Brain maturation: Predicting individual BrainAGE in children and adolescents using structural MRI

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Introduction

Human brain development involves highly coordinated and sequenced events characterized by both progressive (e.g., cell growth and myelination) and regressive (e.g., synaptic pruning) processes (Silk and Wood, 2011). Especially with the advent of magnetic resonance imaging (MRI), cross-sectional as well as longitudinal neuroimaging studies contributed to a better understanding of healthy brain maturation. In addition, with the availability of automated computational methods for analyzing MRI data, such as voxel-based morphometry (VBM; Ashburner and Friston, 2000), it has become feasible to quantify and visualize structural brain changes in vivo (May, 2011) in truly healthy children, which effectively was not possible before (Giedd et al., 1996).

Volumetric MRI studies have reliably established the overall pattern of an initial rapid increase in total gray matter (GM) volume, followed by a phase of slower growth and, after reaching a peak in childhood, by a slow but continued reduction. In contrast, total white matter (WM) volume increases rapidly until the age of 10–15 years, with continued gain well beyond adolescence (Giedd et al., 1999; Groeschel et al., 2010; Silk and Wood, 2011). With the growing number of studies that have investigated both normal and abnormal brain changes with age, most major neuropsychiatric disorders are now thought to arise due to deviations from normal brain development during childhood and/or adolescence (Giedd et al., 2009; Paus et al., 2008). For some of these (e.g., childhood-onset schizophrenia or pediatric bipolar disorder),
early detection afforded by a brain maturation reference curve would be clinically relevant.

Recently, Dosenbach et al. (2010) emphasized the need of maturation curves for pediatric brain development to aid in the early detection of neurodevelopmental disorders. They reported how brain maturity across development can be predicted with functional connectivity MRI (fcMRI). Using fcMRI data of 238 healthy subjects (aged 7 to 30 years), they predicted a maturation curve that accounted for 55% of the sample variance. Given the clinical potential of such predictions, approaches that lead to accounted variances of even more than 55% would be highly attractive. At the same time, it would be desirable to keep the duration of image acquisition as short as possible due to the known difficulties of motion artifacts in pediatric MRI studies (Wilke et al., 2008; Yuan et al., 2009). Moreover, such approaches will maintain a high impact on clinical diagnosis and intervention only if they are less prone to measurement bias due to individual alertness and vigilance (Van Dijk et al., 2012).

Focusing on these facts, our group has recently developed a new approach based on structural MRI data that enables one to reliably estimate the brain age of any given subject (Franke et al., 2010). By employing kernel regression methods in a large training database, the complex multidimensional aging patterns across the whole brain are detected and aggregated to one single value (i.e., the estimated brain age). Consequently, although using only one MRI scan per subject, the degree of acceleration or deceleration of brain aging can be directly quantified in terms of years allowing a wide range of analyses and predictions on an individual level. In an exemplary analysis with elderly adults, this brain age estimation model showed its potential to provide clinically relevant information by reporting a statistically significant, positive deviation of 10 years between the estimated and chronological ages in patients with Alzheimer’s disease, indicating accelerated brain atrophy and underlining the diagnostic potential of such an approach.

In the present study we show the potential of our BrainAGE framework to reliably predict structural maturity levels of brains from healthy children and adolescents ranging between 5 and 18 years based on one structural MRI scan per subject. Further, the age estimation framework will be exemplarily applied to a clinical sample of adolescents born preterm. We hypothesize that the group with a very low gestational age (GA~27 weeks) would have a significantly lower estimated brain age than the group with a higher gestational age (GA~29 weeks) due to decelerated brain maturation, which is presumed to be caused by the extremely premature birth status.

Methods

Subjects/database

Data used in the preparation of this article were obtained from the Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development. This multisite study of typically developing children and adolescents was conducted by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Evans, 2006). We used structural MRI data from objective 1, which included 432 healthy children and adolescents of either sex aged 5–18 years (one T1-weighted image per subject). As data quality interfered with data processing (see Image processing), the data of a total of 38 subjects was excluded, leaving a final sample of 394 subjects that were included in the present study.

Image acquisition

Images were obtained in six different sites on 1.5 T systems from either General Electric (GE) or Siemens Medical Systems (Siemens) using a 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence with the following parameters: TR=22–25 ms, TE=10–11 ms, excitation pulse=30°, refocusing pulse=180°, orientation: sagittal, field of view: AP=256 mm; LR=160–180 mm (whole-head coverage), and in-plane resolution=1×1×1 mm, where the maximum number of slices on the GE scanners was 124, and hence the slice thickness was 1.5 mm (Siemens: 1 mm).

Image processing

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). All T1-weighted images were corrected for bias-field inhomogeneities, then spatially normalized and segmented into GM, WM, and cerebrospinal fluid (CSF) within the same generative model (Ashburner and Friston, 2005). The segmentation procedure was further extended by accounting for partial volume effects (Tohka et al., 2004), by applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997), and by using a hidden Markov Random Field model (Cuadra et al., 2005), as described previously (Gaser, 2009).

In order to avoid introducing a systematic bias into the segmentation routine by using the standard adult reference data (Wilke et al., 2003), the Template-O-Matic toolbox (Wilke et al., 2008) was used within the unified segmentation framework to generate a sample-specific template. Thus, tissue segmentation does not rely on prior information maps, but solely on voxel intensity. This novel approach has already demonstrated robustness of the segmentation when handling MRI data from children (Altaye et al., 2008; Smith et al., 2011; Wilke et al., 2008). Since the removal of the prior tissue information makes the algorithms slightly less robust when confronted with lower quality input data (Wilke et al., 2008), all segmentation results were screened visually by one experienced rater (CG). The result was considered inadequate in 38 subjects.

Following the sequence proposed by Franke et al. (2010), the images were processed with affine registration and smoothed with 8 mm full-width-at-half-maximum (FWHM) smoothing kernels. Spatial resolution was set to 8 mm. Data reduction was performed by applying principal component analysis (PCA), utilizing the “Matlab Toolbox for Dimensionality Reduction” (http://ict.ewi.tudelft.nl//Lvandermaaten/Home.html).

Relevance vector regression (RVR)

Relevance vector machines (RVM) were introduced by Tipping (2000) as a Bayesian alternative to support vector machines (SVM) for obtaining sparse solutions to pattern recognition tasks. The main idea behind traditional SVMs is the transformation of training data from an input space into a high-dimensional space – the feature space – via a mapping function Φ (Bennett and Campbell, 2003; Schölkopf and Smola, 2002). For the purpose of classification, the hyperplane that best separates the groups is computed within this feature space, resulting in a nonlinear decision boundary within the input space. The best separating hyperplane is found by maximizing the margin between the two groups. The data points lying on the margin boundaries are called support vectors since only these are used to specify the optimal separating hyperplane. For the case of real-valued output functions (rather than just binary outputs as used in classification), the SV algorithm was generalized to a regression estimation (Bennett and Campbell, 2003; Schölkopf and Smola, 2002). In support vector regression (SVR), a function that fits as many data points as possible has to be found. Analogous to the margin in classification, the regression line is surrounded by a tube. Data points lying within that tube do not influence the course of the regression line. Data points lying on the edge or outside that tube are called support vectors.
In contrast to the support vectors in SVM, the relevance vectors in RVM represent the prototypical examples within the specified classification or regression task, instead of solely representing separating attributes. Furthermore, severe overfitting associated with the maximum likelihood estimation of the model parameters was avoided by imposing an explicit zero-mean Gaussian prior (Ghosh and Mujumdar, 2008; Zheng et al., 2008). This prior is a characteristic feature of the RVM, and its use results in a vector of independent hyperparameters that reduces the data set (Faul and Tipping, 2002; Tipping, 2000; Tipping and Faul, 2003). Therefore, in most cases the number of relevance vectors is much smaller than the number of support vectors. In SVR, some additional parameters have to be determined or statistically optimized (e.g. with cross-validation loops) in order to control for model complexity and model fit. To control the behavior of the RVR, only the type of kernel has to be chosen. All other parameters are automatically estimated by the learning procedure itself. More details can be found elsewhere (Bishop, 2006; Schölkopf and Smola, 2002; Tipping, 2000).

Estimating BrainAGE

The BrainAGE framework utilizes RVR (Tipping, 2001) and was recently developed to estimate individual brain ages based on T1-weighted images (Franke et al., 2010). In general, the model is trained with preprocessed whole brain structural MRI data of the training sample. Subsequently, the brain age of a test subject can be estimated using the individual tissue-classified MRI data, aggregating the complex multidimensional aging pattern across the whole brain into one single value (Fig. 1A). The difference between the estimated and true chronological ages will reveal the individual brain age gap estimation (BrainAGE) score: the closer the estimated and the chronological ages are, the smaller is this value (Fig. 1B).

Within this study, the framework was applied using the linear combination of preprocessed GM and WM images. Since a leave-one-out approach is widely used in machine learning approaches and has been shown to provide a conservative estimate of a predictor’s true accuracy (Dosenbach et al., 2010), model training and individual brain age estimation were done using leave-one-out-loops (i.e., the preprocessed GM and WM images of all subjects, except one, were used for training). Subsequently, the brain age of the left-out subject was estimated. PCA was performed on the training sample and the estimated parameters were subsequently applied to the test subjects. For training the model as well as for predicting individual brain ages, we utilized “The Spider” (http://www.kyb.mpg.de/bi/people/spider/main.html), a freely available toolbox running under MATLAB. For more detailed information please refer to Franke et al. (2010).

Statistical analysis

First, volumes of GM, WM, CSF, as well as total brain volume (TBV) were analyzed to explore the volume changes over development within this sample. To evaluate the accuracy of the age estimations, Pearson’s linear correlation coefficient as well as the mean absolute error (MAE) between each subject’s age and the age estimated by the regression model was established. Then, the brain maturation curve, including the 95% confidence interval for the prediction of brain age, was calculated using a regression model with a quadratic fit. To exclude unintended amplification effects while using coarse smoothing (i.e., 8 mm), training and testing of the BrainAGE framework were repeated with GM and WM images that were smoothed with a 4 mm FWHM smoothing kernel. Again, the accuracy of the new age estimations was evaluated using Pearson’s linear correlation coefficient and MAE.

To assess the stability of BrainAGE estimation across different MRI scanner sites, age estimation was repeated for each of the six scanner sites separately. In other words, the BrainAGE model was trained with the data of five scanner sites and then applied to the data of the one left out in training. Pearson’s linear correlation coefficient and the MAE between each subject’s chronological age and the estimated age were calculated for each of the six scanner sites.

To exemplarily show the potential of the BrainAGE framework to differentiate between age groups, we divided the final 394 subjects into five age groups; each group spanned three consecutive years of age (Table 1). That is, preschool childhood (5–7 years), late childhood (8–10 years), early adolescence (11–13 years), middle adolescence (14–16 years), and late adolescence (17–19 years). The estimated brain ages as well as the volumes of GM, WM, CSF, and TBV were compared between these five age groups using analysis of variance (ANOVA). Post-hoc analyses (with Bonferroni adjustment to compensate for multiple comparisons) were conducted to explore significant group differences (p < 0.05).

To further show the potential of the BrainAGE estimation framework with respect to modeling healthy brain maturation, receiver operating characteristics (ROC) for discriminating children (5–10 years) from adolescents (13–18 years) were computed for estimated brain age, GM volume, WM volume, CSF volume, and TBV, in order to demonstrate whether the brain age score adds information above and beyond that derived from tissue volumes alone. All statistical testing was performed using MATLAB.

Fig. 1. The BrainAGE concept. A: The model of healthy brain aging is trained with preprocessed structural MRI data of a training sample (green). Subsequently, the individual brain ages of previously untested subjects are estimated, based on their MRI data (red). B: The difference between the estimated and chronological age results in the BrainAGE score. Consequently, negative BrainAGE scores indicate delayed brain maturation (red area). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Panel A picture is modified from Schölkopf and Smola (2002).
Since multivariate pattern recognition techniques such as RVR are shown in Fig. S1 for GM and Fig. S2 for WM.

When the BrainAGE model was trained with the data of five MRI scanner sites and then applied to the one left out in training, estimation accuracy proved to remain stable across all scanner sites. The correlations between the chronological and estimated ages ranged between r = 0.90 and r = 0.95 (p < 0.001). The MAEs ranged between 1.1 and 1.3 years (Table 3).

When exemplarily comparing the five predefined age groups (i.e., preschool childhood, late childhood, early adolescence, middle adolescence, and late adolescence), the estimated brain ages differed between the age groups (F = 439.9; p < 0.001; Table 1), with post-hoc t-tests resulting in differences (p < 0.05) between all five age groups (Fig. 4). For volumes of GM, WM, CSF, and TBV the ANOVA also resulted in significant differences (Table 1), but post-hoc t-tests did not result in differences between all of the five age groups.

Based on these encouraging results, we conducted an exemplary ANOVA to explore group differences with respect to estimated brain ages between neighboring ages (i.e., 5-years old vs. 6-years old, etc.). Again, the results showed differences in estimated brain ages between neighboring age groups (F = 208.9; p < 0.001; Fig. S3), suggesting the existence of specific, and therefore identifiable, age-dependent brain maturation patterns.

Binary classification of individuals as either children (aged 5–10 years) or adolescents (aged 13–18 years), based on their estimated brain age, was 97% accurate (sensitivity = 98%, specificity = 96%). The area under the ROC curve (AUC), which is also known as the c-statistic or c-index, shows the quality of the classification, with 1.0 indicating a perfect discrimination and 0.5 indicating a result obtained by chance only. As demonstrated in Fig. 5, AUC was 0.996 when discriminating children and adolescents using the estimated brain ages. In contrast, when using CSF volume to classify individuals as either children or adolescents, the accuracy rate was 73% and AUC was 0.78. Other parameters were even less sensitive (i.e., accuracy: GM volume = 63%; WM volume = 72%; TBV = 59%; AUC: GM volume = 0.65; WM volume = 0.70; TBV = 0.61).

Finally, the BrainAGE framework was exemplarily applied to structural MRI data of preterm-born adolescents, aged between 12 and 16 years at the time of the MR scan. The BrainAGE scores differed significantly (p < 0.01; df = 23) between group GA < 27 (i.e., subjects who were born before the end of the 27th week of gestation) and group GA > 29 (i.e., subjects who were born after the end of the 29th week of gestation) and revealed the following means (SD): GA < 27 = −1.96

an exemplary illustration, the most important features (i.e., the importance of voxel locations for regression with age) that were used by the RVR are shown in Fig. S1 for GM and Fig. S2 for WM.

Table 2

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Mean (SD) age at gestation (weeks)</th>
<th>Mean (SD) age at MR scan (years)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>25.4 (0.8)</td>
<td>14.3 (1.4)</td>
</tr>
<tr>
<td>15</td>
<td>30.3 (0.7)</td>
<td>14.7 (1.5)</td>
</tr>
</tbody>
</table>

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(0.68) years, GA > 29 = −0.40 (1.50) years (Fig. 6). Although the mean difference in the gestation age between both groups was only 5 weeks, these results show a systematically and dramatically lower BrainAGE score in the group of adolescents who were born extremely preterm, implying delayed brain maturation.

In both groups, prediction accuracy was high resulting in correlation coefficients between the estimated and chronological ages of $r = 0.89$ ($p < 0.001$) and $r = 0.75$ ($p < 0.01$) for the groups GA < 27 and GA > 29, respectively. After adjusting the estimated ages to a zero mean, MAE would result in 0.5 years and 1.1 years, respectively. Again the BrainAGE framework proved to provide reliable estimations even with entirely new data that differed from the training data by scanner and by scanning parameters.

### Discussion

The present study provides a sensitive and easy-to-use reference curve for structural brain maturation during childhood and adolescence. The novel BrainAGE concept adopted here combines the complex multidimensional maturation pattern across the whole brain into one single value. Using structural MRI data of 394 healthy subjects (aged 5 to 18 years) acquired on six different scanners, we predicted a maturation curve that accounted for 87% sample variance. Furthermore, a strong stability of the estimated brain ages across different MRI scanner sites was demonstrated. The framework showed exemplary predictive value, classifying individuals as children (age range 5–10 years) or adolescents (age range 13–18 years) with 97% accuracy. Moreover, the predicted brain age demonstrated its potential to differentiate between all age groups (i.e., preschool childhood, late childhood, early adolescence, middle adolescence, and late adolescence) and even between neighboring ages. Finally, the BrainAGE framework exemplarily showed its potential to provide clinically relevant information. With a mean difference in BrainAGE scores of −1.6 years between the early preterms and the late preterms, the adolescents who were born extremely preterm showed clear signs of delayed brain maturation.

![Fig. 2. Brain tissue and brain volume trajectories across development. The change of individual tissue volumes across development with 95% confidence intervals (light lines) of the quadratic fits (bold lines) for GM (A), WM (B), CSF (C), and TBV (D).](http://dx.doi.org/10.1016/j.neuroimage.2012.08.001)
Several structural MRI studies of brain maturation have already shown the age-dependent development of a variety of brain measures in children and adolescents. Although the human brain has reached 95% of its maximum size by the age of six, the cortical and subcortical components of the brain still change dramatically during childhood and adolescence (Lenroot and Giedd, 2006). While GM volumes follow regionally-specific inverted U-shaped developmental curves, with volumes peaking at different times across the different lobes, WM volume changes were thought to be more linear and less variant across regions (Giedd et al., 1999; Lenroot and Giedd, 2006). Recently, Lebel and Beaulieu (2011) showed significant nonlinear development trajectories also for WM, with maturation being complete by late adolescence for projection and commissural tracts, but association tracts maturing well beyond adolescence. Furthermore, GM and WM development during childhood and adolescence appeared to reveal regionally specific, age-dependent variations (Wilke and Holland, 2003). Taken together, brain maturation is not only a very complex multidimensional but also a highly variable process. In the light of the multitude of these brain changes, it is remarkable that the concept of brain age, which was not included during the training of the algorithm, which was not included during the training of the algorithm, can achieve an even higher accuracy, although the required multidimensional dataset from each subject would constitute a clear drawback. Importantly, structural MRI is already the imaging modality of choice in most centers and especially with children. Moreover, structural imaging avoids the possible bias due to individual differences in aliveness and vigilance, a severely confounding factor when using functional MRI (Van Dijk et al., 2012). Luckily, given the novel results of the BrainAGE algorithm, the aforementioned need for multidimensional data is no longer pressing.

Fig. 4. Age group differentiation using BrainAGE. Mean of estimated brain ages by predefined age groups. Error bars depict the standard error of the mean (SEM). Post-hoc t-tests resulted in significant differences between all five age groups (p < 0.05; red lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Interestingly though, these accelerated GM deficits are not likely to be the result of WM overgrowth because WM growth itself was shown to be decelerated by about 2% in patients with childhood-onset schizophrenia compared to healthy controls (Gogtay et al.; Gogtay and Thompson, 2010; Paus et al., 2001).

Using only one structural MR image per subject, the maturation curve predicted by the BrainAGE framework accounted for 87% of the sample variance and proved its potential to recognize delayed brain maturation in a clinical sample. Hence, our novel BrainAGE framework is a valuable complement to Dosenbach’s maturation index of functional connectivity that accounted for 55% sample variance (Dosenbach et al., 2010). It is conceivable that the combination of structural and functional image data might achieve an even higher accuracy, although the required multidimensional dataset from each subject would constitute a clear drawback. Importantly, structural MRI is already the imaging modality of choice in most centers and especially with children. Moreover, structural imaging avoids the possible bias due to individual differences in aliveness and vigilance, a severely confounding factor when using functional MRI (Van Dijk et al., 2012). Luckily, given the novel results of the BrainAGE algorithm, the aforementioned need for multidimensional data is no longer pressing.

An additional challenge when establishing a clinically valuable reference curve for structural brain maturation is developing an algorithm, which allows combining MRI data from different scanners. When applying the estimation procedures to MRI data from a scanner, which was not included during the training of the algorithm, the BrainAGE framework demonstrated strong stability of the estimated brain age (r = 0.90–0.95). Even with entirely new data that differed from the training data not only by scanner but also by scanning parameters, the BrainAGE framework proved to provide reliable estimates plus clinically valuable information. Thus, our results are in line with those of Klöppel et al. (2008), indicating that the effect of the scanner parameters is sufficiently different from that of the aging process and that linear RVR generalizes well across different scanners.

However, given the nature of data included in this study, our conclusions are limited to MRI data obtained with 1.5 T field strengths. As already shown previously (Franke et al., 2010), numerous variables have the potential to influence the accuracy of age prediction, such as the number of subjects constituting the training sample (which added most on variability), various parameters pertaining to data acquisition (e.g., field strength, scanning sequence) and data preprocessing (e.g., registration, smoothing), as well as the chosen approach to reduce data dimensionality (e.g. PCA). Therefore, these aforementioned aspects need to be carefully controlled in future studies. Future work will further explore the influences of varying parameters in data acquisition on prediction accuracy.

In order to facilitate usability in a clinical routine, the algorithm should work fast and fully automatic. As already indicated in Franke et al. (2010), a fairly rapid preprocessing of the MRI data can be achieved by performing affine registration with a large smoothing kernel (e.g., 8 mm). Even in estimating the brain maturation in children and adolescents a coarse spatial resolution (e.g., 8 mm) can be used without losing estimation accuracy. Unlike approaches that make use

### Table 3

<table>
<thead>
<tr>
<th>Scanner site (as test sample)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>53</td>
<td>76</td>
<td>71</td>
<td>75</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>4.8–17.8</td>
<td>4.8–18.5</td>
<td>5.1–18.6</td>
<td>4.8–18.0</td>
<td>5.0–17.8</td>
<td>62–18.4</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>10.7 (4.0)</td>
<td>10.5 (3.8)</td>
<td>11.8 (4.1)</td>
<td>10.4 (4.0)</td>
<td>9.8 (3.8)</td>
<td>10.8 (3.4)</td>
</tr>
<tr>
<td>r</td>
<td>0.95</td>
<td>0.92</td>
<td>0.92</td>
<td>0.93</td>
<td>0.91</td>
<td>0.90</td>
</tr>
<tr>
<td>MAE (years)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
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</tbody>
</table>

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To summarize, we demonstrated the potential of the BrainAGE framework to reliably predict brain maturity in children and adolescents and to provide a clinically sensitive as well as easy-to-use reference curve of healthy brain maturation. We have also shown that this method can be used across different scanners (see also Franke et al., 2010), which is an important prerequisite for use in clinical routines. Given that the BrainAGE framework is validated as well as fast and easy to use, this method holds great potential for application in daily clinical routine, especially since brain imaging has become part of the standard diagnostic work-up for many developmental neuropsychiatric disorders. Nevertheless, combining different imaging techniques holds the potential to further improve existing analysis streams (e.g., Dosenbach et al., 2010; Franke et al., 2010), and combining structural and functional connectivity imaging may reveal a valuable biomarker in the future to guide early detection in the prodromal phase of diseases.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.08.001.

Disclosure

The authors report no conflict of interest.

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This manuscript reflects the views of the authors and may not reflect the opinions or views of the Brain Development Cooperative Group Investigators or the NIH. A listing of the participating sites in the NIH MRI study of normal brain development and a complete listing of the study investigators can be found at the website of the data coordinating center at https://nihpd.crbs.ucsd.edu/nihpd/info/participating_centers.html.

Fig. 5. ROC curves of subject classification using BrainAGE. ROC curves of individual subject classification as either children (aged 5–10 years) or adolescents (aged 13–18 years) based on estimated brain age (red; AUC = 0.99), GM volume (dark blue; AUC = 0.65), WM volume (light blue; AUC = 0.74), and TBV (green; AUC = 0.61). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. BrainAGE scores in preterm-born adolescents. Shown are box plots with BrainAGE scores (in years) for those adolescents who were born before the end of the 27th week of gestation (mean = −2.0) vs. those who were born after the end of the 29th week of gestation (mean = −0.4). The gray boxes contain the values between the 25th and 75th percentiles of the samples, including the median (dashed line). Lines extending above and below each box symbolize data within 1.5 times the interquartile range (outliers are displayed with a +). The width of the boxes depends on the sample size. Student’s t-test resulted in a significant difference between both groups (p < 0.01; red lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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