

# Neuroimaging-based brain-age prediction of first-episode schizophrenia and the alteration of brain age after early medication

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## Background

Neuroimaging- and machine-learning-based brain-age prediction of schizophrenia is well established. However, the diagnostic significance and the effect of early medication on first-episode schizophrenia remains unclear.

## Aims

To explore whether predicted brain age can be used as a biomarker for schizophrenia diagnosis, and the relationship between clinical characteristics and brain-predicted age difference (PAD), and the effects of early medication on predicted brain age.

## Method

The predicted model was built on 523 diffusion tensor imaging magnetic resonance imaging scans from healthy controls. First, the brain-PAD of 60 patients with first-episode schizophrenia, 60 healthy controls and 21 follow-up patients from the principal data-set and 40 pairs of individuals in the replication data-set were calculated. Next, the brain-PAD between groups were compared and the correlations between brain-PAD and clinical measurements were analysed.

## Results

The patients showed a significant increase in brain-PAD compared with healthy controls. After early medication, the brain-

PAD of patients decreased significantly compared with baseline ( $P < 0.001$ ). The fractional anisotropy value of 31/33 white matter tract features, which related to the brain-PAD scores, had significantly statistical differences before and after measurements ( $P < 0.05$ , false discovery rate corrected). Correlation analysis showed that the age gap was negatively associated with the positive score on the Positive and Negative Syndrome Scale in the principal data-set ( $r = -0.326$ ,  $P = 0.014$ ).

## Conclusions

The brain age of patients with first-episode schizophrenia may be older than their chronological age. Early medication holds promise for improving the patient's brain ageing. Neuroimaging-based brain-age prediction can provide novel insights into the understanding of schizophrenia.

## Keywords

First-episode schizophrenia; brain-PAD; neuroimaging; medication; cognitive.

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## Background

Schizophrenia is considered as a neurodevelopmental disorder that starts very early. Patients with schizophrenia have structural and functional brain abnormalities that are usually observed in elderly people, and associated with this increased incidence of brain ageing, cognitive decline. A new neuroimaging-based strategy, namely, brain-age prediction, may reveal the relationship between brain structural and functional changes and age. Also, it offers a novel way for searching for brain ageing biomarkers.

Previous work indicates that schizophrenia is associated with accelerated brain ageing when comparing the estimated brain age from brain images with chronological age.<sup>1,2</sup> The establishment of age prediction models based on brain magnetic resonance imaging (MRI) is a popular trend in neuroscience, which is used to recognise patterns in ageing-associated brain tissue.<sup>1,3,4</sup> Predictive analytical models may be instrumental in increasing our understanding of brain structural and functional changes with age.

The difference between predicted and chronological age could serve as an important biomarker reflecting pathological processes in the brain. A higher brain-predicted age difference (PAD) score indicates an older brain age than chronological age, which might reflect how far a brain deviates from the normal ageing trajectory.<sup>1</sup> Exploring this 'gap' between predicted and chronological age may help us better understand the mechanisms involved. The scores calculated from patients with schizophrenia and healthy individuals

could further be used for regression analysis with clinical symptoms. Increases in brain-PAD indicate that the brain ageing process is accelerated and imply risks for neurodegeneration and other age-related issues, which have been widely revealed in individuals with psychiatric disorders and neurological diseases.<sup>5</sup> The pathophysiology of schizophrenia needs to be elucidated for identification and well-directed interventions within the early-psychosis period. Therefore, we believe that exploring the difference between predicted and chronological age might be conducive to identifying a biomarker for early diagnosis and clinical outcome.

## Aims

A series of studies have shown that schizophrenia is associated with accelerated brain ageing as estimated from brain images. However, whether it occurs in people with first-episode schizophrenia needs to be elucidated. Although existing studies have suggested that the age gap may serve as a biomarker for schizophrenia, it remains unclear which factors (for example severity of symptoms, cognitive function, medication) could affect the brain-age gap and what the relationships between the gap and those factors are. Thus, the aim of the current study was to explore these issues by assessing the characteristics of the brain-age difference between patients and healthy controls. With our brain-age prediction model, we not only compared the age gap between patients with schizophrenia and healthy controls, but also investigated the association between the age gap and symptoms and medication. We assumed the deviation from normal ageing may reflect important neurological changes relating to disease and medical treatment.

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## Method

### Participants

The recruitment of first-episode schizophrenia patients could be conducive to minimising the confounding factors of research (e.g., prior therapeutic exposure and the potential influence of chronicity).<sup>6</sup> We included 60 patients (principal data-set) and 40 patients (replication data-set) with first-episode schizophrenia from the Department of Psychiatry at Xijing Hospital. In addition, 60 (principal data-set) and 40 (replication data-set) age- and gender-matched healthy controls were recruited by advertisement from the local community. The age range of all participants was 18–44 years. There was no history of neurological or psychiatric diseases and no use of medication affecting the central nervous system in the healthy participants.

All patients underwent a careful clinical diagnosis and met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.<sup>7</sup> Only a small number of patients (15 patients in the principal data-set) had been exposed to antipsychotic treatment within 2 weeks, and the rest patients were medication-naïve. Two senior clinical psychiatrists performed clinical psychometric assessments. Patients were assessed with the Positive and Negative Syndrome Scale (PANSS)<sup>8</sup> on the day of scanning. Of the 60 patients in the principal data-set, 21 medication-naïve patients who were successfully followed up were included in the longitudinal study. All follow-up patients received second-generation antipsychotics, including paliperidone (4 patients), risperidone (10 patients), olanzapine (7 patients), amisulpride (2 patients) and quetiapine (1 patient) (partial patients received multi-therapy). They underwent clinical assessments and MRI scans at a mean of 4.7 months after recruitment. Dose of current antipsychotic medication at the time of MRI scan was converted to defined daily dose.<sup>9</sup>

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the local Research Ethics Committee (Xijing Hospital, Fourth Military Medical University) with the approval number XJYYLL-2015047. All participants signed informed consent forms after a complete description of this study.

### Demographic, clinical measures and neurocognitive assessment

Sociodemographic information was collected for all participants including age, gender and level of education. Symptom severity was characterised by the PANSS.<sup>8</sup> Cognition was assessed with the digit symbol and digit span test (including forward and backward) from the Wechsler Adult Intelligence Scale revised in China,<sup>10</sup> and semantic (category) fluency from the Beijing version of the Montreal Cognitive Assessment.

### MRI image acquisition

In the test sets, diffusion tensor imaging (DTI) was acquired on General Electric Discovery MR750 3.0 T scanner (principal data-set) and on Siemens Magnetom Trio Tim MR 3.0 T scanner (replication data-set). The protocols of the two data-sets have been published. The participants wore a custom-built MRI-compatible head coil fitted with foam pads and earplugs to minimise head motion and dampen scanner noise. The diffusion sensitising gradients were applied along 64 non-parallel directions ( $b = 1000 \text{ s/mm}^2$ ) and one without diffusion weighting ( $b = 0$ ). The parameters were as follows.

- General Electric MR scanner: repetition time (TR)/echo time (TE), 10 000 ms/84.8 ms; flip angle, 90°; field of view (FOV), 240 mm × 240 mm; matrix, 128 × 128; 2.0 mm effective slice thickness with no gap; 70 slices; scanning time was about 22 min.
- Siemens MR scanner: TR/TE, 7000 ms/91 ms; flip angle, 90°; FOV, 256 mm × 256 mm; matrix, 128 × 128; 3.0 mm effective slice thickness with no gap; 50 slices; scanning time was about 8 min.

### Image analysis

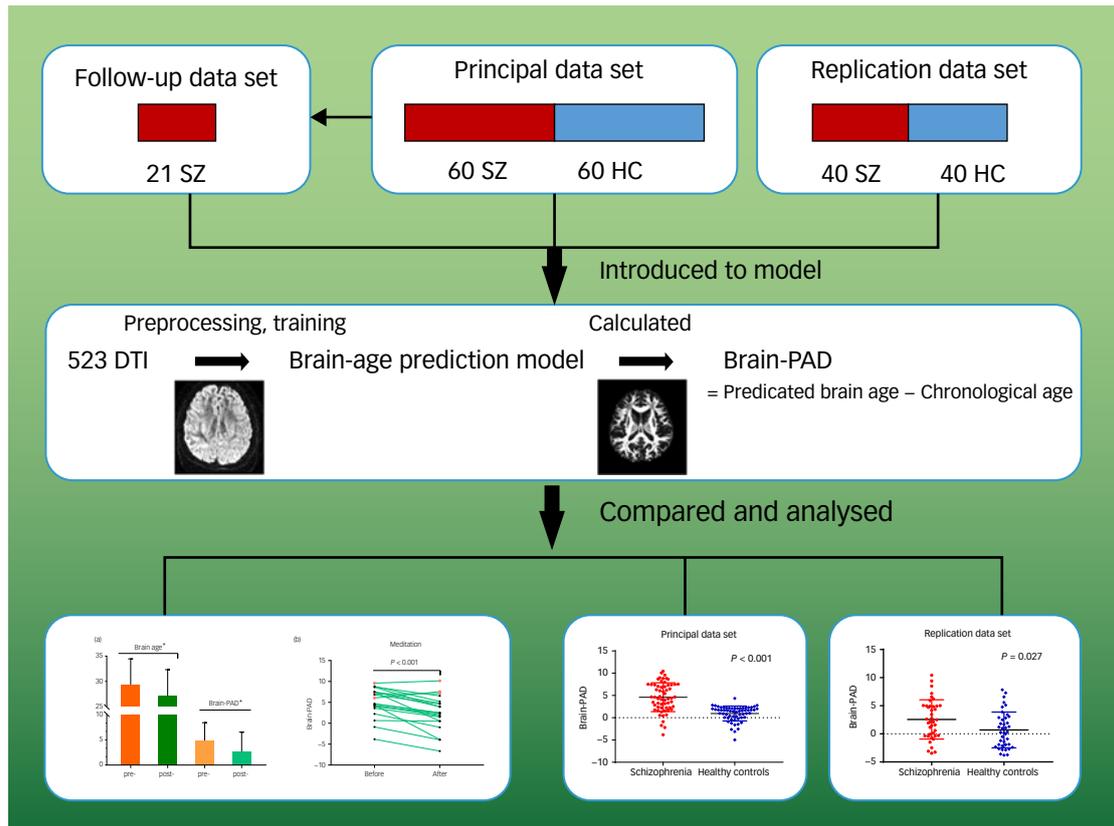
Raw diffusion tensor scans in the training set were drawn from the publicly accessible IXI cohort (<http://brain-development.org/ixi-dataset/>), the International Neuroimaging Data Sharing Initiative (INDI) online database ([http://fcon\\_1000.projects.nitrc.org/](http://fcon_1000.projects.nitrc.org/)), Cyclotron Research Centre (University of Liège) (<https://www.nitrc.org/projects/parktdi/>) and the First Affiliated Hospital of Xi'an Jiaotong University (non-public data).

In total, DTI scans from 523 healthy individuals with age ranging from 11 to 86.2 years were used to build a brain-age prediction model. Briefly, images both in the training set and test sets were preprocessed using the FSL (FMRIB Software Library v6.0, <http://www.fmrib.ox.ac.uk/fsl>). The preprocessing procedure<sup>11</sup> includes skull and non-brain tissue removal, head motion and eddy current correction. The individual spatial fractional anisotropy (FA) images were calculated by the diffusion tensor model. Then the FA images were registered to the FA template (FMRIB58\_FA) using a non-linear registration routine.<sup>11</sup> Average FA values of 50 white matter regions (i.e. 50 fibres) were extracted according to the rICBM\_DTI\_81\_WMPM\_FMRIB58 1 mm atlas.

### Machine-learning brain-age estimation

Relevance vector regression (RVR)<sup>11</sup> was introduced for model training of the relationship between FA values and chronological age in the training set, using the Scikit-learn Python library. In the feature selection, Pearson correlation ( $r$ ) between the mean FA value of each fibre and the chronological age was calculated. The fibres survived when they were correlated with the chronological age ( $|r| > 0.25, P < 0.001$ ). Then principal component analysis (PCA) was conducted to reduce the dimension, and then the top 90% of variance was taken as the input for the brain-age prediction model. The PCA components were registered into high-dimensional feature space by using the linear kernel function, obtaining the feature vector. Maximum likelihood estimation was used to estimate the weight in the regression model through the type-II maximum likelihood algorithm.

To avoid the possibility of overfitting, we used automatic correlation determination to converge the weights of some eigenvectors to zero. Relevance vectors were those feature vectors with non-zero weights. To assess the ability of the proposed regression model, we conducted internal validation in both data-sets. Tenfold cross-validation on the training set (i.e. 523 healthy individuals) was performed, with onefold in each iteration considered as the test set and the remaining folds considered as the training set. The final brain-age prediction model was determined by the relevant vectors and their corresponding weights. The Pearson correlation ( $r$ ) between chronological age and predicted brain age, the proportion of variation ( $R^2$ ), the mean absolute error (MAE), and root mean squared error (RMSE) of the brain-PAD scores were measured as the model performance. Based on the age-predicted model, we calculated each participant's brain-PAD in test sets (brain-PAD = predicted age – chronological age) (Fig. 1).



**Fig. 1** Pipeline of analysis. Overview of data-sets, prediction model establishment, brain-predicted age difference (brain-PAD) calculation, and statistical analysis.

The images in the final row are shown full size in Figs 2 and 3. DTI, diffusion tensor imaging; HC, healthy controls; SZ, patients with schizophrenia.

## Statistical analysis

Brain-PAD scores were statistically analysed in SPSS software (version 25.0) using the analysis of paired sample *t*-test (normal distribution) or Wilcoxon signed-rank test (non-normal distribution) to compare the differences between patients with schizophrenia and the healthy controls in the principal and replication data-sets. Pearson correlation, Spearman correlation and partial correlation analysis were used to examine the association between brain-PAD and clinical characteristics, such as PANSS scores and cognitive function. The chi-square test was conducted on the difference by gender between groups. Significance was set at  $P$  value  $< 0.05$ , with statistical rigidity tested by using the replication data-set. Finally, the paired *t*-test was used for observing the impact of early medication on brain age and clinical variables, and the differences compared with healthy controls. Between-group comparisons of brain-PAD scores for the schizophrenia group and healthy controls were conducted using ANCOVA. Multiple comparisons were corrected using the false discovery rate (FDR) method with a significance threshold of  $P < 0.05$ . Using linear mixed-effects model analysis to rule out the potential impact of illness duration on the comparison of brain age at baseline and after medication.

## Results

### Clinical characteristics of participants

Sociodemographic, clinical and cognitive characteristics of the patients and healthy controls are shown in Table 1. Except for education level in the principal data-set, there were no significant

differences between the schizophrenia group and healthy controls for age, gender and education level.

### Brain-age prediction

The accuracy of the model was assessed via the FA values ( $r = 0.96$ ,  $R^2 = 0.93$ ,  $MAE = 3.74$ ,  $RMSE = 5.03$ ) from the training set. The predicted ages of participants were highly correlated with their chronological age in the whole group ( $P < 0.001$ ). In the principal data-set, the mean brain-PAD values in the schizophrenia group was 4.6 (s.d. = 3.2) years, whereas healthy controls showed a difference of only 0.9 (s.d. = 1.7) years. In the replication data-set, the mean brain-PAD value in the schizophrenia group and healthy controls were 2.6 (s.d. = 3.5) years and 0.7 (s.d. = 3.2) years, respectively (Table 1). The differences between the two patient groups were also compared (Supplementary Table 1 available at <https://doi.org/10.1192/bjp.2021.169>). The schizophrenia groups had significantly higher brain-PAD values than the healthy control groups in both data-sets ( $t = 7.933$ ,  $P < 0.001$ ;  $t = 2.295$ ,  $P = 0.027$ ) (Fig. 2); the difference in brain-age estimation was higher, with statistical significance, in the principal data-set ( $Z = -2.312$ ,  $P = 0.021$ ). After adjusting for education level and age, the differences still existed (Table 1).

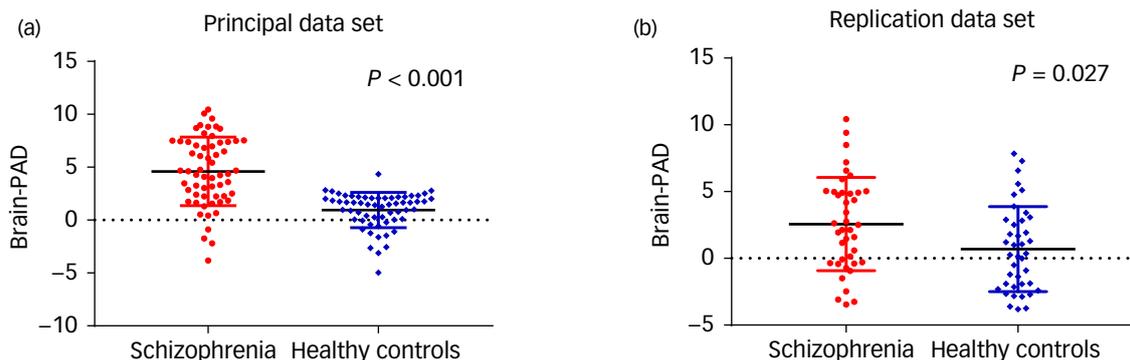
### Changes with early medication

After early medication (4.743 months, s.d. = 1.535), 21 patients in the principal data-set had a significant reduction in brain-PAD compared with their baseline state (2.718 (s.d. = 3.818) v. 4.9323 (s.d. = 3.486),  $t = 5.495$ ,  $P < 0.001$ ) (Fig. 3). Their clinical

**Table 1** Demographic and clinical characteristics of the patients with schizophrenia and healthy controls

Characteristic	Principal data-set			Replication data-set		
	Patients ( <i>n</i> = 60)	Healthy controls ( <i>n</i> = 40)	<i>P</i>	Patients ( <i>n</i> = 40)	Healthy controls ( <i>n</i> = 60)	<i>P</i>
Age, years: mean (s.d.)	24.7 (5.2)	26.4 (4.5)	0.054 <sup>a</sup>	25.4 (6.3)	28.26 (6.3)	0.059 <sup>a</sup>
Gender, male/female: <i>n</i>	33/27	27/33	0.273 <sup>b</sup>	24/16	18/22	0.179 <sup>b</sup>
Education level, years: mean (s.d.)	12.0 (3.1)	17.1 (2.7)	<0.001 <sup>a</sup>	12.7 (3.4)	13.8 (2.7)	0.081 <sup>a</sup>
Illness duration, months: mean (s.d.)	17.0 (25.4)	NA	NA	10.5 (13.7)	NA	NA
PANSS scores, mean (s.d.)						
Positive score	21.7 (5.2)	NA	NA	23.6 (8.5)	NA	NA
Negative score	20.2 (7.6)	NA	NA	22.9 (7.6)	NA	NA
General psychopathology score	43.5 (7.4)	NA	NA	48.7 (8.9)	NA	NA
Total score	85.4 (12.4)	NA	NA	95.2 (18.5)	NA	NA
<i>Cognitive measures, mean (s.d.)</i>						
Digit symbol	44.7 (14.8)	NA	NA	NA	NA	NA
Digit span: Forward	9.1 (1.5)	NA	NA	NA	NA	NA
Digit span: Backward	4.9 (1.8)	NA	NA	NA	NA	NA
Semantic verbal fluency	16.9 (5.5)	NA	NA	NA	NA	NA
Brain-age estimation, mean (s.d.)	29.3 (4.9)	27.3 (3.9)	0.021 <sup>c</sup>	27.9 (6.4)	28.9 (6.9)	0.554 <sup>c</sup>
Brain-age estimation (adjusted)	–	–	<0.001 <sup>d</sup>	–	–	0.211 <sup>d</sup>
Brain-predicted age difference, mean (s.d.)	4.6 (3.2)	0.9 (1.7)	<0.001 <sup>a</sup>	2.6 (3.5)	0.7 (3.2)	0.027 <sup>a</sup>
Brain-predicted age difference (adjusted)	–	–	<0.001 <sup>d</sup>	–	–	0.042 <sup>d</sup>

NA, not applicable; PANSS, the Positive and Negative Syndrome Scale.  
a. Paired sample *t*-test.  
b. Chi-square test.  
c. Wilcoxon signed-rank test was performed owing to the non-normal distribution of samples.  
d. ANCOVA, adjusting for education level, age.

**Fig. 2** Brain-predicted age difference (brain-PAD) in the patients with schizophrenia and healthy controls. Scatter plot of brain-PAD scores in the principal data-set (a) and replication data-set (b).

The brain-PAD was higher in patients with schizophrenia than in the healthy controls with  $P < 0.001$  (a) and  $P = 0.027$  (b). Solid black lines indicate group mean values of brain-PAD. The dotted lines refer to the brain-PAD of 0.

characteristics are shown in Table 2. The post-PANSS scores was significantly lower compared with pre-PANSS scores ( $P < 0.001$ ), whereas early medication had no effect on the changes in cognitive measures ( $P > 0.05$ ). In addition, the correlations were not statistically significant between the changes in brain-PAD and chronological age ( $r = 0.106$ ,  $P = 0.676$ ) and education level ( $r = 0.096$ ,  $P = 0.705$ ) (Supplementary Table 2). When ruled out the effect of illness duration, the difference of PAD before and after medication still existed ( $P = 0.165$ ). In other words, the illness duration was not a factor affecting the changes in PAD after medication.

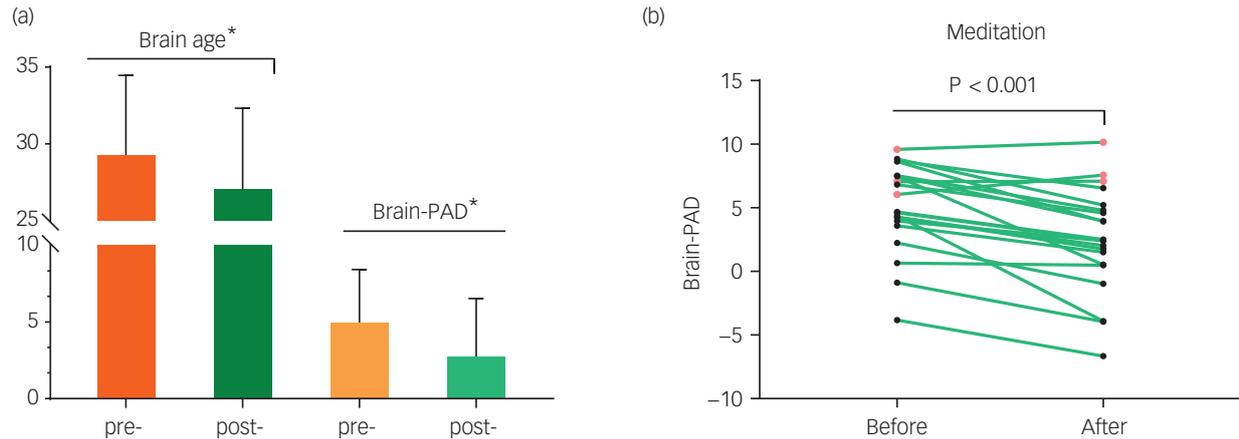
Moreover, when comparing the follow-up patients with 21 healthy controls, there was no significant difference between the patients with schizophrenia and the healthy controls in chronological age ( $P = 0.300$ ), gender ( $P = 0.757$ ) but a significant difference in education ( $P < 0.001$ ). Comparing the follow-up patients after medication for about 4 months with healthy controls, there were significant differences in brain-PAD ( $F = 4.212$ ,  $P = 0.047$ , adjusted), but not in the brain-age estimation (Supplementary Table 3).

### Features associated with brain-PAD scores

In the model training, the  $r$  value between chronological age of healthy people and FA of white matter was calculated to evaluate the contribution of related white matter tracts to brain age. A total of 33 white matter tracts were selected and defined as features. The FA values in 31 white matter tracts (except for the right anterior corona radiata and the left fornix, Supplementary Table 4) that related to the brain-PAD scores, showed significant statistical differences between the two measurements ( $P < 0.05$ , FDR corrected).

### Parameters affecting the brain-PAD

As for the parameters affecting the brain-PAD, correlation analysis was undertaken for chronological age, gender, educational level and illness duration (Supplementary Table 2). The brain-PAD value was negatively associated with the chronological age of the patients in the principal and pooled data-sets ( $P < 0.05$ ), but not in the replication data-set. There were statistically significant correlations



**Fig. 3** (a) Brain age and brain-predicted age difference (PAD) were reduced after early medication with a statistical significance. (b) Changes in brain-PAD in 21 patients at baseline and follow-up.

Error bars represent standard deviations and asterisk indicates significance ( $P < 0.001$ ). In (a), pre- represents before medication baseline, post- represents after medication. In (b), the line between the black dots represents the decrease in PAD after treatment, and the line between the red dots represents the increase in PAD after treatment.

**Table 2** Clinical characteristics of 21 patients with first-episode schizophrenia before and after treatment

	Before medication	After medication	<i>P</i>
PANSS scores, mean (s.d.)			
Positive score	20.95 (4.894)	10.10 (3.375)	<0.001 <sup>a</sup>
Negative score	20.71 (6.820)	13.95 (5.133)	<0.001 <sup>a</sup>
General psychopathology score	42.67 (7.882)	26.38 (6.119)	<0.001 <sup>a</sup>
Total score	84.90 (10.844)	51.76 (11.679)	<0.001 <sup>a</sup>
Cognitive measures, mean (s.d.)			
Digit symbol	44.33 (14.369)	44.78 (13.580) <sup>b</sup>	0.870 <sup>a</sup>
Digit span			
Forward	8.94 (1.110)	8.78 (1.801) <sup>b</sup>	0.703 <sup>c</sup>
Backward	4.78 (2.045)	4.17 (1.295) <sup>b</sup>	0.102 <sup>c</sup>
Semantic verbal fluency	14.94 (4.094)	16.22 (4.066) <sup>b</sup>	0.108 <sup>a</sup>
Scan interval, months: mean (s.d.)	NA	4.7429 (1.535)	NA
Antipsychotic dose, mg/d: mean (s.d.)	NA	11.29 (5.368)	NA
Brain-age estimation: mean (s.d.)	29.265 (5.205)	27.052 (5.273)	<0.001 <sup>a</sup>
Brain-predicted age difference	4.932 (3.486)	2.718 (3.818)	<0.001 <sup>a</sup>

NA, not applicable; PANSS, the Positive and Negative Syndrome Scale.  
 a. Paired sample *t*-test.  
 b. Information available for 18 participants.  
 c. Wilcoxon signed-rank test was performed due to the non-normal distribution of samples.

between brain-PAD and gender in the patient groups of the principal and pooled data-sets ( $P = 0.048$  and  $P = 0.003$ ). The brain-PAD were negatively associated with education level and illness duration in the replication patient group ( $P = 0.027$  and  $P = 0.025$ ).

### Correlation with clinical measurements of patients with schizophrenia

As was shown in Supplementary Table 5, the brain-PAD value was negatively associated with the positive score in the principal data-set ( $r = -0.326$ ,  $P = 0.014$ ), whereas no statistically significant association was found in other symptoms of the PANSS assessment. In addition, there was a negative correlation between brain-PAD

and semantic verbal fluency after medication for about 4 months ( $r = -0.632$ ,  $P = 0.015$ ). Nevertheless, correlation analysis showed that performances on cognitive measures (raw scores) were irrelevant to brain-PAD scores in patients with schizophrenia, including digit symbols, and forward and backward digit span. Moreover, the correlations were not statistically significant between the changes in brain-PAD and current antipsychotic dose and scan interval.

## Discussion

### Main findings

In this study, we aimed to confirm that predicted brain age extracted from structural imaging can be used as a biomarker for schizophrenia diagnosis and medication effect. We performed neuroimaging-based brain-age prediction in people with schizophrenia and healthy controls to assess whether there was accelerated brain ageing in patients with first-episode schizophrenia, the correlation between PAD and clinical characteristics, and the effect of medication on brain age estimation. Based on the advantage of MRI scans, the prediction model was highly accurate at estimating brain age in a relatively large cohort from the perspective of white matter structure. Brain age was estimated to be older than the patient’s chronological age, which was verified in a replication data-set. The brain age of patients with schizophrenia might be altered by medication as we found that features (i.e. white matter fibres) have been significantly improved after treatment, namely, the degree of brain ageing assessed by white matter fiber characteristics was lightened.

Our study partially consolidated and extended previous findings showing the accelerated brain ageing in patients with schizophrenia, and further underscored that this feature may be the result of the disease itself. In addition, although accelerated ageing in schizophrenia has been reported in previous studies,<sup>2,4,12,13</sup> they did not focus on first-episode schizophrenia, where the brain ageing could be affected by illness duration and therapy.

### Interpretation of our findings and comparison with findings from other studies

In the schizophrenia group the difference in the estimated brain age and their chronological age appeared to be 4.6 years older in the principal data-set and 2.6 years older in the replication data-set,

which represented statistically significant differences compared with healthy controls. In the follow-up data-set, we found an average difference of 4.9 years between brain and chronological age at baseline, but only 2.7 years older after early medication. However, Schnack and colleagues reported that the brain age of patients with schizophrenia was progressively increased at a rate of about 1.24 years annually over the 3.5-year follow-up period.<sup>1</sup> The difference between our findings and Schnack et al may be the result of dynamic changes with clinical course and long-term therapy, and further evidence is needed to verify the findings. Moreover, previous studies have verified a trend of accelerated brain ageing similar to those in schizophrenia in other psychiatric disorders.

A comparison of people with schizophrenia with people with bipolar disorder and healthy controls showed that the gap was more prominent in schizophrenia, and was found to a lesser extent in bipolar disorder.<sup>2,13</sup> In a broader study using cross-diagnostic quantitative analysis, the results suggested that accelerated brain ageing might have a particular impact in schizophrenia with an increase of 5.5 years, which could also extend to major depression, borderline personality disorder and individuals with at-risk mental states.<sup>5</sup> In brief, the gap between brain age and the chronological age of patients with schizophrenia was proved to make sense, and may represent an intrinsic feature of schizophrenia.

Combined predictors (such as brain atrophy, iron deposition and alterations of white matter microstructure) have great potential in capturing the various facets of brain ageing.<sup>3</sup> As some researchers pointed out, schizophrenia is a progressive process with progressive brain tissue loss.<sup>1</sup> Neuroimaging techniques have shown structural<sup>2</sup> and functional brain abnormalities<sup>12,14</sup> in patients with schizophrenia, and ventricular enlargement and cortical atrophy have also proved to be progressive, which suggests the existence of brain atrophy. Ageing of the brain involves the shrinkage of the cortex and grey matter structures and loss of white matter. In the brain, the alterations found in schizophrenia are to some extent similar to those observed in healthy ageing, namely, atrophy is also observed in the schizophrenia brain. The current study revealed the existence of brain ageing in schizophrenia using neuroimaging; the DTI MRI sequence in patients with schizophrenia showed the relationship between brain ageing and characteristics of white matter, which was consistent with the results found of structural changes to white matter in our prior study.<sup>6</sup>

Regarding brain-age prediction models,  $T_1$ -weighted MRI is commonly used for morphometric measures, such as regional cortical thickness, surface area and volume. Several studies have shown the robust prediction performance of schizophrenia using support vector machines,<sup>15</sup> Gaussian Process regression,<sup>16</sup> relevance vector machine<sup>17</sup> and deep-learning approaches<sup>18</sup> with  $T_1$ -weighted MRI images.  $T_1$ -weighted and DTI sequences can describe distinct tissue classes, although both of them have the ability to assess and quantify white matter.<sup>19</sup> One hypothesis of accelerated brain ageing that has been reported in schizophrenia is disruption to white matter integrity.<sup>14,20</sup> Focusing on exploring the methodology of a brain-age model, Tonnesen et al indicated that brain-age prediction based on DTI provides<sup>4</sup> the clinical application research with strong supporting evidence to study white matter abnormalities in patients of schizophrenia. In this study, we found that the FA values of most white matter fibre tracts improved after medication, also demonstrating the potential significance of white matter connection disruption in schizophrenia.

We used RVR with DTI sequences to establish the prediction model as DTI has an advantage in estimating white matter microstructures across the brain.<sup>19</sup> Compared with other parameters related to DTI, the brain-age prediction model based on FA showed higher sensitivity than mean diffusivity, radial diffusivity,

or axial diffusivity.<sup>4</sup> To improve the accuracy of prediction, some investigators have combined DTI with  $T_1$ -weighted sequences to compare tissue-specific brain ages and their cognitive sensitivity in healthy controls<sup>19</sup> and delineated the trajectories of brain development in teenagers without mental disorders.<sup>21</sup> In the future, establishing a brain-age prediction model by integrating multiple MRI sequences from both functional and structural aspects of patients with schizophrenia will come closer to being realised.

Impaired white matter bundle connectivity between the brain regions plays a critical role in the neuropathology of schizophrenia.<sup>22</sup> In this study, we did not find consistent significant factors that might influence the white matter connectivity in patients with schizophrenia, such as age, gender, education level, illness duration or symptoms. There was a trend to an increase in brain-PAD with younger age, which did not meet statistical significance in the replication data-set. It has been reported that psychiatric patients who are younger show more severe accelerated brain ageing, which indicates that abnormal white matter integrity may occur at a younger age rather than there being a progressive development with age.<sup>23,24</sup> In other words, early-onset schizophrenia is more symptomatic and has a worse prognosis. Therefore, quantitative studies based on brain age might be conducive in revealing the pathological mechanism involved. There was significant correlation between education level and brain-PAD in our replication patient group, but not in principal patient group and pooled group. A large cohort in a healthy participant brain-age study also reported that brain-PAD was not associated with years of education.<sup>16</sup> Therefore, the effect of education on brain age needs to be further explored.

Cognitive impairments are commonly seen in individuals with schizophrenia, which might be in line with accelerated or premature ageing.<sup>25</sup> The discrepancy between brain age and chronological age might have potential correlation with cognitive impairments. There may be no correlations between the discrepancy and some aspects of cognition impairments,<sup>18</sup> or the correlation was negative, which indicated worse performance with higher brain age difference.<sup>19</sup> In the present study, we observed negative correlations between brain-PAD scores and semantic verbal fluency after medication, as well as the scores on the positive scale of the PANSS in the principal data-set. It has been reported that the FA value of white matter fibres are negatively associated with total PANSS scores in a never-treated schizophrenia group.<sup>24</sup> Nevertheless, no consistent results were found in replication group and pooled group of our study. Overall, patients with schizophrenia might have accelerated brain age and cognitive impairments that exist from an early stage of their illness and then follow a normal rate of age-related changes, which needs to be validated in larger longitudinal studies.

It was reported that antipsychotic treatment may confer benefits on white matter tracts in patient with schizophrenia.<sup>24</sup> In the longitudinal part of our study, we confirmed the effect of early medication on brain-age estimation, PANSS scores and cognitive measurements. The average predicted brain-age gap between baseline and follow-up was reduced by 2.2 years. The PANSS score, which indicates the severity of symptoms, had significantly reduced compared with the baseline assessment. Evidence showed that the brain-age acceleration rate was positively with the PANSS total score at follow-up and cumulative antipsychotic intake, while these were inconsistent with our findings.<sup>1</sup> The differences found in brain age were not related to the current antipsychotic dose in our research. Furthermore, the significant changes in cognitive function were not found, which may be owing to the relatively slight effect of antipsychotics on cognitive function. Cognitive performance seems to be stable over the lifetime in most patients with schizophrenia, and accelerated ageing may occur very early in the illness.<sup>25</sup> The results were coherent with that the early courses of

psychiatric disorders are accompanied by accelerated ageing, and meanwhile, the cognitive function might be intact.<sup>12</sup> That is to say, there is accelerated ageing in schizophrenia and the cognitive function of patients may not be related to this accelerated ageing. This study demonstrates that the estimated brain age of follow-up patients with first-episode schizophrenia became younger after early medication for about 4 months. Antipsychotic treatment might be beneficial to the integrity of white matter tracts. Further research is needed to confirm this effect and explore the neurobiological mechanism of antipsychotics on brain age in schizophrenia.

### Limitations

The present findings should be considered with several limitations. First, the sample size is limited, and only a small number of participants were available for the follow-up data-set and this is likely to have limited statistical power. Second, cognitive measurements were not comprehensive and were only applied in patients in the principal data-set. Third, although we assessed whether the discrepancy of brain-PAD was associated with current medication exposure, it would be more precise to consider cumulative exposure to antipsychotics. Fourth, follow-up patients did not receive the same antipsychotics, which might affect the results. Fifth, the brain-age prediction model only used DTI MRI sequences. As a result, large collaborative longitudinal multimodal imaging studies of schizophrenia will be required to clarify the neurodevelopment trajectory and specific medication influences.

### Implications

In conclusion, we found accelerated brain ageing in patients with schizophrenia and we also found that early medication had an effect on ameliorating it. In other words, our research supports the theory of accelerated ageing in patients with schizophrenia from the perspective of brain structural changes. Quantification of age discrepancy could be useful for screening for schizophrenia and searching for new targeted therapies. Given these findings, measuring brain ageing based on neuroimaging holds promise for establishing biomarkers that could contribute to clinical decision-making of psychiatric disorders.

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### Data availability

The data that support the findings of this study are available from the corresponding author, H.Y., upon reasonable request.

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### Author contributions

Y.-B.X. formulated the research questions, contributed to the design of the study, and supervised data collection and analysis. X.-S.W. ran the statistical analysis and edited the manuscript. L.-B.C. supervised the data collection, modified the original manuscript. L.-J.B. formulated the research questions, supervised data analysis. S.-Q.G. conducted the preliminary analysis and contributed the method of the manuscript. X.-Y.J. processed the data of the participants and conducted the preliminary analysis. X.L. supervised the data analysis and revised the final manuscript. Y.-Q.X. collected the data of the participants and analysed the data. X.-W.K. supervised the design of the study and modified the manuscript. F.G. supervised the design of the study and contributed to an early version of the manuscript. H.Y. formulated the research questions, supervised the design of the study and edited the final manuscript.

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### Declaration of interest

None

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### Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1192/bjp.2021.169>.

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## Psychiatry In Literature

### Grief in *The Epic of Gilgamesh*

Karrish Devan

*The Epic of Gilgamesh* is an Ancient Mesopotamian text chronicling the adventures of Gilgamesh, a demi-god and king, and Enkidu, his faithful companion. The work is often considered to contain great themes of love, war and faith but central too is one of grief. After the pair insult the Gods, Enkidu is cursed and he later dies. Despite being written thousands of years ago, Gilgamesh's experiences fit contemporary understandings of the grief process.

Immediately after learning of Enkidu's death Gilgamesh:

'began to rage like a lion, like a lioness robbed of her whelps. This way and that, he paced round the bed, he tore out his hair and strewed it around. He dragged off his splendid robes and flung them down as though they were abominations.'

A deep depression follows as Gilgamesh sits with Enkidu's body for a week, neglecting himself and his duties. He only leaves when the body starts to rot:

'Seven days and nights I sat beside the body, weeping for Enkidu beside the body, and then I saw a worm fall out of his nose. Must I die too? Must Gilgamesh be like that?'

To avoid confronting this inner turmoil and anxiety, Gilgamesh decides to embark on an epic quest to find immortality – to deny death itself. A lengthy journey follows which cumulates in Gilgamesh being set a seemingly impossible task by a wise sage. Our hero fails and, returning home, he is left only with the sage's words:

'There is no permanence. Do we build a house to stand for ever, do we seal a contract to hold for all time? Do brothers divide an inheritance to keep for ever, does the flood-time of rivers endure? It is only the nymph of the dragon-fly who sheds her larva and sees the sun in his glory. From the days of old there is no permanence.'

On seeing the walls of his city, Gilgamesh realises in a moment of introspection that the journey has changed him profoundly. In processing his grief, he understands that everything on earth is ephemeral and that, eventually, we all will die.

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