Published in final edited form as:

Brain Struct Funct. 2020 November ; 225(8): 2431–2445. doi:10.1007/s00429-020-02132-4.

Developmental Score of the Infant Brain: Characterizing Diffusion MRI in Term- and Preterm-born Infants

Dan Wu¹, Linda Chang^{2,3}, Thomas M. Ernst⁴, Brian S. Caffo⁵, Kenichi Oishi⁶

¹Key Laboratory for Biomedical Engineering of Ministry of Education, College of Biomedical Engineering & Instrument Science, Zhejiang University, Hangzhou, China

²Departments of Diagnostic Radiology and Nuclear Medicine, and Neurology, University of Maryland School of Medicine, Baltimore, Maryland, United States

³Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

⁴Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, Maryland, United States

⁵Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, United States

⁶Russell H. Morgan Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

Abstract

Large-scale longitudinal neuroimaging studies of the infant brain allow us to map the spatiotemporal development of the brain in its early phase. While the postmenstrual age (PMA) is commonly used as a time-index to analyze longitudinal MRI data, the nonlinear relationship between PMA and MRI data imposes challenges for downstream analyses. We propose a mathematical model that provides a Developmental Score (DevS) as a data-driven time-index to characterize the brain development based on MRI features. 319 diffusion tensor imaging (DTI) datasets were collected from 87 term-born and 66 preterm-born infants at multiple visits, which were automatically segmented based on the JHU neonatal atlas. The mean diffusivity (MD) and fractional anisotropy (FA) in 126 brain parcels were used in the model to derive DevS. We demonstrate that transforming the time-index from PMA to DevS improves the linearity of the longitudinal changes in MD and FA in both gray and white matter structures. More importantly, regional developmental differences in DTI metrics between preterm- and term-born infants were identified more clearly using DevS, e.g. 79 structures showed significantly different regression patterns in MD between preterm- and term-born infants, compared to only 27 structures that

Terms of use and reuse: academic research for non-commercial purposes, see here for full terms. <https://www.springer.com/aam-terms-v1>

Correspondence to: Kenichi Oishi, M.D., Ph.D. Department of Radiology, Johns Hopkins University School of Medicine, Traylor 217, 720 Rutland Ave, Baltimore, MD 21215, koishi2@jhmi.edu, Phone: (410) 955-4221 Fax: (410) 614-1948.

Publisher's Disclaimer: This Author Accepted Manuscript is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication but has not been copyedited or corrected. The official version of record that is published in the journal is kept up to date and so may therefore differ from this version.

showed group differences using PMA as the index. Therefore, the DevS model facilitates linear analyses of DTI metrics in the infant brain, and provides a useful tool to characterize altered brain development due to preterm-birth.

1. Introduction

Brain development is a highly dynamic and intricate process that lays the foundation for all aspects of brain function and mental health across the lifespan. MRI studies of brain development have provided unprecedented insights regarding brain structural and functional development, and allow noninvasive monitoring of developmental disorders in the early phases of life. Much of our knowledge regarding early brain development has been generated or is being validated by large-scale brain MRI studies in children and adolescents (Howell et al., 2018; Makropoulos et al., 2018);(Jernigan et al., 2016); (Brain Development Cooperative, 2012); (Di Martino et al., 2017; Hagler et al., 2019; Zuo et al., 2017), and the majority of them have longitudinal designs with multiple visits from different subjects. Analyzing data from longitudinal neuroimaging studies is challenging for several reasons.

In early infancy, postmenstrual age (PMA) is often used as a time index to assess brain development. PMA is typically determined by the mother's first day of the last menstrual period or the first fetal ultrasound. It is a coarse measurement to index the overall developmental status of the fetus, which is not specific to the brain and may not reflect abnormal neurodevelopment. More importantly, the relationships between PMA and structural and functional MRI markers follow non-linear trajectories (Barkovich et al., 1988; Knickmeyer et al., 2008; Mukherjee et al., 2002), imposing challenges in characterizing developmental patterns or standardizing the relationships for group comparisons. Different non-linear functions have been proposed to model these trajectories. For example, Giedd et al. used a second-order polynomial to describe the morphological development of the corpus callosum during childhood and adolescence (Giedd et al., 1999b). Dean et al. used an exponential function to model changes in myelin content in the white matter during early childhood (Dean et al., 2015), while Sadeghi et al. proposed the Gompertz function to characterize the developmental changes of DTI metrics of white matter from birth to 2-year-old (Sadeghi et al., 2013). It is difficult to theoretically identify a valid mathematical formulation to characterize these nonlinear patterns, in particular since the non-linearities are highly variable, depending on the brain region, MRI feature, and the developmental stage under investigation. For instance, substantial regional heterogeneity was found in the developmental trajectories with higher non-linearities in the cerebral cortex compared to the subcortical gray matter and white matter (Giedd et al., 1999a; Ostby et al., 2009). Further complicating matters, since individuals enter studies at different developmental stages and their brains grow at different rates, analyses of such data need to take into account the inter-individual variation between the PMA and neurodevelopmental status.

In order to address these challenges, we propose a mathematical model that generates an underlying developmental score, which we designate as DevS, as a data-driven time index of brain development that linearizes the relationship between the MRI marker and the time index. The concept of DevS shares similarity with the commonly known "brain age" as a

brain maturation index based on structural and/or functional MRI measures (Brown et al., 2012; Dosenbach et al., 2010; Franke et al., 2012), but DevS has its unique purpose. The brain age typically has the same scale as the PMA; in normal development, it should be the same as the PMA, so the nonlinear relationship still holds between brain age and MRI data. Conversely, the DevS measure aims to align longitudinal data from different individuals and to enforce a global linear relationship with MRI measures, which would facilitate downstream statistical analyses.

Here, we developed the DevS model in the setting of a longitudinal study of term- and preterm-born infants during early infancy (Akazawa et al., 2016; Chang et al., 2016a; Wu et al., 2017). Adverse impacts of preterm birth on neurological outcomes have been studied extensively with neuroimaging and non-imaging approaches (Fryer et al., 2008; Ortibus et al., 2012; Van Braeckel et al., 2008; Volpe, 2009). Particularly, diffusion tensor imaging (DTI) (Basser et al., 1994) has played an important role in assessing the brain microstructural development in full-term and premature brains (Akazawa et al., 2016; Brown et al., 2012; Huppi et al., 1998; Mukherjee et al., 2001; Partridge et al., 2004; Saksena et al., 2008; Yap et al., 2013; Yoo et al., 2005; Zhang et al., 2005). Previous studies have found lower fractional anisotropy (FA) values and higher mean diffusivity (MD) in the preterm-born infants compared to their term-born peers (Anjari et al., 2007; Huppi et al., 1998; Rose et al., 2008; Thompson et al., 2011). For these immaturity born infants, the problem of using PMA to index their developmental processes becomes more evident compared to that in normal-developing brains. For instance, reported developmental changes due to preterm birth were 20–35% for MD (Anjari et al., 2007; Counsell et al., 2006; Huppi et al., 1998), depending upon the anatomical region-of-interest and the subject population. Hence, an effect size less than those reported might be hidden under the effects of individual variations, non-linearity in developmental trajectories, and inappropriate analytical approaches. We hypothesized that structures with mild alterations in the developmental trajectory could be more accurately detected using DevS as the time index.

In this work, we first introduce the rationale and mathematical formulation of the DevS model, and then investigate two key questions: 1) whether using the DevS can facilitate linear analysis of longitudinal and cross-sectional infant brain DTI measurements; 2) whether using the DevS can improve the identification of developmental differences between term- and preterm-born infants, compared to the commonly used PMA.

2. Methods

2.1 Participants

The longitudinal infant brain development study was performed on a 3T Siemens Trio scanner at the University of Hawaii and the Queen's Medical Center MR Research Center in Honolulu, HI, between the years of 2012–2016. Written and verbal informed consents were provided by the infants' parents or legal guardians, in accordance with the Cooperative Institutional Review Board (IRB) at the Queen's Medical Center and the University of Hawaii, as well as the IRB at the Johns Hopkins University. The parent(s) or caregiver(s) were interviewed by a trained study physician regarding the medical and family histories of each infant, and any substances or medications used by the mothers or any medical

complications during the pregnancy. The birth records of each infant was also requested and reviewed to corroborate with the histories obtained and for the infants' birth parameters (e.g., birth weight and length APGAR scores, etc.). Each infant was also examined by a trained study physician using a structured physical and neurological examination (the Amiel-Tison Neurological Examination at Term) at baseline and at each follow-up visit to ensure that the infant was healthy and well, meeting all developmental milestones, and fulfilled all study criteria (Chang et al., 2016b). Inclusion criteria for all infants at enrollment were: 1) healthy male or female neonate of any ethnicity; 2) within the first week of life (term-born group) or at term-equivalent age (preterm-born group); 3) parents were 18 years or older and could provide informed consents, with ability to fully understand English. All infants were healthy and normally developing and were excluded if they were or had: 1) required prolonged intensive care after birth (>7 days), except for the preterm-born infants; 2) intracranial hemorrhage; 3) neonatal hypoxic-ischemic encephalopathy; 4) known toxoplasmosis; other (syphilis, varicella-zoster, parvovirus B19); and rubella, Cytomegalovirus (CMV), and Herpes (TORCH) infections; 5) any cardiac, pulmonary or other major organ anomaly; 6) any chromosomal anomaly; 7) been diagnosed with a neurological or medical disorder; 8) exposed to excess alcohol prenatally (>3 drinks/month during the pregnancy) although social occasional alcohol use 3 drinks/month was allowed; 9) prenatally exposed to other substances (except for occasional alcohol, tobacco or methamphetamine), on a regular basis (including cannabis); 10) any contraindications for MR studies (e.g., metallic or electronic implants); 11) any confounding medical or neuropsychiatric disorders in the mother; 12) any significant brain lesions or MRI abnormalities identified by our board-certified Pediatric Neuroradiologist (D.L.); 13) poor quality scans due to excess motion or incorrect MR parameters. Based on these criteria, we initially excluded 56 participants due to the following reasons: excessive alcohol-exposure (>3 drinks/month, n=17), maternal poly-substance (n=2) or cocaine-dependency (n=1), HIV-infected mother taking zidovudine (n=1), prolonged (>1 week) neonatal intensive care in the term infants (n=6), incorrect MRI parameters (n=16), or incomplete (n=6) or unusable (n=9) DTI scans.

Note that the current study also included some MR scans from infants with some prenatal exposure to methamphetamine and/or tobacco (Chang et al., 2016b), but they all fulfilled the inclusion and exclusion criteria detailed above. We used a very low threshold of 1 gram of methamphetamine per pregnancy for methamphetamine-exposure, a threshold of 50 cigarettes (2.5 packs) per pregnancy for tobacco-exposure, and alcohol exposure 10 grams (e.g., a 12 oz. beer or 5.5 oz. of wine has 14 grams of alcohol) per pregnancy for alcohol-exposure to determine whether the infant was exposed to any of these substances.

2.2 MRI data

The infants were scanned during natural sleep without any sedation. A vacuum immobilization mat (Noras MRI Products, Hoechst, Germany) was used to swaddle the infant and to minimize infant motion, and infant earmuffs as well as head phones were used to attenuate the scanner noise. Pulse oximetry and pulse rate were monitored throughout the scan and at least one trained study physician was present for the entire visit and throughout the scan (additional details regarding infant preparation and quality control during the scan

are provided in the Supplementary Methods). Single-shot DTI scans were obtained with a field-of-view of 160×160 mm, matrix size of 80×80 , in-plane resolution of 2×2 mm, 40–50 axial slices with thickness of 2.5 mm, echo time of 106 ms, repetition time of 7–9 s, 12 diffusion directions with a b-value of 1000 s/mm^2 and a non-diffusion-weighted image, two repetitions, and a scan time of approximately 5 min.

In addition to the pre-excluded scans (see 2.1), four scans in the term-born group were excluded due to visible motion artifacts. After exclusion, DTI data from 87 term-born infants (gestational age at birth ≥ 37 weeks) and 66 preterm-born infants (gestational age at birth < 37 weeks) were used in this study. Each infant was followed-up with 1–4 longitudinal scans between postmenstrual ages of 37–57.5 weeks. In total, 169 longitudinal scans from term-born infants and 150 longitudinal scans from preterm-born infants were included in the analyses. Basic demographic and clinical characteristics of these infants at birth are summarized in Table 1 and the basic information of the infants at follow-up scans are provided in Table 2. PMA used in this study was determined based on the first day of the mother's last menstrual period.

2.3 DTI pre-processing

The diffusion-weighted images were first linearly registered to the non-diffusion-weighted image, followed by voxel-wise tensor fitting using DtiStudio (www.mristudio.org) (Jiang et al., 2006) to obtain MD and FA, with an automated outlier rejection function (Li et al., 2013) to reject slices with a relative fitting error of more than 3%. The individual FA and MD images were transformed to the JHU-neonate single brain DTI atlas (Oishi et al., 2011) through linear and nonlinear transformation with dual-channel (FA and MD) Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Christensen et al., 1996; Miller et al., 1993). Brains were parcellated into 126 ROIs, and mean MD and FA values in individual ROIs were used in the following analyses. Voxels with a MD threshold above $2.0 \times 10^{-3} \text{ mm}^2/\text{s}$ were excluded to remove the CSF contamination. Two of the authors (D.W. and K.O.) inspected all segmentation results, and no data were excluded due to registration/segmentation errors. The preprocessing steps are summarized in Supplementary Figure S1, and the 126 ROI names are provided in Supplementary Table S1.

2.4 Developmental score (DevS) model

The DevS model involves two components: the relationship between the DevS and the native time index PMA for each subject; and the relationship between the MRI marker and the DevS, similar to that used in the disease progression score model (Bilgel et al., 2016; Jedynak et al., 2012). The joint model is designed to find a subject-specific transformation between PMA and DevS based on the existing MRI data (e.g., DTI metrics across brain regions), which enforces a global linear relationship between DevS and the MRI markers. Mathematically, the non-linear model can be described in two steps.

$$s_{ij} = \alpha_i \cdot t_{ij} + \beta_i = \mathbf{q}_{ij}^T \mathbf{u}_i \quad \text{Equation 1 (subject-specific model)}$$

$$\mathbf{y}_{ij} = \mathbf{a} \cdot s_{ij} + \mathbf{b} + \epsilon_{ij} \quad \text{Equation 2 (biomarker trajectory model)}$$

where i and j refer to the j^{th} visit of subject i , s_{ij} and t_{ij} are the DevS and PMA of the i^{th} subject at the j^{th} visit, respectively, and α_i and β_i are the slope and intercept of the linear relationship between the DevS and PMA for the i^{th} subject. The vectors $\mathbf{u}_i = \begin{bmatrix} \alpha_i \\ \beta_i \end{bmatrix}$ and $\mathbf{q}_{ij} = \begin{bmatrix} t_{ij} \\ 1 \end{bmatrix}$ are simply used to represent s_{ij} as a vector equation. The parameters $\mathbf{a}$ and $\mathbf{b} \in \mathcal{R}^{K \times 1}$ are the slopes and intercepts for the linear relations between the K -dimensional feature vector $\mathbf{y}_{ij}$ and s_{ij} , and ϵ_{ij} is the observed noise. Vector $\mathbf{u}_i \sim \mathcal{N}_2(\mathbf{m}, \mathbf{V})$ is assumed to follow a bivariate normal distribution with mean $\mathbf{m}$ and covariance matrix $\mathbf{V}$. $\epsilon_{ij} \sim \mathcal{N}_K(\mathbf{0}, \mathbf{R})$ follows K -dimension normal distribution with mean $\mathbf{0}$ and covariance matrix $\mathbf{R}$. Here $K=126$ for MD measurements in 126 brain regions. Since Equation 2 has a subject-dependent coefficient slope and intercept (α_i and β_i), the transformation from t to s is locally linear (within each individual) but globally nonlinear across the entire population.

Optimization of the model involves estimation of model parameters $\boldsymbol{\theta} = [\mathbf{m}, \mathbf{V}, \mathbf{a}, \mathbf{b}, \mathbf{R}]$. An expectation–maximization (EM) approach (Bilgel et al., 2016; Dempster et al., 1976) was used to estimate $\boldsymbol{\theta}$, using the progscore toolkit (<https://www.nitrc.org/projects/progscore/>).

In addition, the DevS model obtained from a training dataset can be used to infer DevS of new subjects. Once $\boldsymbol{\theta}_{\text{training}}$ is obtained from the training data, the maximization step (M-step) of the EM algorithm can be skipped, and the estimation step (E-step) can be performed directly to derive $\mathbf{u}_{i,j(\text{test})}$ and $s_{i,j(\text{test})}$, based on $\boldsymbol{\theta}_{\text{training}}$ and the PMA ($t_{i,j(\text{test})}$) and MRI data ($\mathbf{y}_{i,j(\text{test})}$) of the test subjects, assuming the biomarker trajectories model is transferrable between the training data and new data. The modeling and parameter estimation were performed in Matlab (<https://www.mathworks.com>)

2.5 Model evaluation and statistical tests

We first examined the effectiveness of the DevS model in term-born infants. Model parameters were estimated based on MD measurements in 126 ROIs of the term-born infants. We evaluated the linearity between DevS and MD and that between PMA and MD in each ROI, using R^2 and root-mean-square (RMS) of the regressions. We also tested the model performance on FA measurements.

We then evaluated whether the model is useful in differentiating developmental differences between term-born and preterm-born infants. Since the range of PMA from 55–70 weeks contained relatively few scans ($n = 12$ and 17 in term- and preterm-born groups) and had a marked impact on the developmental trajectories, we excluded the data with PMA > 55 weeks in the group comparison. The term- and preterm-born infants were randomly separated into halves: dataset#1 including 44 term-born infants with 80 longitudinal scans and 33 preterm-born infants with 68 longitudinal scans and dataset#2 including the other 44 term-born infants with 76 longitudinal scans and 33 preterm-born infants with 65 longitudinal scans. Dataset#1 was used as the training data to derive the DevS model parameters $\boldsymbol{\theta}_{\text{training}}$, and then the trained model was applied to the testing dataset#2 to obtain the DevS of each individual. The training and testing datasets were then switched to repeat the procedure, i.e., dataset#2 was used for training and dataset#1 for testing.

In order to assess the developmental differences between the term- and preterm-born groups, we used a linear mixed effect model (LME) (Laird and Ware, 1982) with or without the group effect. Since the percentage of methamphetamine and tobacco was significantly higher in the term-born infants, we included these two factors as covariates in the regression analysis. Therefore, we compared

$$y_{ij} = a_0 + a_1 \cdot s_{ij} * g_i + a_2 \cdot m_i + a_3 \cdot d_i + h_i + e_{ij} \quad \text{Equation 3}$$

versus

$$y_{ij} = a_0 + a_1 \cdot s_{ij} + a_2 \cdot m_i + a_3 \cdot d_i + h_i + e_{ij} \quad \text{Equation 4}$$

using likelihood ratio tests, where g_i is the group indicator, m_i is the methamphetamine-exposure indicator, d_i is the tobacco-exposure indicator, h_i is the subject-specific intercept for the i^{th} subject, and e_{ij} is the error term for the j^{th} visit of the i^{th} subject. The term $s_{ij} * g_i$ accounts for the interaction between DevS and group effect.

Similarly, we evaluated the PMA-based regression patterns by comparing

$$y_{ij} = a_0 + a_1 \cdot t_{ij} * g_i + a_2 \cdot t_{ij}^2 * g_i + a_3 \cdot m_i + a_4 \cdot d_i + h_i + e_{ij} \quad \text{Equation 5}$$

versus

$$y_{ij} = a_0 + a_1 \cdot t_{ij} + a_2 \cdot t_{ij}^2 + a_3 \cdot m_i + a_4 \cdot d_i + h_i + e_{ij} \quad \text{Equation 6}$$

Note that a quadratic term t_{ij}^2 was added for PMA based regression to account for the non-linear relationship between PMA and MD/FA across subjects. The analyses were performed for each ROI measurement individually, followed by multiple comparison correction using the false discovery rate (FDR) (Benjamini and Hochberg, 1995). All statistical tests were performed in R (<https://www.r-project.org/>).

3. Results

We first demonstrated the validity of the DevS model, e.g., whether it could linearize the developmental trajectories by comparing the PMA-based and DevS-based developmental trajectories in the all term-born infants, and also characterized the regional brain development based on DevS in section 3.1. Then, we tested the utility of the DevS model for characterizing the difference between term- and preterm-born infants in section 3.2, by obtaining the DevS model based on a training data and then compared the developmental trajectories in the testing data.

3.1 DevS-based characterization of brain development in term-born infants

A DevS model was established using MD/FA measurements in 126 ROIs of the infant brains, according to section 2.4. Figure 1A shows the mapping relationship between PMA and DevS for all individuals, with DevS of 0 corresponding to PMA in the range of 40–45 weeks (neonatal period). A DevS of −1 indicated term age, and DevS of 1 and 2

corresponded to roughly 45–50 weeks and 50–55 weeks, respectively. Histograms of the subject-specific model parameters α_i 's and β_i 's showed a normal distribution among term-born infants (Figure 1B).

Linear regressions between MD and PMA (top row) and those between MD and DevS (bottom row) were plotted for several representative gray matter (GM, Figure 2A) and white matter (WM, Figure 2B) structures. As expected, the relation between MD and PMA did not follow ideal linear regression; for instance, data were scattered around the regression lines with relatively low R^2 , especially in GM structures. After transforming the time-index to DevS, the linearity of regression was improved with higher R^2 and lower RMS in almost all deep WM and cortical GM structures (Figure 3), indicating that the DevS model successfully linearized data from different individuals and enabled linear analysis in the downstream. A similar analysis was repeated for the FA measures, with similar results as those for MD. Specifically, the linearity between DevS and FA was better compared to that between PMA and FA, and the model was more effective in GM than in WM structures (Supplementary Figures S2 and S3). Note that the FA showed a fast increase with PMA in some cortical regions, possibly because the cortical ROIs defined in the JHU neonatal brain atlas include both the cortical GM and subcortical WM (Supplementary Figure S1).

We characterized the MD values in each structure at sequential developmental stages, based on the DevS. Figure 4A shows MD maps at DevS of -1 , 0 , 1 , and 2 . During early development (DevS = -1), the frontal cortex and major WM fiber tracts (commissural and projection fibers) had relatively high MD compared to the other brain regions, whereas at larger DevS, MD drastically decreased across the brain. Figure 4B reveals the rates of MD decrease with DevS in each brain region, characterized by the parameter α in the model. The greatest rates of MD decrease were observed in the anterior and superior corona radiata, superior longitudinal fasciculus, and posterior thalamic radiation (arrows in Figure 4B). Such linear characterization is appropriate only if the relation between the MRI marker and the time-index is linear.

3.2 DevS-based developmental differences between term-born and preterm-born infants

In order to assess the developmental differences between term- and preterm-born infants, we evaluated the relationship between MD and DevS in individual ROIs, as described in section 2.5. After training the model with dataset#1 (Method section 2.5), we obtained DevS for the other half of the data. In the testing data, the mapping relationship between PMA and DevS appeared to be different for the term- and preterm-born infants, e.g., the same PMA mapped to higher DevS in the term-born group compared to that in the preterm group (Figure 5A). Both of the subject-specific mapping parameters α and β revealed significant differences ($p < 0.001$ by unpaired t-test) between the two groups in the testing data (Figure 5B).

Correlations between DevS and MD, and between PMA and MD were shown for several major GM (Figure 6A) and WM (Figure 6B) structures, both in the term-born infants (blue dots) and the preterm-born infants (red dots) in the testing data. In these structures, the regression lines between term-born and preterm-born data can be separated more easily using the DevS-MD correlations, compared to those using the PMA-MD correlations. For example, compared to term-born infants, the preterm-born infants showed higher MD values

at low DevS and their MDs decreased faster with DevS. LME models were used to evaluate whether the regression lines were different between the two groups. 79 regions showed significant group differences when DevS was used as the developmental index ($p < 0.05$ after FDR correction), but only 27 regions showed significant group differences when PMA was used as the index ($p < 0.05$ after FDR correction). Color maps of differences in the regression slopes between groups (e.g., $|a_{\text{preterm}}| - |a_{\text{term}}|$; Figure 7A) reveal that the largest group differences occur in the superior and anterior corona radiata (SCR and ACR), superior longitudinal fasciculus, superior and middle frontal gyrus (SFG and MFG), and medial fronto-orbital gyrus (MFOG). The PMA-based analyses showed significant group differences in similar areas as those from DevS-based analyses, including the posterior limb of the internal capsule (PLIC), ACR, external capsule (EC), MFOG, and the lateral fronto-orbital gyrus (LFOG), but with smaller effect size as indicated by the color map in Figure 7B. Similarly, group differences in FA became more prominent with DevS based regression than those with PMA (Supplementary Figure S4). Areas showing significant group differences with DevS were widespread across the brain, with the largest differences in the SCR, ACR, anterior and posterior limbs of the internal capsule (ALIC and PLIC), tapetum, and the middle cerebellar peduncle (MCP) (Figure 7C). Conversely, with PMA-based analysis, the group differences were localized in SCR, PLIC, MCP, and the genu of the corpus callosum (Figure 7D).

We further validated the results by switching the training and testing sets. Using dataset#2 for training, 29 regions had significant group differences using PMA as the time index and 74 regions showed group differences using DevS as the index. Regions with group effects detected from the two tests with reversed training datasets showed a moderate overlap, with a Dice index of 0.62 for PMA-based analyses and 0.78 for DevS-based analyses. Note that for PMA-based analyses, no training-testing was required, and the group differences were tested in dataset#1 and dataset#2 separately.

4. Discussion

The MRI-based assessment of brain development with longitudinal and cross-sectional data is challenging for several reasons, including the lack of an objective index that quantifies brain maturation, the lack of methodology to account for subject variations, and non-linear developmental trajectories. This study aimed to address these challenges by introducing a new metric, the DevS, which can be considered an index of brain maturation, and is derived from the PMA and MRI features. The benefit of DevS is twofold. First, it transforms the unknown non-linear relation between PMA and MRI measures to a (globally) linear one. This is likely to facilitate downstream statistical analysis for quantification of developmental patterns across brain regions or group comparison. Second, the derivation of DevS takes into account the PMA and the MRI features of individual subjects, and hence, it accounts not only for the ambiguity of PMA, but also the individual variability due to the inclusion of subject-specific model parameters, similar to the random effect model.

We demonstrated the efficacy of the DevS model using DTI measurements during early infancy, when the brain develops most rapidly. The infant brain DTI data were processed using an atlas-based segmentation (Oishi et al., 2011), and the MD/FA values in 126 GM

and WM ROIs were used collectively in the DevS model. Since different infants entered the study at different PMA and their brains developed at different rates, the relationship between PMA and DTI metrics showed substantial variations, without clear linear or non-linear patterns. By transforming the time index from PMA to DevS, we achieved a global linear relationship between DevS and DTI metrics across subjects. Specifically, the data points fell tightly along the regression lines with higher R^2 and lower fitting errors. The improvement was observed across the brain, but was particularly pronounced in cortical GM regions where the MD/FA values showed large inter-subject differences. The improvement may result from the fact that the DevS model minimized or filtered individual variations by attributing them into the error term (Equation 2). This is beneficial if the goal is to detect anatomical variations due to abnormal brain development, while normal variations are not the primary interest.

Next, we tested whether the linearization and filtering effect of DevS model would help to identify developmental differences due to preterm-birth. The differences in the developmental trajectories were enhanced using DevS as time index; specifically, we observed faster temporal decreases in MD and increases in FA in the preterm-born group compared to the term-born group. This finding is in agreement with previous studies of preterm-born babies (Akazawa et al., 2016; Brossard-Racine et al., 2019; Gimenez et al., 2008) showing accelerated development is associated with preterm-birth, perhaps due to extra-uterine environmental stimuli (Als et al., 2004; Duffy et al., 1990). Brain abnormalities associated with preterm-birth have been reported in previous DTI studies (Anjari et al., 2007; Baldoli et al., 2015; Counsell and Boardman, 2005; Hasegawa et al., 2011; van Kooij et al., 2012), with the major findings pointing to the PLIC, CC, frontal WM, thalamic radiations, and widespread WM alternations, depending on the prematurity at birth, PMA, and whether WM injuries were present. The PMA-based analyses in our study found group differences in the PLIC and ACR, but the regional differences were relatively local compared to previous studies. A potential reason is that the current study included only healthy infants in both groups without evidence of brain injury at birth based on routine radiological examinations and without any delays in developmental milestones (Akazawa et al., 2016). The use of DevS made these differences more obvious, e.g., multiple central and cortical brain regions showed preterm-birth associated alterations. Further studies are required to evaluate the clinical correlates of these findings. Interestingly, we also found that the mapping relationship between PMA and DevS was altered in the preterm-born infants, who showed a lower α and higher β than the term-born infants. Taking the DevS as a data-driven index of brain maturation, the lower α (slope) may indicate slower brain maturation within a given period of postnatal development. This may also explain the faster change in DTI metrics in the preterm-born infants as the DevS axis was rescaled differently, compared to the term-born infants. The β (intercept) is more difficult to interpret since it corresponded to the DevS at PMA of 0.

One major limitation of our study is that the term-born group included both normal term-born infants and infants with prenatal exposure to adverse substances. We evaluated the potential effects of including substance-exposed infants. Since only the alcohol-exposed subgroup in the term-born infants had significantly lower gestational age and head circumference at birth compared to the unexplored subgroup, we excluded these infants and

repeated the analysis in 3.1. Supplementary Figure S5 compared the DevS models derived from all term-born infants ($n = 87$) with that from term-born infants without alcohol-exposure ($n = 58$). We found a high similarity between the model parameters, in terms of α , β , $DevS$, a , and b (Equation 1 and 2), e.g., the correlation coefficients were between 0.99–1.0, indicating that excluding the alcohol-exposed infants did not alter the DevS model. Nevertheless, we are aware that prenatal exposure to substances may adversely impact brain development. Several studies from our group and others have found altered brain development in selected brain regions due to prenatal tobacco, methamphetamine or excess alcohol exposure (Chang et al., 2009; Roos et al., 2015; Roussotte et al., 2011; Sowell et al., 2010). Therefore, the observed developmental differences between term and preterm groups might have been minimized due to the potential confounding effects of the higher proportion of prenatal substance-exposed infants in the term born group. This potential confounding effect may have been mitigated since we included the substance exposure information as covariates in the LME models.

There are also other limitations in the current study. Although we demonstrated the efficacy of DevS model with MD and FA data, many other MRI markers were not investigated. Due to the difficulty of segmenting neonatal brains (Shi et al., 2011; Weisenfeld and Warfield, 2009), morphological indices, such as cortical thickness, surface area, and sulcal depth were not analyzed. Furthermore, some advanced dMRI indices and microstructural analyses were not available because only 12 diffusion directions were acquired. Future extensions of the model to incorporate multiple MRI markers as a multivariate model are possible, similar to that performed in an adult imaging study (Bilgel et al., 2016; Jedynak et al., 2012). We chose an atlas-based ROI analysis approach in the current study, which reduced the dimension of the input data to the DevS model, while preserving the spatial information. Voxel-based analyses are also feasible for our DevS model; however, the spatial correlation between voxels needs to be corrected, either before or during the modeling (Bilgel et al., 2016). In addition, we used linear and quadratic regressions to analyze the PMA-based developmental trajectories, since there is no clear understanding or consensus regarding the appropriate type of nonlinear models, which are dependent on the brain regions and the developmental stages under investigation. Nevertheless, this is the first study to use the concept of developmental score, and validated its efficacy of linearizing the developmental trajectories of MRI measurements that would facilitate downstream analysis. The approach is technically transferrable to other age ranges, e.g., older infants and toddlers, given sufficient data to train the model in the desired age range.

5. Conclusion

We propose the DevS as an index of brain development to characterize MRI measurements in longitudinal studies of the developing brain. Our results demonstrate that the DevS model enabled linear characterization of DTI measurements in the infant brains, and might facilitate downstream linear analyses. As an unbiased, data-driven index, the DevS improved the identification of developmental differences between term- and preterm-born infants compared to the standard and commonly used PMA. Therefore, DevS may be used as an efficient and objective metric in future large-cohort longitudinal studies of brain development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We would like to thank Dr. Murat Bilgel at the National Institute for Aging for the important discussions of the mathematical model and the optimization procedures, Dr. Steven Buchthal for the MRI data acquisition and image quality control, and Dr. Doris Lin, a board-certified Neuroradiologist, for MRI reading. This grant is made possible by the following funding supports: Ministry of Science and Technology of the People's Republic of China (2018YFE0114600, DW), National Natural Science Foundation of China (61801424 and 81971606, DW) and National Institutes of Health (R01HD065955, KO; U54NS056889 and 2K24DA16170, LC). None of the authors has a conflict of interest to declare.

References

- Akazawa K, Chang L, Yamakawa R, Hayama S, Buchthal S, Alicata D, Andres T, Castillo D, Oishi K, Skranes J, Ernst T, Oishi K, 2016 Probabilistic maps of the white matter tracts with known associated functions on the neonatal brain atlas: Application to evaluate longitudinal developmental trajectories in term-born and preterm-born infants. *Neuroimage* 128, 167–179. [PubMed: 26712341]
- Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, Warfield SK, Huppi PS, Butler SC, Conneman N, Fischer C, Eichenwald EC, 2004 Early experience alters brain function and structure. *Pediatrics* 113, 846–857. [PubMed: 15060237]
- Anjari M, Srinivasan L, Allsop JM, Hajnal JV, Rutherford MA, Edwards AD, Counsell SJ, 2007 Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. *Neuroimage* 35, 1021–1027. [PubMed: 17344066]
- Baldoli C, Scola E, Della Rosa PA, Pontesilli S, Longaretti R, Poloniato A, Scotti R, Blasi V, Cirillo S, Iadanza A, Rovelli R, Barera G, Scifo P, 2015 Maturation of preterm newborn brains: a fMRI–DTI study of auditory processing of linguistic stimuli and white matter development. *Brain Structure and Function* 220, 3733–3751. [PubMed: 25244942]
- Barkovich AJ, Kjos BO, Jackson DE Jr., Norman D, 1988 Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology* 166, 173–180. [PubMed: 3336675]
- Basser PJ, Mattiello J, LeBihan D, 1994 MR diffusion tensor spectroscopy and imaging. *Biophys J* 66, 259–267. [PubMed: 8130344]
- Benjamini Y, Hochberg Y, 1995 Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 57, 289–300.
- Bilgel M, Prince JL, Wong DF, Resnick SM, Jernigan BM, 2016 A multivariate nonlinear mixed effects model for longitudinal image analysis: Application to amyloid imaging. *Neuroimage* 134, 658–670. [PubMed: 27095307]
- Brain Development Cooperative G, 2012 Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cereb Cortex* 22, 1–12. [PubMed: 21613470]
- Brossard-Racine M, McCarter R, Murnick J, Tinkleman L, Vezina G, Limperopoulos C, 2019 Early extra-uterine exposure alters regional cerebellar growth in infants born preterm. *Neuroimage Clin* 21, 101646. [PubMed: 30630759]
- Brown TT, Kuperman JM, Chung Y, Erhart M, McCabe C, Hagler DJ Jr., Venkatraman VK, Akshoomoff N, Amaral DG, Bloss CS, Casey BJ, Chang L, Ernst TM, Frazier JA, Gruen JR, Kaufmann WE, Kenet T, Kennedy DN, Murray SS, Sowell ER, Jernigan TL, Dale AM, 2012 Neuroanatomical assessment of biological maturity. *Curr Biol* 22, 1693–1698. [PubMed: 22902750]
- Chang L, Akazawa K, Yamakawa R, Hayama S, Buchthal S, Alicata D, Andres T, Castillo D, Oishi K, Skranes J, Ernst T, Oishi K, 2016a Delayed early developmental trajectories of white matter tracts of functional pathways in preterm-born infants: Longitudinal diffusion tensor imaging data. *Data Brief* 6, 1007–1015. [PubMed: 26958632]

- Chang L, Cloak C, Jiang CS, Farnham S, Tokeshi B, Buchthal S, Hedemark B, Smith LM, Ernst T, 2009 Altered neurometabolites and motor integration in children exposed to methamphetamine in utero. *Neuroimage* 48, 391–397. [PubMed: 19576287]
- Chang L, Oishi K, Skranes J, Buchthal S, Cunningham E, Yamakawa R, Hayama S, Jiang CS, Alicata D, Hernandez A, Cloak C, Wright T, Ernst T, 2016b Sex-Specific Alterations of White Matter Developmental Trajectories in Infants With Prenatal Exposure to Methamphetamine and Tobacco. *JAMA Psychiatry* 73, 1217–1227. [PubMed: 27829078]
- Christensen GE, Rabbitt RD, Miller MI, 1996 Deformable templates using large deformation kinematics. *Ieee Transactions on Image Processing* 5, 1435–1447. [PubMed: 18290061]
- Counsell SJ, Boardman JP, 2005 Differential brain growth in the infant born preterm: current knowledge and future developments from brain imaging. *Semin Fetal Neonatal Med* 10, 403–410. [PubMed: 15993667]
- Counsell SJ, Shen YJ, Boardman JP, Larkman DJ, Kapellou O, Ward P, Allsop JM, Cowan FM, Hajnal JV, Edwards AD, Rutherford MA, 2006 Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics* 117, 376–386. [PubMed: 16452356]
- Dean DC 3rd, O'Muircheartaigh J, Dirks H, Waskiewicz N, Walker L, Doernberg E, Piryatinsky I, Deoni SC, 2015 Characterizing longitudinal white matter development during early childhood. *Brain Struct Funct* 220, 1921–1933. [PubMed: 24710623]
- Dempster AP, Laird NM, D.B., R., 1976 Maximum likelihood from incomplete data via the EM algorithm. *International Conference of the Royal Statistical Society*.
- Di Martino A, O'Connor D, Chen B, Alaerts K, Anderson JS, Assaf M, Balsters JH, Baxter L, Beggiato A, Bernaerts S, Blanken LME, Bookheimer SY, Braden BB, Byrge L, Castellanos FX, Dapretto M, Delorme R, Fair DA, Fishman I, Fitzgerald J, Gallagher L, Keehn RJ, Kennedy DP, Lainhart JE, Luna B, Mostofsky SH, Müller R-A, Nebel MB, Nigg JT, O'Hearn K, Solomon M, Toro R, Vaidya CJ, Wenderoth N, White T, Craddock RC, Lord C, Leventhal B, Milham MP, 2017 Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Scientific Data* 4, 170010. [PubMed: 28291247]
- Dosenbach NU, Nardos B, Cohen AL, Fair DA, Power JD, Church JA, Nelson SM, Wig GS, Vogel AC, Lessov-Schlaggar CN, Barnes KA, Dubis JW, Feczko E, Coalson RS, Pruett JR Jr., Barch DM, Petersen SE, Schlaggar BL, 2010 Prediction of individual brain maturity using fMRI. *Science* 329, 1358–1361. [PubMed: 20829489]
- Duffy FH, Als H, McAnulty GB, 1990 Behavioral and electrophysiological evidence for gestational age effects in healthy preterm and fullterm infants studied two weeks after expected due date. *Child Dev* 61, 271–286. [PubMed: 2209195]
- Franke K, Luders E, May A, Wilke M, Gaser C, 2012 Brain maturation: predicting individual BrainAGE in children and adolescents using structural MRI. *Neuroimage* 63, 1305–1312. [PubMed: 22902922]
- Fryer SL, Frank LR, Spadoni AD, Theilmann RJ, Nagel BJ, Schweinsburg AD, Tapert SF, 2008 Microstructural integrity of the corpus callosum linked with neuropsychological performance in adolescents. *Brain Cogn* 67, 225–233. [PubMed: 18346830]
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL, 1999a Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2, 861–863. [PubMed: 10491603]
- Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, Berry YC, Tobin M, Nelson J, Castellanos FX, 1999b Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 23, 571–588. [PubMed: 10390717]
- Gimenez M, Miranda MJ, Born AP, Nagy Z, Rostrup E, Jernigan TL, 2008 Accelerated cerebral white matter development in preterm infants: a voxel-based morphometry study with diffusion tensor MR imaging. *Neuroimage* 41, 728–734. [PubMed: 18430590]
- Hagler DJ Jr., Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS, Sutherland MT, Casey BJ, Barch DM, Harms MP, Watts R, Bjork JM, Garavan HP, Hilmer L, Pung CJ, Sicat CS, Kuperman J, Bartsch H, Xue F, Heitzeg MM, Laird AR, Trinh TT, Gonzalez R, Tapert SF, Riedel MC, Squeglia LM, Hyde LW, Rosenberg MD, Earl EA, Howlett KD, Baker FC, Soules M, Diaz J, de

Leon OR, Thompson WK, Neale MC, Herting M, Sowell ER, Alvarez RP, Hawes SW, Sanchez M, Bodurka J, Breslin FJ, Morris AS, Paulus MP, Simmons WK, Polimeni JR, van der Kouwe A, Nencka AS, Gray KM, Pierpaoli C, Matochik JA, Noronha A, Aklin WM, Conway K, Glantz M, Hoffman E, Little R, Lopez M, Pariyadath V, Weiss SR, Wolff-Hughes DL, DelCarmen-Wiggins R, Feldstein Ewing SW, Miranda-Dominguez O, Nagel BJ, Perrone AJ, Sturgeon DT, Goldstone A, Pfefferbaum A, Pohl KM, Prouty D, Uban K, Bookheimer SY, Dapretto M, Galvan A, Bagot K, Giedd J, Infante MA, Jacobus J, Patrick K, Shilling PD, Desikan R, Li Y, Sugrue L, Banich MT, Friedman N, Hewitt JK, Hopfer C, Sakai J, Tanabe J, Cottler LB, Nixon SJ, Chang L, Cloak C, Ernst T, Reeves G, Kennedy DN, Heeringa S, Peltier S, Schulenberg J, Sripada C, Zucker RA, Iacono WG, Luciana M, Calabro FJ, Clark DB, Lewis DA, Luna B, Schirda C, Brima T, Foxe JJ, Freedman EG, Mruzek DW, Mason MJ, Huber R, McGlade E, Prescott A, Renshaw PF, Yurgelun-Todd DA, Allgaier NA, Dumas JA, Ivanova M, Potter A, Florsheim P, Larson C, Lisdahl K, Charness ME, Fuemmeler B, Hettema JM, Maes HH, Steinberg J, Anokhin AP, Glaser P, Heath AC, Madden PA, Baskin-Sommers A, Constable RT, Grant SJ, Dowling GJ, Brown SA, Jernigan TL, Dale AM, 2019 Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *Neuroimage* 202, 116091. [PubMed: 31415884]

Hasegawa T, Yamada K, Morimoto M, Morioka S, Tozawa T, Isoda K, Murakami A, Chiyonobu T, Tokuda S, Nishimura A, Nishimura T, Hosoi H, 2011 Development of Corpus Callosum in Preterm Infants Is Affected by the Prematurity: In Vivo Assessment of Diffusion Tensor Imaging at Term-Equivalent Age. *Pediatric Research* 69, 249–254. [PubMed: 21131895]

Howell BR, Styner MA, Gao W, Yap PT, Wang L, Baluyot K, Yacoub E, Chen G, Potts T, Salzwedel A, Li G, Gilmore JH, Piven J, Smith JK, Shen D, Ugurbil K, Zhu H, Lin W, Ellison JT, 2018 The UNC/UMN Baby Connectome Project (BCP): An overview of the study design and protocol development. *Neuroimage* 185:891–905. [PubMed: 29578031]

Huppi PS, Maier SE, Peled S, Zientara GP, Barnes PD, Jolesz FA, Volpe JJ, 1998 Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res* 44, 584–590. [PubMed: 9773850]

Jedynak BM, Lang A, Liu B, Katz E, Zhang Y, Wyman BT, Raunig D, Jedynak CP, Caffo B, Prince JL, Alzheimer's Disease Neuroimaging I, 2012 A computational neurodegenerative disease progression score: method and results with the Alzheimer's disease Neuroimaging Initiative cohort. *Neuroimage* 63, 1478–1486. [PubMed: 22885136]

Jernigan TL, Brown TT, Hagler DJ Jr., Akshoomoff N, Bartsch H, Newman E, Thompson WK, Bloss CS, Murray SS, Schork N, Kennedy DN, Kuperman JM, McCabe C, Chung Y, Libiger O, Maddox M, Casey BJ, Chang L, Ernst TM, Frazier JA, Gruen JR, Sowell ER, Kenet T, Kaufmann WE, Mostofsky S, Amaral DG, Dale AM, Pediatric Imaging N, Genetics S, 2016 The Pediatric Imaging, Neurocognition, and Genetics (PING) Data Repository. *Neuroimage* 124, 1149–1154. [PubMed: 25937488]

Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S, 2006 DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed* 81, 106–116. [PubMed: 16413083]

Knickmeyer RC, Gouttard S, Kang C, Evans D, Wilber K, Smith JK, Hamer RM, Lin W, Gerig G, Gilmore JH, 2008 A structural MRI study of human brain development from birth to 2 years. *J Neurosci* 28, 12176–12182. [PubMed: 19020011]

Laird NM, Ware JH, 1982 Random-effects models for longitudinal data. *Biometrics* 38, 963–974. [PubMed: 7168798]

Li Y, Shea SM, Lorenz CH, Jiang H, Chou MC, Mori S, 2013 Image corruption detection in diffusion tensor imaging for post-processing and real-time monitoring. *PLoS One* 8, e49764. [PubMed: 24204551]

Makropoulos A, Robinson EC, Schuh A, Wright R, Fitzgibbon S, Bozek J, Counsell SJ, Steinweg J, Vecchiato K, Passerat-Palmbach J, Lenz G, Mortari F, Tenev T, Duff EP, Bastiani M, Cordero-Grande L, Hughes E, Tusor N, Tournier JD, Hutter J, Price AN, Teixeira R, Murgasova M, Victor S, Kelly C, Rutherford MA, Smith SM, Edwards AD, Hajnal JV, Jenkinson M, Rueckert D, 2018 The developing human connectome project: A minimal processing pipeline for neonatal cortical surface reconstruction. *Neuroimage* 173, 88–112. [PubMed: 29409960]

- Miller MI, Christensen GE, Amit Y, Grenander U, 1993 Mathematical textbook of deformable neuroanatomies. *Proc Natl Acad Sci U S A* 90, 11944–11948. [PubMed: 8265653]
- Mukherjee P, Miller JH, Shimony JS, Conturo TE, Lee BC, Almli CR, McKinstry RC, 2001 Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. *Radiology* 221, 349–358. [PubMed: 11687675]
- Mukherjee P, Miller JH, Shimony JS, Philip JV, Nehra D, Snyder AZ, Conturo TE, Neil JJ, McKinstry RC, 2002 Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *AJNR Am J Neuroradiol* 23, 1445–1456. [PubMed: 12372731]
- Oishi K, Mori S, Donohue PK, Ernst T, Anderson L, Buchthal S, Faria A, Jiang H, Li X, Miller MI, van Zijl PC, Chang L, 2011 Multi-contrast human neonatal brain atlas: application to normal neonate development analysis. *Neuroimage* 56, 8–20. [PubMed: 21276861]
- Ortibus E, Verhoeven J, Sunaert S, Casteels I, de Cock P, Lagae L, 2012 Integrity of the inferior longitudinal fasciculus and impaired object recognition in children: a diffusion tensor imaging study. *Dev Med Child Neurol* 54, 38–43. [PubMed: 22171928]
- Osby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB, 2009 Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *J Neurosci* 29, 11772–11782. [PubMed: 19776264]
- Partridge SC, Mukherjee P, Henry RG, Miller SP, Berman JJ, Jin H, Lu Y, Glenn OA, Ferriero DM, Barkovich AJ, Vigneron DB, 2004 Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. *Neuroimage* 22, 1302–1314. [PubMed: 15219602]
- Roos A, Kwiatkowski MA, Fouche JP, Narr KL, Thomas KG, Stein DJ, Donald KA, 2015 White matter integrity and cognitive performance in children with prenatal methamphetamine exposure. *Behav Brain Res* 279, 62–67. [PubMed: 25446763]
- Rose SE, Hatzigeorgiou X, Strudwick MW, Durbridge G, Davies PS, Colditz PB, 2008 Altered white matter diffusion anisotropy in normal and preterm infants at term-equivalent age. *Magnetic Resonance in Medicine* 60, 761–767. [PubMed: 18816850]
- Roussotte FF, Bramen JE, Nunez SC, Quandt LC, Smith L, O'Connor MJ, Bookheimer SY, Sowell ER, 2011 Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: the effects of methamphetamine, alcohol, and polydrug exposure. *Neuroimage* 54, 3067–3075. [PubMed: 21040792]
- Sadeghi N, Prastawa M, Fletcher PT, Wolff J, Gilmore JH, Gerig G, 2013 Regional characterization of longitudinal DT-MRI to study white matter maturation of the early developing brain. *Neuroimage* 68, 236–247. [PubMed: 23235270]
- Saksena S, Husain N, Malik GK, Trivedi R, Sarma M, Rathore RS, Pandey CM, Gupta RK, 2008 Comparative evaluation of the cerebral and cerebellar white matter development in pediatric age group using quantitative diffusion tensor imaging. *Cerebellum* 7, 392–400. [PubMed: 18581196]
- Shi F, Yap PT, Wu GR, Jia HJ, Gilmore JH, Lin WL, Shen DG, 2011 Infant Brain Atlases from Neonates to 1-and 2-Year-Olds. *Plos One* 6.
- Sowell ER, Leow AD, Bookheimer SY, Smith LM, O'Connor MJ, Kan E, Rosso C, Houston S, Dinov ID, Thompson PM, 2010 Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. *J Neurosci* 30, 3876–3885. [PubMed: 20237258]
- Thompson DK, Inder TE, Faggian N, Johnston L, Warfield SK, Anderson PJ, Doyle LW, Egan GF, 2011 Characterization of the corpus callosum in very preterm and full-term infants utilizing MRI. *Neuroimage* 55, 479–490. [PubMed: 21168519]
- Van Braeckel K, Butcher PR, Geuze RH, van Duijn MA, Bos AF, Bouma A, 2008 Less efficient elementary visuomotor processes in 7- to 10-year-old preterm-born children without cerebral palsy: an indication of impaired dorsal stream processes. *Neuropsychology* 22, 755–764. [PubMed: 18999349]
- van Kooij BJ, de Vries LS, Ball G, van Haastert IC, Benders MJ, Groenendaal F, Counsell SJ, 2012 Neonatal tract-based spatial statistics findings and outcome in preterm infants. *AJNR Am J Neuroradiol* 33, 188–194. [PubMed: 21998101]
- Volpe JJ, 2009 Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 8, 110–124. [PubMed: 19081519]

- Weisenfeld NI, Warfield SK, 2009 Automatic segmentation of newborn brain MRI. *Neuroimage* 47, 564–572. [PubMed: 19409502]
- Wu D, Chang LD, Akazawa K, Oishi K, Skranes J, Ernst T, Oishi K, 2017 Mapping the critical gestational age at birth that alters brain development in preterm-born infants using multi-modal MRI. *Neuroimage* 149, 33–43. [PubMed: 28111189]
- Yap QJ, Teh I, Fusar-Poli P, Sum MY, Kuswanto C, Sim K, 2013 Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. *J Neural Transm (Vienna)* 120, 1369–1395. [PubMed: 23328950]
- Yoo SS, Park HJ, Soul JS, Mamata H, Park H, Westin CF, Bassan H, Du Plessis AJ, Robertson RL Jr., Maier SE, Ringer SA, Volpe JJ, Zientara GP, 2005 In vivo visualization of white matter fiber tracts of preterm- and term-infant brains with diffusion tensor magnetic resonance imaging. *Invest Radiol* 40, 110–115. [PubMed: 15654256]
- Zhang L, Thomas KM, Davidson MC, Casey BJ, Heier LA, Ulug AM, 2005 MR quantitation of volume and diffusion changes in the developing brain. *AJNR Am J Neuroradiol* 26, 45–49. [PubMed: 15661698]
- Zuo X-N, He Y, Betzel RF, Colcombe S, Sporns O, Milham MP, 2017 Human Connectomics across the Life Span. *Trends in Cognitive Sciences* 21, 32–45. [PubMed: 27865786]

Figure 1:

(A) Relation between the postmenstrual age (PMA) and the developmental score (DevS) in all 87 term-born infants. Light blue dots denote data from male subjects and pink dots denote data from female subjects. Note DevS of 0 (unit-less) corresponds to PMA of 40–45 weeks. (B-C) The histograms of the subject-specific model parameters, namely α_i (B) and β_i (C) in Equation 1, derived from the 87 term-born infants.

Figure 2.

Linear relationship between mean diffusivity (MD) and the postmenstrual age (PMA, top row), and that between MD and developmental score (DevS, bottom row), in several representative gray matter (A) and white matter (B) structures across all term-born infants. Light blue dots denote data from male infants and pink dots denote those from female infants. Black lines indicate the linear fitting of MD with respect to the corresponding x-axis. The R^2 values of the linear regression (including boys and girls) are labeled on corresponding plots, and $p < 0.001$ for all regressions.

Figure 3.

The R^2 and root-mean-square (RMS) fitting errors of linear regressions between MD and DevS (blue dots) or that between MD and PMA (orange dots) in 126 brain structures across all term-born infants. By transforming the x -axis from PMA to DevS, R^2 was higher and RMS were lower in most ROIs, indicating improved linearity. Abbreviations for the 126 structures are provided in Supplementary Table S1.

Figure 4.

MD values predicted based on the DevS model, using data from all term-born infants. (A) Estimated MD values are overlaid on 126 brain structures at DevS of -1, 0, 1, and 2. (B) Maps of the rates of MD decrease with DevS (parameter a in the model) across the brain. White arrows indicate structures that had the fastest decreasing rates (B). The color bar indicates the amount of MD reduction per DevS, i.e., the amount of MD reduction as DevS increased from 0 to 1. Abbreviations: ACR—anterior corona radiata; SCR—superior corona radiata; SLF—superior longitudinal fasciculus; PTR—posterior thalamic radiation.

Figure 5.

Characteristics of DevS model parameters in the term- and preterm-born infants in the testing dataset (dataset#2 as described in 2.5), after the model was trained with a separate dataset (dataset #1). (A) The relation between PMA and DevS in the term-born (blue dots) and preterm-born (red dots) infants. (B) The subject-specific model parameters α and β both showed significant differences between the term- and preterm-born groups. * denotes $p < 0.001$ by unpaired t-test with unequal variance.

Figure 6.

Developmental changes in MD in preterm- and term-born infants in the testing dataset (dataset#2 as described in 2.5), with respect to PMA (top row) or DevS (bottom row) in several gray matter (A) and white matter (B) structures. Blue dots denote term-born infant data, red dots denote preterm-born infant data, and blue and red lines denote the linear fitting of MD with respect to the corresponding x -axis. The R^2 values of the linear regression for term-born and preterm-born infants are labeled on corresponding plots, and $p < 0.001$ for all regressions.

Figure 7.

Brain regions that show significantly different ($p < 0.01$ after FDR correction) developmental trajectories in MD (A-B) and FA (C-D) between preterm- and term-born infants from the testing dataset (dataset#2 as described in 2.5), using DevS or PMA as the time-index. The color map indicates differences in the regression slopes between two groups (e.g., $|a_{\text{preterm}}| - |a_{\text{term}}|$). Abbreviations: SCR- superior corona radiata, ACR- anterior corona radiata; SLF- superior longitudinal fasciculus, SFG- superior frontal gyrus, MFG- middle frontal gyrus, MOFG- medial fronto-orbital gyrus; EC- external capsule; ALIC- anterior limb of the internal capsule; PLIC- posterior limb of the internal capsule; Tap- tapetum; GCC- genu of the corpus callosum; MCP- middle cerebellar peduncle.

Table 1:

Demographic and clinical characteristics of the term- and preterm-born infants at birth. Unless specified, the data was represented as median (5th – 95th percentile).

	Term-born (<i>n</i> = 87)	Preterm-born (<i>n</i> = 66)	<i>p</i> -value ^{<i>b</i>}
Gestational age at birth (weeks)	39.6 (37.4–41.1)	33.1 (24.6–36.7)	< 0.001 ^{<i>b</i>}
Sex: Female (%) / Male (%)	42 (48.3%) / 45 (51.7%)	34 (51.2%) / 32 (48.8%)	0.815 ^{<i>d</i>}
Body weight at birth (kg)	3.33 (2.59–4.08)	1.94 (0.71–3.08)	< 0.001 ^{<i>b</i>}
Length at birth (cm)	50.8 (46.7–55.4)	44.0 (31.0–50.8)	< 0.001 ^{<i>b</i>}
Head circumference at birth (cm)	34.3 (31.8–36.2)	30.0 (21.3–34.4)	< 0.001 ^{<i>c</i>}
% with <i>in utero</i> tobacco exposure ^{<i>e</i>}	27 (31.0%)	15 (17.0%)	< 0.001 ^{<i>d</i>}
% with <i>in utero</i> occasional alcohol exposure ^{<i>f</i>}	29 (33.3%)	19 (21.6%)	0.112 ^{<i>d</i>}
% with <i>in utero</i> methamphetamine+tobacco exposure ^{<i>g</i>}	18 (20.7%)	6 (6.8%)	0.004 ^{<i>d</i>}
Delivery methods (Vaginal/C-section)	64 (73.6%) / 23 (26.4%)	31 (47.0%) / 35 (53.0%)	<0.001 ^{<i>d</i>}
APGAR ^{<i>a</i>} at 1minute (median [IQR ^{<i>h</i>}])	8 [8, 8]	8 [6, 8]	0.008 ^{<i>b</i>}
APGAR ^{<i>a</i>} at 5 minutes (median [IQR ^{<i>h</i>}])	9 [9, 9]	9 [8, 9]	< 0.001 ^{<i>b</i>}

^{*a*}APGAR = Activity, Pulse, Grimace, Appearance, & Respiration

^{*b*}*p*-values based on two-tailed t-test with unequal variance

^{*c*}*p*-values based on Wilcoxon's rank-sum test

^{*d*}*p*-values based on Chi-square test

^{*e*}Tobacco exposure 50 cigarettes (2.5 pack) throughout the pregnancy

^{*f*}Alcohol exposure 10 grams (more than one drink, but < 3 drinks/month throughout the pregnancy)

^{*g*}Methamphetamine exposure 1 gram throughout the pregnancy

^{*h*}IQR: interquartile range

Table 2:

Clinical information of the term- and preterm-born infants at each scan

	Term-born	Preterm born	<i>p</i> -values
Sample size			
Baseline	N = 87	N = 66	N/A
1-month follow-up	N = 50	N = 46	
2-month follow-up	N = 32	N = 38	
Postmenstrual age (weeks)			
Baseline	42.0 ± 0.24	42.4 ± 0.49	0.43
1-month follow-up	45.6 ± 0.23	46.9 ± 0.56	0.02
2-month follow-up	50.4 ± 0.33	52.4 ± 0.68	0.01
Body weight (kg)			
Baseline	3.8 ± 0.06	3.9 ± 0.12	0.38
1-month follow-up	4.9 ± 0.07	4.9 ± 0.12	0.79
2-month follow-up	5.9 ± 0.08	6.0 ± 0.15	0.47
Length (cm)			
Baseline	52.3 ± 0.38	51.9 ± 0.48	0.22
1-month follow-up	55.7 ± 0.46	54.5 ± 0.83	0.06
2-month follow-up	60.1 ± 0.26	59.88 ± 0.58	0.74
Head circumference (cm)			
Baseline	34.9 ± 0.47	35.6 ± 0.51	0.76
1-month follow-up	37.5 ± 0.40	37.3 ± 0.89	0.19
2-month follow-up	39.5 ± 0.35	40.4 ± 0.28	0.09

The p-values are bold where they are less than 0.05