# BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder

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## ARTICLE INFO

## ABSTRACT

BrainAGE (brain age gap estimation) is a novel morphometric parameter providing a univariate score derived from multivariate voxel-wise analyses. It uses a machine learning approach and can be used to analyse deviation from physiological developmental or aging-related trajectories. Using structural MRI data and BrainAGE quantification of acceleration or deceleration of in individual aging, we analysed data from 45 schizophrenia patients, 22 bipolar I disorder patients (mostly with previous psychotic symptoms / episodes), and 70 healthy controls. We found significantly higher BrainAGE scores in schizophrenia, but not bipolar disorder patients. Our findings indicate significantly accelerated brain structural aging in schizophrenia. This suggests, that despite the conceptualisation of schizophrenia as a neurodevelopmental disorder, there might be an additional progressive pathogenic component.

## 1. Introduction

The clinical course of schizophrenia often involves a progressive deterioration of cognition, as well as affective symptoms and social functioning. Although conceptualised as a neurodevelopmental disorder, there is an ongoing debate on the combination of developmental and progressive pathologies (Kochunov and Hong, 2014). Studies of cognition and brain structure support an early neurodevelopmental factor (Bora and Pantelis, 2015; Douaud et al., 2009), but there is also evidence for progressive changes in some brain grey and white matter structures, which start only after disease onset (Chiapponi et al., 2013). Several recent studies have therefore continued to provide evidence for an accelerated aging hypothesis, i.e. the assumption that some of the changes seen in schizophrenia resemble those in physiological aging (Douaud et al., 2014; Nenadic et al., 2012). A limitation in some previous studies has been the use of cross-sectional data or longitudinal data with limited follow-up periods, which makes it difficult to assess differences in life-span trajectories.

In this study, we use a novel method for assessing deviation of age-related trajectories. The BrainAGE (brain age gap estimate) score was developed to estimate the age from individual magnetic resonance images (MRI), based on the reduction of multi-variate age-related grey matter effects across the whole brain (Franke et al., 2010a). The difference between each individual's estimated and chronological age results in the BrainAGE providing an indication of deviation from normal aging trajectories. While lower scores (e.g. in adolescents or young adults) might indicate developmental delays, a higher BrainAGE score is indicative of accelerated aging, i.e. an individual or a group showing grey matter structural changes that would be expected at higher age. The BrainAGE score has been applied in several studies, including aging effects in the elderly (Franke et al., 2014; Lowe et al., 2016), in diabetes (Franke et al., 2013), and other studies (Luders et al., 2016).

We tested the hypothesis, that schizophrenia patients show accelerated brain structural aging as indicated by elevated BrainAGE scores, and contrasted this to both healthy controls, as well as a psychiatric control group of bipolar I disorder patients, most with a history of psychotic symptoms resembling those of our schizophrenia patients, yet with no presumed progressive brain structural change in order to expand on previous findings (Koutsouleris et al., 2014).

## 2. Methods

### 2.1. Sample

We included a total of 137 subjects in this study: 45 patients with DSM-IV-R schizophrenia (29 male, 16 female), 70 healthy controls (40 male, 30 female), and 22 patients with DSM-IV-R bipolar disorder (10

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male, 12 female). All subjects provided written informed consent to a study protocol approved by the Ethics Committee of Jena University Medical School, and in accordance with the Declaration of Helsinki. Samples did not differ in age (Sz mean 33.7a, SD 10.5, range 21.4–64.9; HC mean 33.8, SD 9.4, range 21.7–57.8; BP mean 37.7, SD 10.7, range 23.8–57.7; ANOVA, $F_{(2,136)}$ = 1.443; p = 0.240), gender distribution (chi square = 2.199; p = 0.333), or handedness (laterality quotient derived from Edinburgh handedness scale; ANOVA, $F_{(2,134)}$ = 1.501; p = 0.227). Handedness distributions were as follows: Sz mean 56.97 (SD 52.79); BP mean 70.85 (SD 48.23); HC mean 72.06 (SD 41.27).

Patients were recruited from in- and out-patient services and referring hospitals. Diagnosis according to DSM-IV-R criteria was established through either case review or SCID-I interview by a board-certified psychiatrist (I.N.). Schizophrenia patients were scanned while in remission, and concurrent psychopathology was assessed using the SANS and SAPS. Bipolar disorder patients were euthymic at the time of scanning, defined by a) absence of a concurrent affective episode (depressive, hypomanic, manic, or mixed episode), and b) a maximum score of 7 on either the Young Mania Rating Scale (YMRS) or Hamilton Depression Scale (HAMD). Out of the 22 bipolar disorder patients, 17 had bipolar I disorder, and a history of psychotic symptoms (albeit not at the time of scanning).

Healthy subjects were screened, prior to scanning, using a healthy questionnaire, in order to exclude a history of psychiatric disorders, psychiatric or psychological treatment or counselling, first-degree psychotic or affective disorders in their families, as well as substance abuse. Further general exclusion criteria for all participants were active substance abuse disorders, neurological or major medical conditions, a history of traumatic brain injury with loss of consciousness. Conventional voxel-based morphometry analyses of part of this cohort have been published previously, including clinical details of patients (Nenadic et al., 2015), and the samples have been extended for the present analysis; patients with schizophrenia were on antipsychotic medication, while patients with bipolar disorder were on mood stabilisers and in some cases antispychotics, as described previously (Nenadic et al., 2015).

### 2.2. MRI scanning and BrainAGE score analysis

For each subject, we acquired high-resolution anatomical MRI data on a 3 T Siemens Tim Trio MRI system (Siemens, Erlangen, Germany) using a T1-weighted MPRAGE sequence (TR 2300 ms, TE 3.03 ms, TI 900 ms, alpha 9°) with 192 contiguous slices covering the entire brain, slice thickness 1 mm, field of view: 256 × 256, isotropic voxel resolution of $1 \times 1 \times 1$ mm$^3$.

All MRI scans passed both a visual inspection for exclusion of gross artefacts, as well as an automated quality control (implemented in the VBM8 package; http://dbm.neuro.uni-jena.de/vbm8/).

BrainAGE scores were calculated for each individual according to a protocol described previously (Franke et al., 2012, 2010a). The BrainAGE approach comprises well established and fully automated processing of structural MR images to aggregate the complex, regions-specific, and non-linear patterns of age-related changes across the whole brain into one single value, thus providing a reference curve for healthy brain aging. The algorithm makes use of the pattern in the whole brain image and also takes into account inter-regional dependencies. A BrainAGE score > 0 indicates accelerated aging.

As described previously (Franke et al., 2010b), preprocessing of the T1-weighted images was done using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de), running under Matlab. All T1-weighted images were corrected for bias-field inhomogeneities, then spatially normalized and segmented into grey matter (GM), white matter (WM), and CSF within the same generative model (Ashburner and Friston, 2005). The segmentation procedure was further extended (Gaser, 2009) by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum

a posteriori estimations (Rajapakse et al., 1997), and using a hidden Markov Random Field model (Cuadra et al., 2005). Preprocessing the images further included affine registration and smoothing with 4-mm full-width-at-half-maximum (FWHM) smoothing kernels. Spatial resolution was set to 4 mm. Data were further reduced by applying principal component analysis (PCA) in order to reduce computational costs, to avoid severe over-fitting, as well as to get a robust and widely applicable age estimation model, utilizing the "Matlab Toolbox for Dimensionality Reduction" (http://ict.ewi.tudelft.nl/~lvandermaaten/Home.html).

#### 2.2.1. Age estimation framework

The BrainAGE framework utilizes a machine-learning pattern recognition method, namely relevance vector regression (RVR; Tipping, 2001). It was recently developed to model healthy brain aging and subsequently estimate individual brain ages based on T1-weighted images (Franke et al., 2010b). As suggested previously (Franke et al., 2010b), a linear kernel was chosen, since age estimation accuracy was shown not to improve when choosing non-linear kernels. Thus and in contrast to support vector machines, parameter optimization during the training procedure was not necessary.

In general, the age regression model is trained with chronological age and preprocessed whole brain structural MRI data (as described above) of the training sample, resulting in a complex model of healthy brain aging. Put in other words, the algorithm uses those whole-brain MRI data from the training sample that represent the prototypical examples within the specified regression task (i.e., healthy brain aging). Additionally, voxel-specific weights are calculated that represent the importance of each voxel within the specified regression task (i.e., healthy brain aging). For an illustration of the most important features (i.e., the importance of voxel locations for regression with age) that were used by the RVR to model normal brain aging and more detailed information please refer to (Franke et al., 2010b).

Subsequently, the brain age of a test subject can be estimated using the individual tissue-classified MRI data (as described above), aggregating the complex, multidimensional aging pattern across the whole brain into one single value. In other words, all the voxels of the test subject's MRI data are weighted by applying the voxel-specific weighting matrix. Then, the brain age is calculated by applying the regression pattern of healthy brain aging and aggregating all voxel-wise information across the whole brain. The difference between estimated and chronological age will reveal the individual brain age gap estimation (BrainAGE) score, with positive values indicating accelerated structural brain aging and negative values indicating decelerated structural brain aging. Consequently, the BrainAGE score directly quantifies the amount of acceleration or deceleration of brain aging. For example, if a 70 years old individual has a BrainAGE score of + 5 years, this means that this individual shows the typical structural pattern of a 75 years old individual.

For statistical analysis, we considered a univariate analysis of variance (ANOVA) to assess effects of factor group (Sz, BP, HC), and followed-up these results with two-tailed T-Tests testing each group against another one. (Fig. 1).

### 3. Results

We found a significant effect of group on the BrainAGE score (ANOVA, p = 0.009). Mean values of BrainAGE score for total samples and split by gender are given in Table 1. Post hoc T-Tests showed significant differences schizophrenia patients and healthy controls (p = 0.01287), as well as between schizophrenia patients and bipolar disorder patients (p = 0.0097), and in both cases, schizophrenia patients had a higher mean of the BrainAGE score. There was no difference between bipolar disorder patients and healthy controls (p = 0.34). An additional analysis of gender is given in Fig. 2.
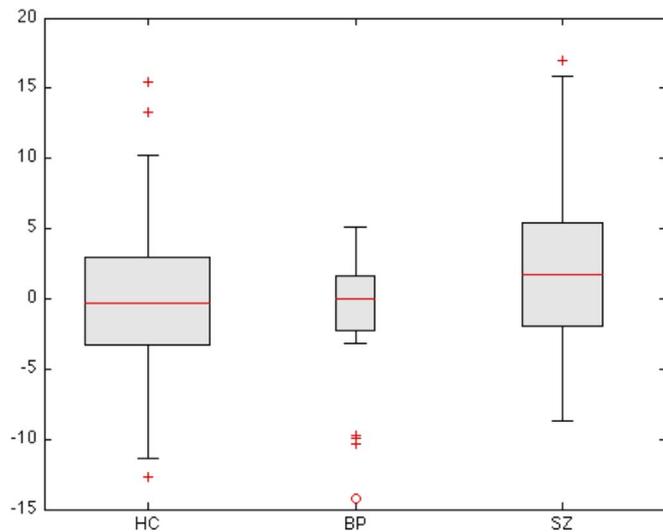
**Fig. 1.** Box-plot of BrainAGE scores in years (x-axis) in healthy controls (HC), bipolar disorder patients (BP), and schizophrenia patients (SZ) with significant group effect (ANOVA, p = 0.009), and schizophrenia patients showing higher BrainAGE scores than either HC or BP.

**Table 1**
Mean values (and SD) of BrainAGE score in schizophrenia patients, bipolar disorder patients, and healthy controls (total and split by gender).

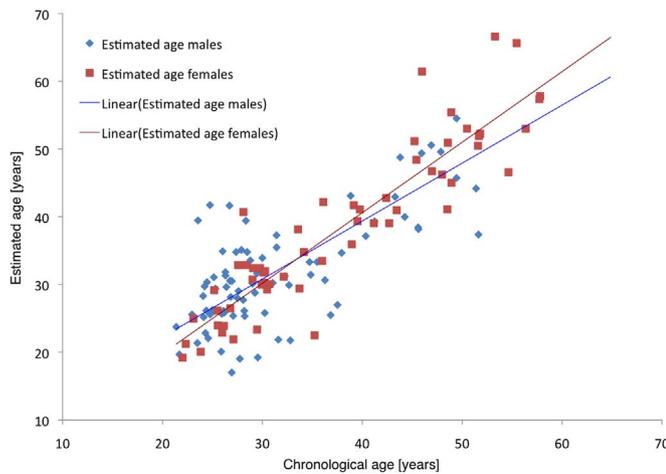| group | Total sample | Male subjects | Female subjects |
|---|---|---|---|
| schizophrenia | 2.56 (6.00) | 3.37 (6.75) | 1.07 (4.13) |
| bipolar disorder | −1.25 (4.63) | −1.85 (6.09) | −0.76 (3.17) |
| healthy controls | −0.22 (5.57) | −0.93 (5.26) | 0.71 (5.90) |



**Fig. 2.** Scatter plot of gender effects on BrainAGE score.

## 4. Discussion

Our findings support the hypothesis that accelerated brain aging is evident from structural imaging in schizophrenia, and that this seems to be relatively specific, as we did not find a similar change in a subgroup of psychotic bipolar disorder patients. This not only corroborates previous initial findings on similar metrics in schizophrenia (Koutsouleris et al., 2014), but also extends them to test the comparison with another psychotic disorder with a similar clinical phenotype.

Most previous studies of morphometry in schizophrenia vs. bipolar disorder have used standard voxel-based morphometry to compare each brain region (or rather voxels) separately, resulting in studies on the pattern of brain structural deficits compared to healthy controls (Maggioni et al., 2016). There is some heterogeneity across studies, but

more importantly, these studies have mostly focused on the regional differences and overlaps, rather than on issues like neurodevelopmental vs. progressive changes.

Although schizophrenia has been conceptualised as a neurodevelopmental disorder, and this remains the major research paradigm, our findings add to the current research by providing additional support for a progressive component (Kochunov and Hong, 2014). It should be stressed that this is not necessarily an indication of a neurodegenerative process. As recent findings indicate there is an overlap of structural age-related changes in physiological aging with those seen in major psychiatric disorders including schizophrenia (Douaud et al., 2014). While this would suggest that accelerated aging might be inherent to several psychiatric disorders, our findings suggest relative specificity for schizophrenia as compared to a subgroup of bipolar patients. This subgroup was selected to be similar in many phenotypic aspects, including early disease onset and psychotic symptoms. Hence, the mere diathesis for psychosis does not seem sufficient to explain our findings.

Several recent studies have suggested accelerated brain aging in schizophrenia. A most recent study using longitudinal MRI data and a support vector regression approach found evidence for a difference between estimated brain age and chronological age, in particular during the first years after disease onset (Schnack et al., 2016). Similarly, there has been evidence for such effects in white matter, with a most recent study showing not only reductions of fractional anisotropy (FA), but also a steeper age-related decline in patients as compared to healthy controls (Kochunov et al., 2016). A functional MRI study using resting state data found evidence for an age-related decline in the local efficiency of a fronto-parietal and a cingulo-opercular network, which would support a functional impact on particular networks (Sheffield et al., 2016).

There are several explanations for accelerated aging, both neuronal and systemic. The latter include effects induced by conditions like diabetes, which has been shown to affect brain aging in the elderly, as demonstrated by BrainAGE scores (Franke et al., 2013). While none of our patients or controls suffered from diabetes, metabolic syndrome is more prevalent in patients with schizophrenia compared to the general population (Vancampfort et al., 2015), and its effects on brain aging deserve further study. Interestingly, there is also evidence for accelerated aging in non-neuronal tissue, as shown through analysis of telomere length in leukocytes (Czepielewski et al., 2016; Polho et al., 2015).

Limitations of our study include medication effects; however, these would be expected to affect certain regions, but not the entire brain. Also, narrowing down inclusion criteria for bipolar disorder patients resulted in a smaller cohort. Finally, we also need to consider that the accelerated aging process might affect only part of certain subgroups of schizophrenia patients (Nenadic et al., 2012).

Taken together, our findings challenge a pure neurodevelopmental model, suggesting that the pathogenesis of schizophrenia might involve several stages including abnormal development as well as aging.

## Acknowledgements

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