measures, specifically in males, compared to control neonates (Gilmore et al., 2010), as well as altered connectomic characteristics (Shi et al., 2012) and a significantly thinner cortical thickness in the right lateral occipital cortex in female offspring (Li et al., 2016). Deviations in brain structure taking place early in life is in line with genome-wide association studies that show cortical thickness and surface area to be highly heritable and strongly determined by genetic components (Grasby et al., 2020; Strike et al., 2019) and with studies linking psychiatric risk genes with pathways for brain development from the prenatal period to young adulthood (Alex et al., 2023; Birnbaum and Weinberger, 2017; Douet et al., 2014; Knickmeyer et al., 2014). Although neuroimaging studies in neonates provide first evidence that brain development is already abnormal in the neonatal period in individuals at high familial risk of SZ, these studies lack in statistical power owing to the difficulty in recruitment, and thus findings should be interpreted cautiously. Thus, in addition to studies that follow child and adolescent offspring into adulthood in order to predict transitions into a psychosis or mood diagnosis, longitudinal studies during the prenatal and neonatal period are also required to gain more insight in when structural brain alterations start to occur in high-familial-risk individuals.

Thus far, BASYS (age range: 6–17 years at inclusion) is the only other cohort study that also has directly compared structural brain development between BDo, SZo and controls. They found greater cortical thinning of the frontal lobe over time (2-year follow-up) in BDo compared to controls, albeit uncorrected for multiple comparisons (Sugranyes et al., 2017b). After a 4-year follow-up, high-familial-risk individuals (BDo and SZo combined) who developed psychotic symptoms showed greater mean cortical thinning over time than those who did not, and than controls (Sugranyes et al., 2021). In the two-year follow-up BASYS study, adding measures of psychopathology to the analyses did not have a substantial impact in their findings. However, in the four-year follow-up study of the Spanish cohort, psychosis spectrum symptoms exacerbated group differences between high-familial-risk individuals who did or did not develop psychotic symptoms, and we find suggestive evidence for this as well. Adding summed present symptom scores of depression, mania and psychosis yielded findings largely similar to our main analyses, while also aggravating group differences in age trajectories, with trajectories of cortical gray matter volume now reaching statistical significance in SZo versus controls, and trajectories of mean cortical thickness and cerebral white matter volume now reaching statistical significance in SZo versus BDo. The finding that effects do not weaken after accounting for psychopathology further substantiates the relationship between familial risk of SZ and global structural brain developmental trajectories. Importantly, participants with more psychotic symptoms at the first wave were more likely to be excluded, e.g., due to dropping out or having a scan of poor quality, resulting in a sample biased towards lower psychotic symptoms, in turn limiting the variation in dimensional psychopathology. For example, the sample might be missing the more vulnerable SZo at later ages, leading to potentially underestimating effects of psychopathology. With respect to the effect of IQ, our sensitivity analyses revealed that the group differences in age trajectories were no longer significant. However, changes in *p*-values were only marginal, and visually comparing Fig. 1 and Supplemental Fig. S5 shows highly similar age trajectories before and after adding IQ to the model.

Several methodological limitations must be considered with respect to the findings of this study. First, while the longitudinal examination of a part of the high-familial-risk and control samples using brain imaging makes this a unique study, the relatively modest sample size and the resulting statistical power may have hampered our efforts to detect subtle deviations of structural brain trajectories. Indeed, effect sizes of abnormalities in global brain measures in first-degree relatives of BD and SZ patients have been shown to be small (de Zwarte et al., 2019), as are the effect sizes of the global brain measures in the current offspring sample ($|d| \leq 0.23$). Additionally, the outer ends of the current study sample's age range ($\leq$10 years and $\geq$22 years) contain relatively few data points in all three groups. Moreover, the BDo group contained significantly older participants at wave 2 than SZo, resulting in a more precise fit in BDo than in SZo around later ages, which could at least partially explain group differences in the right tail of the trajectories. Our sample size also did not enable us to investigate sex-related effects as it lacks the statistical power for a three-way interaction of sex, age and group. Given reported sex differences in brain development and prevalence of psychiatric disorders (Merikangas et al., 2010; Salminen et al., 2022), future studies should investigate this in larger samples. Second, related to the previous point, within-subject data was limited to two scans for 60% of the sample. Additional time points within the same participants would have provided more power to capture non-linear trends (King et al., 2018; Parsons and McCormick, 2022). However, while our analyses did reveal non-linearity in the age trajectories of global brain measures in all three groups, most prominently in SZo and more subtly in BDo and controls, we expect a distinctly wiggly fit to be improbable biologically. For example, measures such as total brain volume and mean cortical thickness are not likely to develop in a complex non-linear manner over a couple of years (Bethlehem et al., 2022; Mills et al., 2016). Moreover, increasing *k* past four did not impact the shape of the fits nor the statistical outcome substantially, which suggests that this level is sufficient for the current dataset. Third, the majority of the offspring in this study have not yet reached the typical age of onset at which intergenerational homotypic continuity of psychopathology from parent to offspring can be observed (Dalsgaard et al., 2020; Kessler et al., 2005; Solmi et al., 2022). Over time, more high-familial-risk offspring are likely to develop psychotic or mood symptoms or disorders (Mesman et al., 2013; Rasic et al., 2014; Uher et al., 2023), thus following these offspring further into adulthood is imperative to determine how structural brain development pertains to risk of or resilience against severe mood or psychotic disorder. Fourth, two scanners have been used for data acquisition due to an upgrade mid-study, which may introduce bias and reliability issues (Medawar et al., 2021). Therefore, the scanner was added as a covariate in the analyses to correct for its effect on the variance. Importantly, there were no (age-related) group differences in scanner use.

In conclusion, our findings suggest that high familial risk of schizophrenia may be associated with divergent development of global, but not regional, brain morphometric measures particularly around the end of adolescence. Specifically, SZo exhibited differential non-linear developmental trajectories of mean cortical thickness and cerebral white matter volume compared to controls and, specifically when correcting for psychopathology, BDo. Our findings of smaller total brain volume and lower mean cortical thickness in SZo across the entire included age range suggests that global alterations in brain morphometry may have already been taking place during early childhood or sooner. Prospectively following up offspring beyond the typical age of illness onset of mood and psychosis-spectrum disorders is crucial. This will improve our understanding in two key areas: firstly, how neurodevelopment relates not only to high familial risk of mental illness but also to severity of psychopathology, and whether trajectories have value in prediction who develop mental illness later in life; and secondly,

whether resilience factors that counteract risk of mental illness can be detected, potentially benefiting tailored intervention.

Contributors

Simon R. Poortman - Conceptualization; Data Curation; Formal Analysis; Methodology; Software; Validation; Visualization; Writing – Original Draft Preparation; Writing – Review & Editing

Nikita Setiaman - Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Project Administration; Software; Writing – Original Draft Preparation; Writing – Review & Editing

Marjolein E.A. Barendse - Conceptualization; Formal Analysis; Methodology; Supervision; Validation; Writing – Review & Editing

Hugo G. Schnack - Formal Analysis; Methodology; Software; Validation; Writing – Review & Editing

Manon H.J. Hillegers - Conceptualization; Funding Acquisition; Project Administration; Resources; Writing – Review & Editing

Neeltje E.M. van Haren - Conceptualization; Formal Analysis; Funding Acquisition; Investigation; Methodology; Project Administration; Resources; Supervision; Writing – Original Draft Preparation; Writing – Review & Editing

All authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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