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Brain Age in Early Stages of Bipolar Disorders or Schizophrenia

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Background: **The greater presence of neurodevelopmental antecedants may differentiate schizophrenia from bipolar disorders (BD). Machine learning/pattern recognition allows us to estimate the biological age of the brain from structural magnetic resonance imaging scans (MRI). The discrepancy between brain and chronological age could contribute to early detection and differentiation of BD and schizophrenia.** Methods: **We estimated brain age in 2 studies focusing on early stages of schizophrenia or BD. In the first study, we recruited 43 participants with first episode of schizophrenia-spectrum disorders (FES) and 43 controls. In the second study, we included 96 offspring of bipolar parents (48 unaffected, 48 affected) and 60 controls. We used relevance vector regression trained on an independent sample of 504 controls to estimate the brain age of study participants from structural MRI. We calculated the** brain-age gap estimate (BrainAGE) **score by subtracting the chronological age from the brain age.** Results: **Participants with FES had higher** BrainAGE **scores than controls (**$F(1, 83) = 8.79$**, corrected** $P = .008$**, Cohen's** $d = 0.64$**). Their brain age was on average 2.64 ± 4.15 years greater than their chronological age (matched** $t(42) = 4.36$, $P < .001$**). In contrast, participants at risk or in the early stages of BD showed comparable** BrainAGE **scores to controls (**$F(2,149) = 1.04$**, corrected** $P = .70$, $\eta^2 = 0.01$**) and comparable brain and chronological age.** Conclusions: **Early stages of schizophrenia, but not early stages of BD, were associated with advanced** BrainAGE **scores. Participants with FES showed neurostructural alterations, which made their brains appear 2.64 years older than their chronological age.** BrainAGE **scores could aid in early differential diagnosis between BD and schizophrenia.**

Key words: first episode/schizophrenia-spectrum disorders/*BrainAGE* score/brain maturation

Introduction

Bipolar disorders (BD) and schizophrenia are among the leading causes of morbidity and mortality worldwide,[1,2] due in part to their early onset and lifelong nature.[3,4] In addition, both of these conditions are often correctly diagnosed only years after the initial manifestations,[5,6] which leads to delayed treatment and contributes to poor prognosis.[6–9] Thus, we need more studies attempting to identify illness specific biological alterations early in the course of BD and schizophrenia.

Brain imaging has the unique ability to noninvasively investigate brain structure and function. Access to large normative databases of brain scans and advances in neuroimaging analyses involving machine learning/pattern recognition, allow us to estimate the biological age of the brain from structural magnetic resonance imaging (MRI).[10,11] The discrepancy between brain age and chronological age captures diffuse, multivariate morphological alterations across the whole brain, which may be relevant to early detection and differentiation of BD and schizophrenia.

Although much has been written about the overlap between BD and schizophrenia, there are salient differences between the 2 conditions,[12,13] which may assist in their early differentiation. Specifically, schizophrenia is frequently conceptualized as a neurodevelopmental disorder.[14–16] Individuals with schizophrenia often have a history of obstetrical complications, minor physical abnormalities, soft neurological signs, early developmental, social and cognitive delays, which may translate into poor premorbid academic performance and impaired functioning.[12,15–18] Brain maturation in schizophrenia is characterized by exaggerated developmental trajectories, accelerated age-related gray matter (GM) loss.[14,19–21] Consequently, we could hypothesize, that already early

in the course of illness, the brains of participants with schizophrenia would appear older than their chronological age.[21,22]

On the other hand, neurodevelopmental antecedents are mostly absent in individuals with BD, who typically do not demonstrate minor physical anomalies and congenital malformations,[23,24] show intact[25] or even above average premorbid functioning,[18,26,27] preserved brain structure[28] and even evidence for larger regional GM volumes in the early stages of the illness.[29–33] Consequently, we could expect that the brain age of participants during the early stages of BD would be comparable to their chronological age.

Cross diagnostic brain imaging studies, especially those focusing on early stages of illness, are relatively rare in psychiatry. Thus, here we used machine learning to investigate the differences between brain and chronological age early in the course of schizophrenia or BD.

Methods

We report results from 2 related studies aimed at identifying neurobiological alterations in the early stages of schizophrenia or BD.

Study 1

This was a part of the ongoing Early Stages of Schizophrenia study.[34] To ensure generalizability, we recruited participants during their first hospitalization in Psychiatric Hospital Bohnice, a large general psychiatry hospital (1200 beds), which serves the Prague and part of Central Bohemia regions—catchment area of over 1.5 million subjects. To limit the effects of medication and illness burden, we focused on individuals with first episode of schizophrenia-spectrum disorders (FES), who met the following inclusion criteria: (1) had the ICD-10 diagnosis of schizophrenia, or acute and transient psychotic disorders; (2) were undergoing their first psychiatric hospitalization; (3) were medication naïve prior to the first admission; (4) had less than 24 months of untreated psychosis; (5) were 15–35 years of age. Patients with psychotic mood disorders (including schizoaffective disorder, BD, and unipolar depression with psychotic symptoms), were excluded from the study. Participants who were hospitalized within 1 month of developing symptoms received the working diagnosis of acute and transient psychotic disorders, which is congruent with DSM-IV brief psychotic disorder. These criteria are in keeping with stringent definitions of first episode psychosis.[35]

Control participants 18–35 years old, were recruited via advertisement, and matched to FES participants by age and sex on an individual basis. The exclusion criteria for control participants included: (1) lifetime history of any psychiatric disorders and (2) psychotic disorders in first or second-degree relatives.

Additional exclusion criteria for both groups included history of neurological or cerebrovascular disorders and any MRI contraindications.

The diagnoses were made by a board certified psychiatrist (F.S.) using the Mini-International Neuropsychiatric Interview (MINI).[36]

Study 2

Participants were recruited from an ongoing Offspring Risk for Bipolar disorders Imaging Study—ORBIS[31] in Halifax, Canada and from a parallel arm of the study performed in Prague, Czech Republic. To isolate biological risk factors for BD, we recruited offspring from families of well-characterized adult patients with BD, as described previously.[31] Families were identified through adult patients with BD, who had participated in: previous genetic and high-risk studies[37,38] for the Halifax sample; the Czech Bipolar Disorder Case Registry[39] for the Prague sample. Only the offspring from these families, not the probands/parents, were a part of the MRI study. In keeping with previous studies,[38,40] we included participants with BD type I or type II, but not with BD NOS as probands for this study. The average genetic liability among unaffected offspring of BD patients decreases with age, as an increasing proportion of those with higher liability become affected. Therefore, we focused on individuals around the typical age of onset, who remain at a substantial risk of future onset of BD.[3,41] Thus, the main inclusion criterion for all groups in both centers was age between 15 and 35 years.

The offspring of BD patients were divided into 2 subgroups. (1) The high-risk (HR) unaffected group, which consisted of offspring with no lifetime Axis I diagnosis of mood disorders (ie, a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria). These individuals were at an increased risk for BD because they had one parent affected with a primary mood disorder. (2) The affected familial group, which consisted of offspring who met criteria for a lifetime Axis I diagnosis of mood disorders (ie, a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria) and had one parent affected with a primary mood disorder. This definition stems from clinical HR studies by us and others, which clearly showed, that the index mood episode in majority of offspring of bipolar parents is typically depression and that young participants with personal history of depression and family history of BD often develop BD later in life.[41–45] Not combining the unaffected and affected participants and focusing on fully unaffected group, allowed us to maximize the main advantage of a genetic high-risk design, which is the ability to study participants who carry the genetic risk, but have not been exposed to the effects of the illness episodes or treatment.

Control participants 18–35 years old, without any personal or family history of DSM-IV Axis I psychiatric disorders, were recruited from similar socioeconomic background.

Common exclusion criteria for all groups in both centers included any serious medical/neurological disorders, substance abuse/dependence during the last 6 months and any MRI contraindications.

Probands, offspring and control subjects were interviewed by pairs of clinicians (psychiatrists and/or nurses) using Schedule for Affective Disorders and Schizophrenia–Lifetime version[46] or Schedule for Affective Disorders and Schizophrenia for School-Age Children[47] in participants under 18 years of age. Diagnoses were made based on DSM-IV[48] in a blind consensus review, by an independent panel of senior clinical researchers using all available clinical materials.

MRI Methods

Study 1. We acquired T1-weighted 3D MPRAGE scans (TE = 4.63 ms, TR = 2300 ms, bandwidth 130 Hz/pixel, FOV = 256 × 256 mm, matrix 256 × 256, voxel size 1 × 1 × 1 mm^3) on 3T Siemens Trio MRI scanner equipped with standard head coil.

Study 2. Participants were scanned at 2 sites, Prague and Halifax. At both sites, all MR acquisitions were performed with a 1.5 Tesla General Electric Signa scanner and a standard single-channel head coil. We acquired T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle = 40°, TE = 5 ms, TR = 25 ms, FOV = 24 cm × 18 cm, matrix = 256 × 160 pixels, NEX = 1, no inter-slice gap, 124 coronal, 1.5 mm thick slices.

BrainAGE *Estimation*

We estimated brain age from structural MRI scans using machine learning. We used a standard, previously validated implementation of this method, which accurately and reliably estimates the age of individual brains,[49,50] is sensitive to pathological processes beyond aging[10,51] and robust to differences in scanner strength.[52] The analyses included: (1) Preprocessing of MRI Data using standard voxel-based morphometry, (2) Data reduction using smoothing and principal component analysis, (3) Estimation of brain age using relevance vector regression (RVR). We trained the RVR model using an independent sample of 504 healthy individuals (230 males) from the IXI database (http://www.brain-development.org). In keeping with other studies,[10,53] the *brain-age gap estimate* (*BrainAGE*) model was trained on a sample containing both males and females. As the number of training samples has been shown to be the most important factor for model performance,[49] training separate *BrainAGE* models for males and females would have reduced prediction accuracy. We used the resulting age prediction model to individually estimate brain age in our study participants, thus aggregating the complex, multidimensional age related structural alterations across the whole brain into one single value (ie, estimated brain age).

Our outcome measure was the *BrainAGE* score, which is the difference between estimated brain age and chronological age.[49] To evaluate the contribution of each tissue type to the whole brain changes, we also acquired separate *BrainAGE* score estimates from only GM and only WM.

Of note, the *BrainAGE* scores do not reflect a unitary molecular process. Depending on developmental period or particular illness, very different mechanisms may underly changes in *BrainAGE* scores.

For detailed description of the method, see[10,49,52] and supplementary material.

Statistical Analyses

All statistical analyses were conducted in R Studio (R version 3.3.2). To compare clinical and demographic variables, we used *t* test, 1-way ANOVA or chi-square test, as appropriate. Our primary outcome measure in both studies was the whole brain *BrainAGE* score. In each study, we initially tested for association between age or sex and *BrainAGE* scores, to select, which demographic variables to control for. In Study 1 we then performed analysis of covariance with *BrainAGE* scores as the dependent variable, status (FES, control) as the grouping variable, while covarying for demographic variables, which were significantly associated with *BrainAGE* scores (primary analysis # 1). To compare brain and chronological age within subjects, we used paired *t* test. In Study 2, we performed analysis of covariance with *BrainAGE* scores as the dependent variable, status (HR unaffected, affected familial, control groups) and site (Halifax, Prague) as the grouping variables, while covarying for demographic variables, which were significantly associated with *BrainAGE* scores (primary analysis # 2). To compare brain and chronological age within subjects, we used repeated measures ANOVA with site (Halifax, Prague) as the grouping factor and type of age (chronological, brain) as the repeated measure. To calculate effect size in the primary analyses, we used Cohen's *d* when comparing 2 groups (Study 1, FES vs control participants) and η^2 when comparing 3 groups (Study 2, HR unaffected, affected familial, control participants).

To explore association between *BrainAGE* scores and clinical variables, we utilized Pearson correlations or 2 sample *t* tests, where appropriate. To further control for sex, we repeated the primary analyses with sex as additional covariate. In post hoc analyses, we separately compared the GM and WM *BrainAGE* scores between the groups in each site. For tissue types, showed between group differences in BrainAGE scores, we also performed

voxel based morphometry analyses, using the preprocessed scans, to identify regions, which were associated with *BrainAGE* scores. As these analyses primarily served for visualization, we used uncorrected *P* value of .001, cluster extent of 50 voxels.

To quantify the agreement between brain and chronological age, we calculated the ICC estimate and 95% CIs in controls using psych package, ICC command in R based on a mean-rating, as we used both chronological and brain age for calculation of *BrainAGE* scores, consistency-agreement, 2-way mixed-effects model.

In the primary and post hoc analyses, we corrected the *P* values for multiple comparisons. The remaining analyses were exploratory.

Results

Study 1: Early Stages of Schizophrenia

For Study 1, we recruited 86 participants, including 43 previously unmedicated individuals with FES and 43 age and sex matched controls, see table 1. *BrainAGE* scores were associated with age ($r(84) = -.43$, $P < .001$), but not sex ($t(84) = -0.44$, $P = .66$). We thus adjusted for age in the following analyses.

Participants with FES had higher *BrainAGE* scores relative to controls ($F(1, 83) = 8.79$, corrected $P = .008$, Cohen's $d = 0.64$). The proportion of participants who had a greater biological than chronological age was higher among the FES patients (74.41%) than controls (46.51%, $\chi^2(1) = 7.00$, $P = .008$).

The brain age in participants with FES was higher than their chronological age by an average of 2.64 ± 4.15 years (matched $t(42) = 4.36$, $P < .001$), see figure 1.

BrainAGE scores were not associated with duration of illness ($r(41) = .01$, $P = .97$) or, duration of untreated psychosis ($r(41) = 0.02$, $P = .89$). There were no differences in *BrainAGE* scores between the diagnoses ($t(41) = 0.19$, $P = .85$). When we controlled for both age and sex, the differences in *BrainAGE* scores between FES and controls remained significant ($F(1, 82) = 8.70$, $P = .004$).

Post hoc analyses showed that participants with FES differed from controls in *BrainAGE* scores estimated from GM ($F(1, 83) = 8.21$, corrected $P = .01$), but not WM ($F(1, 83) = 4.71$, corrected $P = .06$). The *BrainAGE* scores were negatively associated with GM volume diffusely throughout the brain, see figure 2. There was no positive association between *BrainAGE* scores and GM even at an uncorrected threshold of $P = .001$.

Study 2: Early Stages of BD

For Study 2, we recruited 156 participants, including 48 HR unaffected, 48 affected familial and 60 control subjects, see table 2. *BrainAGE* scores were associated with age ($r(154) = -.24$, $P = .002$), but not sex ($F(1, 152) = 2.79$, $P = .10$).We thus adjusted for age in the following analyses.

BrainAGE scores were comparable between HR unaffected, affected familial and control participants ($F(2,149) = 1.04$, corrected $P = .70$, $\eta^2 = 0.01$), with no differences between the 2 acquisition sites ($F(1,149) = 0.39$, $P = .53$) and no site by group interaction ($F(2,149) = 0.04$,

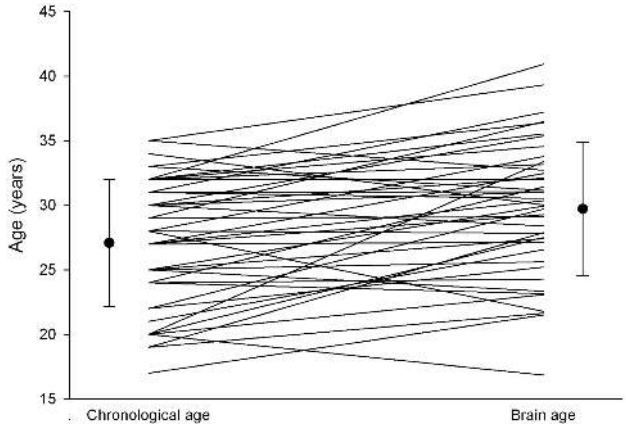

Fig. 1. Comparison of brain age and chronological age in participants with first episodes of schizophrenia-spectrum disorders (inidividual subject data and mean ± SD).

Table 1. Description of Study 1

	FES	Control Participants	*P*
N	43	43	N/A
Sex, *N* (%) female	17 (39.53)	17 (39.53)	NS
Age, mean (SD) years	27.09 (4.93)	27.05 (4.40)	NS
Diagnosis schizophrenia/acute and transient psychotic disorders, *N*(%)	25(58.14)/18(41.86)	N/A	N/A
Illness duration mean (SD) months	4.61 (5.39)	N/A	N/A
Duration of untreated illness, mean (SD) months	3.38 (5.05)	N/A	N/A
Duration of treatment, mean (SD) months	1.23 (0.95)	N/A	N/A
Proportion of participants with greater brain than chronological age, *N* (%)	32 (74.41)	20 (46.51)	.008
BrainAGE score, mean (SD), years[a]	2.64 (4.15)	−0.01 (4.15)	.004

Note: *BrainAGE*, brain-age gap estimate.
[a]Means adjusted for age.

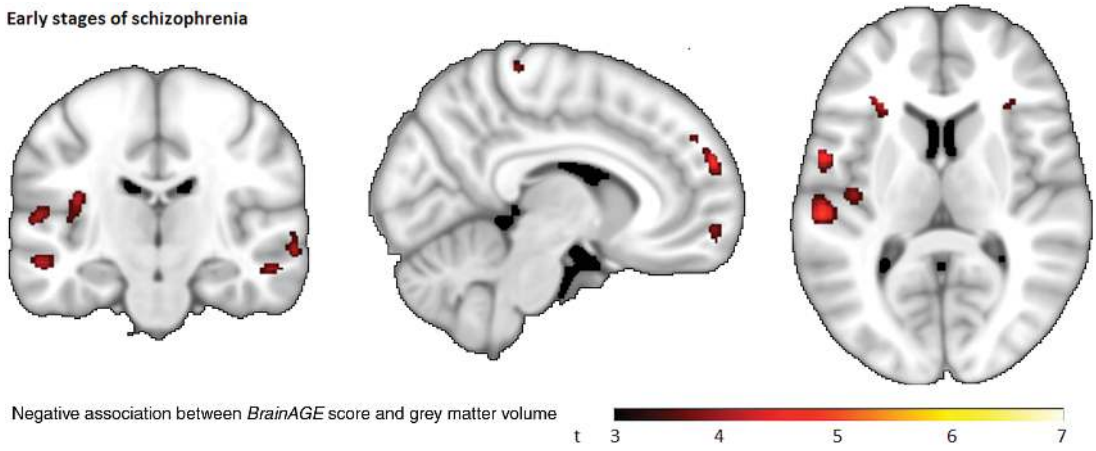

Fig. 2. Negative association between gray matter volume and *brain-age gap estimate* (*BrainAGE*) in participants with first episodes of schizophrenia-spectrum disorders ($P \leq .001$, cluster extent = 50).

Table 2. Description of Study 2

Halifax	Unaffected HR Participants	Affected Familial Participants	Control Participants	*P*
N (Halifax/Prague)	48 (28/20)	48 (33/15)	60 (42/18)	N/A
Sex, *N* (%) female	29 (60.42)	33 (68.75)	36 (60.00)	NS
Age, mean (SD) years	20.91 (4.15)	23.09 (4.51)	23.41 (2.93)	.002
Diagnosis	N/A	MD = 26, BDI = 10, BDII = 7, BD NOS = 2, Psychosis NOS = 1, ADO = 2	N/A	N/A
Treatment at the time of scanning, *N* (%)	N/A	24 (50.00)	N/A	N/A
Medication Type at the Time of Scanning	N/A	AC = 5,AD = 11, AP = 9, Li = 2	N/A	N/A
Lifetime history of Li treatment	N/A	7 (14.58)	N/A	N/A
Age of onset, mean (SD), years[a]	N/A	17.39 (3.58)	N/A	N/A
N Episodes, mean (SD)[b]	N/A	3.04 (3.18)	N/A	N/A
N hospitalizations, mean (SD)	N/A	0.60 (1.25)	N/A	N/A
Personal history of psychotic symptoms, *N* (%)	N/A	7 (14.58)	N/A	N/A
Family history of psychotic symptoms in probands, *N* (%)	17 (35.41)	15 (31.25)	N/A	NS
Proband diagnosis, bipolar I *N* (%) / bipolar II *N* (%)	37 (77.08)/11 (22.92)	36 (75.00)/12 (25.00)	N/A	NS
Proportion of participants with greater brain than chronological age, *N* (%)	21 (43.75)	19 (39.58)	29 (48.33)	NS
BrainAGE score mean (SD), years[c]	−1.02 (5.02)	−0.96 (5.18)	0.25 (5.27)	NS

Note: AC, anticonvulsants; AD, antidepressants; ADO, adjustment disorder with depressed mood; AP, antipsychotics; BD, bipolar disorder; HR, high risk; Li, lithium; MD, major depression; NOS, not otherwise specified; N/A, not applicable; NS, not significant; *BrainAGE*, brain-age gap estimate.
[a]Data missing in 2 participants.
[b]Data missing in 3 participants.
[c]Means adjusted for age and site.

$P = .96$). The proportion of participants who had a greater brain than chronological age did not differ between the groups ($\chi^2(2) = 0.83$, $P = .66$, see table 1).

The brain age in the HR unaffected ($F(1,46) = 0.50$, $P = .48$) or in the affected familial participants ($F(1,46) = 1.46$, $P = .23$) was comparable to their chronological age, see figure 3.

BrainAGE scores were not associated with number of episodes ($r(43) = -.28$, $P = .07$), number of hospitalizations ($r(46) = -.09$, $P = .55$) or duration of illness, when controlling for age ($B = 0.04$, SE of $B = 0.25$, $t = 0.16$, $P = .87$). There were no differences in *BrainAGE* scores between the diagnoses ($F(2,45) = 1.75$, $P = .19$) or between participants with vs without lifetime history of lithium treatment ($t(46) = -1.21$, $P = .23$), although only 7 participants had a lifetime history of Li treatment. When we controlled for both age and sex, the differences in *BrainAGE* scores between the groups remained non-significant ($F(2, 148) = 0.97$, $P = .38$).

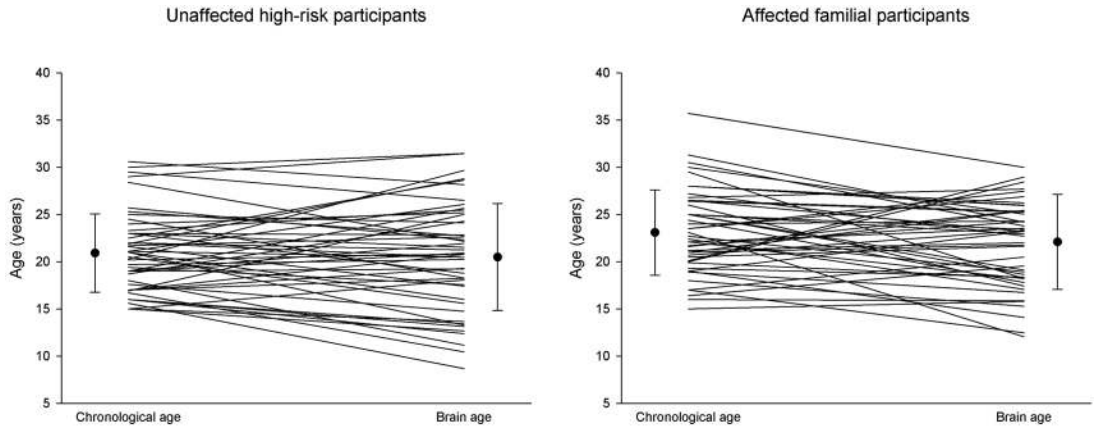

Fig. 3. Comparison of brain age and chronological age in participants at genetic risk (unaffected high-risk participants) and early in the course of bipolar disorders (affected familial participants) (inidividual subject data and mean ± SD).

Post hoc analyses showed no differences between the groups in *BrainAGE* scores estimated from GM ($F(2,149) = 1.43$, corrected $P = .48$) or WM ($F(2,149) = 1.93$, corrected $P = .30$).

There was a good agreement between the chronological and brain age in a combined sample of controls from both studies (ICC = 0.69, 95% CI = 0.55–0.79, $t(101) = 6.44$, $P < .001$).

Discussion

Participants with FES showed greater, whereas individuals at risk or in the early stages of BD showed comparable *BrainAGE* scores to controls. The brains of participants with FES appeared on average 2.64 years older than their chronological age. In contrast, the brain age in participants early in the course of BD was nonsignificantly lower than their chronological age. The higher *BrainAGE* scores in participants with FES were associated with smaller GM volume diffusely throughout the brain.

Our findings are congruent with previous investigations using a range of techniques. Three previous studies also demonstrated greater differences between brain and chronological age in participants with schizophrenia than in controls.[11,53,54] The *BrainAGE* scores in participants with FES in our study (2.64 y), were between the *BrainAGE* scores of participants at clinical risk for schizophrenia (1.7 y[11]) and those with established illness (3.36 y[54] or 5.5 y[11]). No previous study investigated *BrainAGE* scores in early stages of BD. A single previous study found no association between *BrainAGE* scores and BD.[53] As this study included only 22 BD participants and did not provide information about duration of illness or medications exposure, we do not know whether brain and chronological age remain comparable even later in the course of BD.

Our results are also congruent with structural brain imaging studies and fit within a model positing a greater neurodevelopmental contribution to schizophrenia than BD. A number of cross sectional studies have found either preserved or even larger regional brain volumes in participants at risk or in the early stages of BD.[29–32,55] In contrast, participants at risk or in the early stages of schizophrenia typically show smaller global as well as regional brain volumes.[56–59] Longitudinal studies have also suggested that whereas the trajectory of brain development tends to be altered already before the onset or early in the course of schizophrenia,[14,19–21] similar maturational brain changes are not typically seen in the early stages of BD.[21,24,28] Our cross sectional studies, closely converge with the results of previous longitudinal observations, which have suggested that accelerated brain maturation may have diagnostic specificity for schizophrenia and is not found in participants who later develop BD.[21]

More broadly, the pattern of differences observed in our study fits with epidemiological studies, which have demonstrated that premorbid academic performance was below average in those who went on to develop schizophrenia,[12,15–18] but intact or above average in those who later developed BD.[18,26,27] Similarly, cognitive functioning in participants with FES is typically impaired relative to controls[18,60] or participants with first episode of BD, who tend to demonstrate preserved or even above average cognitive performance.[26,27]

The presence of diffuse structural alterations, as suggested by the elevated *BrainAGE* scores, already early in the course of schizophrenia is concerning. Preventing the development of these changes, which are detectable already within months from the first diagnosis, would be difficult. It puts an emphasis on studies attempting to better understand the underpinnings of these alterations[61] and to devise methods to treat them. The comparable *BrainAGE* scores in offspring of bipolar parents and controls suggest preserved brain structure early in the course of BD. Many previous studies have demonstrated that structural brain alterations are frequent later in the course of illness.[62,63] This puts an emphasis on

studies attempting to prevent the development of brain structural alterations during the course of BD.[64]

This study has several limitations. In Study 2, data were collected at 2 acquisition sites. We controlled for differences between the sites in our statistical analyses. In addition, *BrainAGE* score estimation is scanner-independent and has been validated for multisite/mutiscanner setting.[49] Indeed, the brain-age scores in our study did not differ between the 2 sites. In Study 1, all data were acquired at a single site. Due to this, it would not be possible to directly compare the patient groups and control for site and study effects.

We applied different strategies to recruit participants in early stages of BD and early stages of schizophrenia. This was motivated by the fact that whereas genetic high-risk design is well suited for BD, it is difficult to use in schizophrenia, which is associated with lower fecundity.[65] Despite the differences in design, both studies focused on participants early in the course of illness and thus reduced potential sources of heterogeneity, including long-term effects of medication and illness burden. There may have been differences in illness severity between the studies, as the FES were recruited at the point of their first hospitalization. If *BrainAGE* scores primarily reflected illness severity, affected offspring of BD parents would show greater *BrainAGE* scores than unaffected high-risk individuals; which was not the case. Consequently, it is unlikely that *BrainAGE* scores represented a non-specific measure of illness severity.

This study has several advantages, including the sample size (N = 242), the cross diagnostic nature, the focus on clinically interesting group of participants with FES and those at risk and in the early stages of BD. There is evidence for acceleration of brain changes post onset in both BD and schizophrenia. Therefore, it is particularly important that we recruited participants at the early stages of illness. There is also evidence for effects of medications on brain structure.[66,67] To minimize this potential confounder, we focused on medication naïve unaffected participants and on FES participants who were medication naïve prior to the inclusion in the study. The focus on unaffected participants at risk for BD also allowed us to verify that *BrainAGE* scores did not appear to be a non-specific marker of disease severity. We used machine learning to capture the multivariate, diffuse patterns of brain changes into a single measure, ie, the *BrainAGE* score. This allowed us to preserve the complex patterns of subtle brain changes and interactions, derive a relatively unbiased measure of effect size and limit the issue of multiple comparisons.[68] To make the analyses conservative and limit overfitting, we trained the brain age model on an independent dataset and thus completely separated the training and testing stages.

To conclude, we found neurostructural changes in participants with FES, which made their brains appear 2.64 years older than their chronological age. In contrast, participants in the early stages of BD had comparable *BrainAGE* scores to controls and comparable brain and chronological age. These findings are congruent with previous cognitive, developmental and brain imaging studies and lend further support to the model of greater neurodevelopmental contributions to schizophrenia than BD. Perhaps, *BrainAGE* scores could aid in differential diagnosis between BD and schizophrenia early in the course of illness.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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