# Validating a cross-sectional brain development index with longitudinal brain images

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**Background:** Several psychiatric disorders are associated with abnormal brain development. Magnetic resonance imaging (MRI) provides objective quantitative markers that can be used to follow the neuroanatomical changes non-invasively during normal brain development. Consequently, numerous studies[1-4] have hypothesized that a brain development index (BDI) capable of capturing patterns of altered growth may reliably predict and identify individual subjects deviating from a normative neurodevelopmental trajectory. An accurate BDI may elicit timely clinical interventions and ultimately lead to better clinical outcomes. However, while recent studies have shown great promise in developing a highly accurate BDI using brain image data and multivariate machine learning techniques[2-4], this approach has not been robustly validated using a large population sample with longitudinal data on developing child brain.

**Subjects and Methods:** Anatomical $T_1$-weighted brain data from 303 healthy children aged 4.88 to 18.35 years (162 females, 53%; age-matched for gender) at the first visit were acquired from the National Institute of Health (NIH) pediatric repository[5] (www.**pediatricmri.nih**.gov/). 115 subjects (61 females, 53%; age-matched for gender) were re-scanned at the second visit after 2 years. MRI Data Processing: The brain anatomical data were pre-processed and automatically segmented using Freesurfer software version 5.3 and neuroanatomical volumes for the segmented regions were extracted[6, 7]. Data Analysis: The least absolute shrinkage and selection operator (LASSO) algorithm[8] was 'trained' to summarize patterns of neuroanatomical volume changes with chronological age and generate a BDI for each individual subject. The BDI can be considered as the predicted 'biological age'. For the first visit, the BDI was cross-validated with the leave-one-out procedure. Each individual's BDI was predicted based on the rest of the subjects of the first visit. For the longitudinal validation, only the brain features that appeared all the time for the individual predictions during the cross-validation were used as predictors in a further LASSO regression for all the first visit subjects. Then the coefficients of resulting LASSO regression were directly used to predict the brain maturity of the subjects who came about two years later. The LASSO regression based on the first visit data was never exposed to any data from the second visit. Thus, it would be an objective validation of the BDI generated by LASSO based on cross-sectional data (the first visit) with longitudinal data (the second visit). The point of longitudinal validation is to see if the BDI can correctly predict that the subjects grew two years older at the second visit.

**Results:** The BDI of the first visit significantly correlated with the chronological age, with an r of 0.82 and a mean absolute error (MAE) of 1.69 years. Only 37 brain regions objectively selected by the LASSO during the cross-validation of the first visit data were used in the LASSO regression, which was used to validate BDI with longitudinal data. The BDIs of all the 303 subjects of the first visit correlated with the chronological age with an r of 0.89 and an MAE of 1.57, as shown in **Figure 1a** (light grey dots). The thick black line shows the linear fitting of the BDI with the chronological age, and the thin black lines indicate the 95% confidence interval.

BDIs of the 115 subjects who had a second visit were predicted with the same coefficients derived from the LASSO regression based on the first visit cross-sectional data. The predicted BDI for the second visit correlated with the chronological age significantly, with an r of 0.83 and an MAE of 1.71 (Figure 1a blue dots). The accuracy of the predictions on the longitudinally measured second-visit data is similar to the cross-validated prediction accuracy on the first visit cross-sectional data. Moreover, the BDI captured the brain growth between the first and second visits over the 1.96-year period with MAE of only 0.27 years as shown in **Figure 1b**. The normalized average volume changes of the 37 brain regions between the two visits are shown in **Figure 1c**. The pattern of these volume changes is quite similar to what was reported in the literature, even within just two years: significant grey matter volume decreases of cortical regions, such as both sides of pre-cuneus and rostro-middle-frontal cortices, and significant volume increases of cortical white matter and many subcortical regions, such as brain stem and both sides of amygdalae. The brain features used to predict BDI are conservative, meaning that only the most reliable brain regions for individual predictions are used to generate individual BDI.

**Discussion and Conclusions:** In this study, we introduced a novel brain development index using cross-sectional atlas-based brain images. The cross-sectional BDI was validated with longitudinal brain images for the first time. The BDI could accurately predict individual subjects' neurodevelopment changes. The BDI has a strong clinical potential and can detect psychiatric disorders due to abnormal neurodevelopment during brain development, which may lead to efficient clinical interventions and ultimately favorable clinical outcomes.

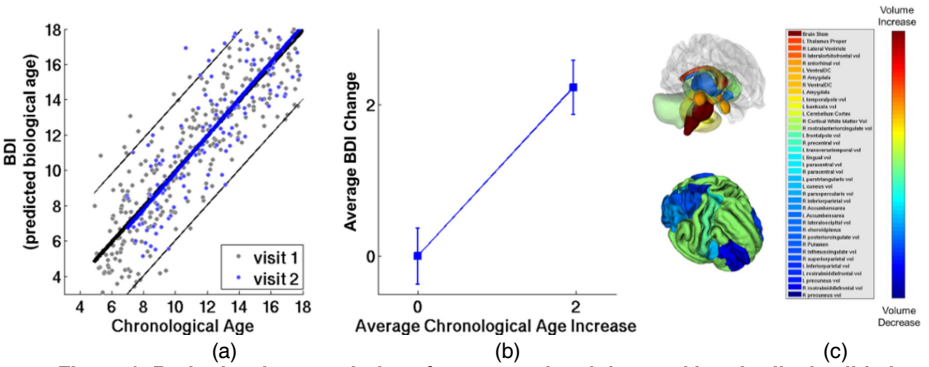


**Figure 1. Brain development index of cross-sectional data and longitudinal validation.**

**References**

1. Raznahan A., et al. How does your cortex grow? J. Neurosci. 2011; 31, 7174–7177.
2. Franke K, et al. Brain maturation: Predicting individual BrainAGE in children and adolescents using structural MRI. Neuroimage 2012; 63: 1305–1312.
3. Erus G, et al. Imaging Patterns of Brain Development and their Relationship to Cognition. Cereb Cortex. 2014 (doi: 10.1093/cercor/bht425).
4. Mwangi B, et al. Prediction of individual subject's age across the human lifespan using diffusion tensor imaging: A machine learning approach. Neuroimage 2013; 75: 58–67.
5. Evans AC. The NIH MRI study of normal brain development. Neuroimage 2006; 30:184–202.
6. Fischl B, et al. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 2002; 33: 341–355.
7. Dale AM, et al Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999; 9:179–194.
8. Tibshirani R, Society RS. Regression and shrinkage via the Lasso. J R Stat Soc, Ser B 1996; 58: 267–288.