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Development and validation of a brain maturation index using longitudinal neuroanatomical scans

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ABSTRACT

Background: Major psychiatric disorders are increasingly being conceptualized as 'neurodevelopmental', because they are associated with aberrant brain maturation. Several studies have hypothesized that a brain maturation index integrating patterns of neuroanatomical measurements may reliably identify *individual* subjects deviating from a normative neurodevelopmental trajectory. However, while recent studies have shown great promise in developing accurate brain maturation indices using neuroimaging data and multivariate machine learning techniques, this approach has not been validated using a large sample of longitudinal data from children and adolescents.

Methods: T_1-weighted scans from 303 healthy subjects aged 4.88 to 18.35 years were acquired from the National Institute of Health (NIH) pediatric repository (http://www.pediatricmri.nih.gov). Out of the 303 subjects, 115 subjects were re-scanned after 2 years. The least absolute shrinkage and selection operator algorithm (LASSO) was 'trained' to integrate neuroanatomical changes across chronological age and predict each *individual*'s brain maturity. The resulting brain maturation index was developed using first-visit scans only, and was validated using second-visit scans.

Results: We report a high correlation between the first-visit chronological age and brain maturation index ($r = 0.82$, mean absolute error or MAE = 1.69 years), and a high correlation between the second-visit chronological age and brain maturation index ($r = 0.83$, MAE = 1.71 years). The brain maturation index captured neuroanatomical volume changes between the first and second visits with an MAE of 0.27 years.

Conclusions: The brain maturation index developed in this study accurately predicted individual subjects' brain maturation longitudinally. Due to its strong clinical potentials in identifying individuals with an abnormal brain maturation trajectory, the brain maturation index may allow timely clinical interventions for individuals at risk for psychiatric disorders.

Introduction

Psychiatric disorders are a leading global cause of all non-fatal burden of disease (Whiteford et al., 2013). One important reason for the high morbidity is that many psychiatric disorders tend to arise early in life, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), mood disorders, and schizophrenia (Kessler et al., 2005). Most of these disorders, when manifest in children and adolescence, are increasingly considered to be the result of impaired brain maturation (Hendren, De Backer, and Pandina, 2000; Rapoport, Addington, Frangou, and Psych, 2005; Roybal et al., 2012; Yeo et al., 1997).

The in-vivo human brain maturation process can be studied non-invasively using anatomical magnetic resonance imaging (MRI) (Ashburner et al., 2003; Paus, 2005; Paus et al., 1999). Several MRI studies have consistently shown that human brain undergoes significant changes during childhood and adolescence (Casey, Giedd, and Thomas, 2000; Giedd and Rapoport, 2010; Giedd et al., 1999, 2009; Matsuzawa et al., 2001; Raznahan et al., 2011; Thompson et al., 2005; Toga, Thompson, and Sowell, 2006). Briefly, gray matter volumes of most cortical regions decrease substantially after peaking at early age (about 7–11 years depending on the regions), while a majority of lobar cortical white matter and subcortical region volumes increase during normal brain maturation (Giedd et al., 2014; Gogtay et al., 2004; Lenroot and Giedd, 2006; Lenroot et al., 2007; Sowell, Trauner, Gamst, and Jernigan, 2002).

Abnormal brain maturation has been reported in patients with psychiatric disorders. Shaw and colleagues recently reported that 50% of the human cortex attains maximal thickness at 7.5 years in typically

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developing youths as compared to 10.5 years in attention deficit hyperactivity disorder (ADHD)—indicating a cortical maturation delay (Shaw et al., 2007). The delay was also observed with cortical surface area and gyrification (Shaw et al., 2012). Douaud and colleagues reported delayed gray and white-matter neurodevelopment in patients with schizophrenia as compared to healthy controls (Douaud et al., 2009).

As we elucidate average group-level changes in different brain regions during both normal and abnormal brain maturation, identifying abnormal brain maturation at an individual subject level will be crucial to transfer these scientific findings to clinical applications. In order to identify individual abnormal brain maturation, a reliable indicator of individual normal brain maturation must be established. This indicator can be a composite index that integrates the complex patterns of all brain regions during maturation, for example, the volume changes shown in Fig. 1a. This index, namely a brain maturation index, tells us the biological age or the maturity of the brain. For the purpose of clinical applications, the brain maturation index should be capable of predicting the brain maturity of an individual based on measurements derived from brain scans. This means that the brain maturation index should be generalizable to new or 'unseen' individual subject data, in addition to providing a good fit for the existing data. After the normal maturation trajectory has been established with brain maturation index (Fig. 1b, blue), it will then be possible to identify any individual subject with a brain maturation trajectory deviating away normal maturation (Fig. 1b, red dashed line).

Recent studies using the concept of brain maturation index have shown promising advancement of predicting individual brain maturity in healthy children, adolescents and young adults (Brown et al., 2012; Chen et al., 2007; Dosenbach et al., 2010; Erus et al., 2014; Franke, Luders, May, Wilke, and Gaser, 2012; Khundrakpam, Tohka, and Evans, 2015), as well as aging over the human lifespan (Franke, Ziegler, Klöppel, and Gaser, 2010; Mwangi, Hasan, and Soares, 2013). By using machine learning technique and cross validation among large amount of data, these studies can account for as high as 92% of variance

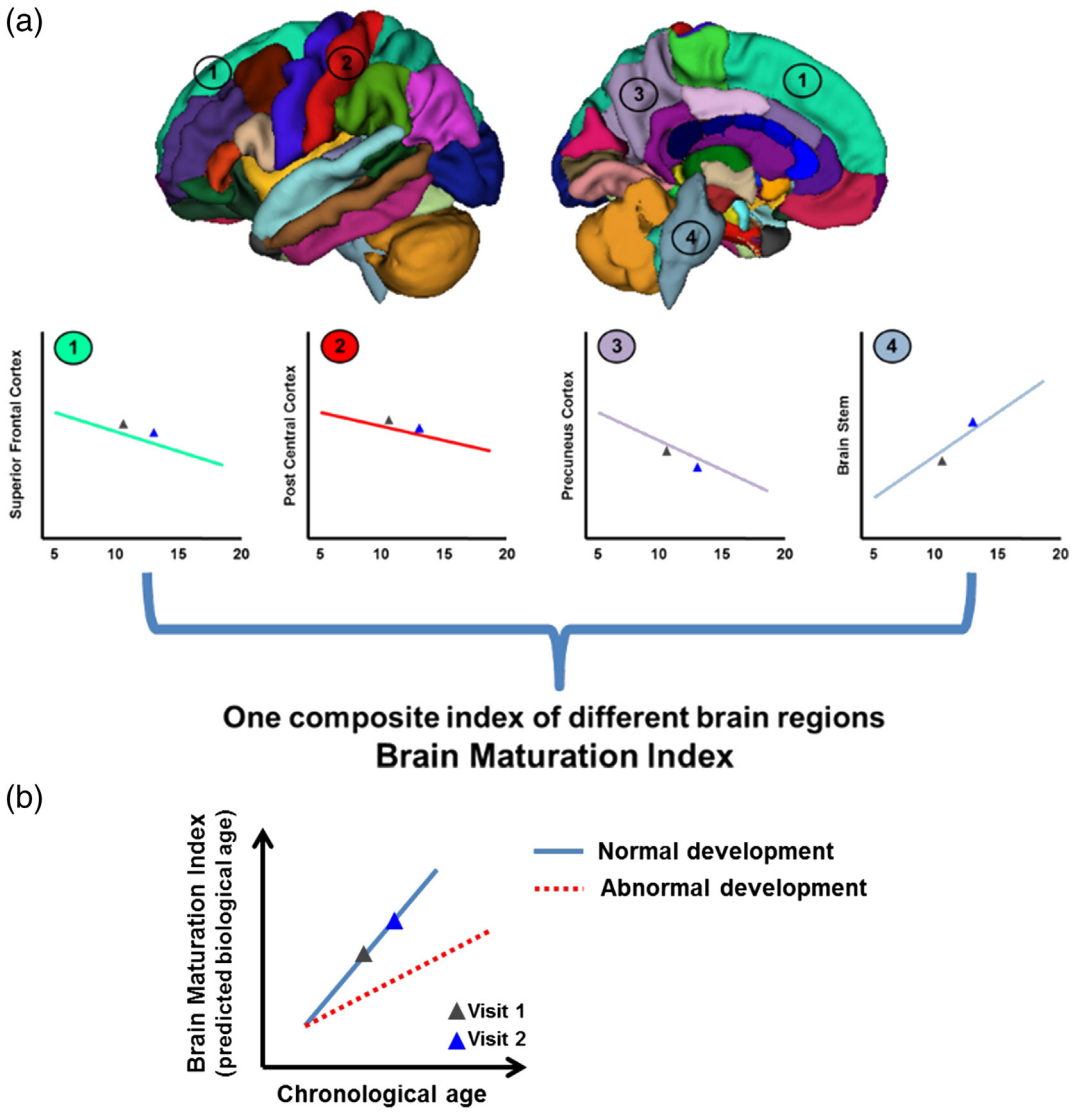

Fig. 1. The concept of brain maturation index. (a) An illustration of varied patterns of brain maturation. During maturation, brain regions change volumes in different patterns. The variations of volumes from different subjects also vary. Brain maturation index is a composite index that unifies these different brain region volume changes during maturation. The cartoon of the four brain regions illustrates the different volume changes during the maturation according to the literature. The gray and blue triangles represent the volumes of the corresponding regions for a hypothesized subject at the first and second visits, respectively. The volume changes of this subject can be slightly different from the average changes in each of these regions, so a single composite index will be necessary to integrate these differences, such as a brain maturation index. (b) Validation of the brain maturation index with longitudinal scans. The brain maturation index is the predicted biological age based on individual brain maturity. For normal maturation, the brain maturation index should have a high correlation with the chronological age, while for abnormal maturation, the correlation may be low and the slope can be shallow for delayed maturation. The brain maturation index can be validated with longitudinal scans. The brain maturation index for these scans for each subject should follow the trajectory of the brain maturation index against the chronological age for the normal maturation.

in predicting individual brain maturation (Brown et al., 2012). However, most of these studies have largely used cross-sectional data to train and test the predicting models, albeit a recent study that validated a predictive brain aging model using adult samples (Franke and Gaser, 2012). It remains an open question whether the brain maturation index based on cross-sectional data can make valid individual predictions in children and adolescents, when tested with longitudinal data. Thus, it is important to test a cross-sectional brain maturation index with its predictions on each of the subjects that were scanned longitudinally. Furthermore, the index should provide valuable insights of tractable brain changes that contribute significantly to individual brain maturation prediction.

The main aim of this study was to develop a brain maturation index using atlas-based cortical and subcortical anatomical regions derived from cross-sectional structural MRI and validate this cross-sectional brain maturation index with longitudinal neuroanatomical scans from the same subjects 2 years after the baseline assessment. We hypothesize that: the cross-sectional brain maturation index can accurately predict individual brain maturation longitudinally; the accuracy of predictions on longitudinal scans should be similar to the accuracy of predictions on cross-sectional scans with internal cross-validation; the atlas-based brain regions with high predicting powers in the brain maturation index should give us an overall reliable picture of brain maturation.

Materials and methods

Participants

The brain image data of subjects were obtained from Pediatric MRI Data Repository of the National Institute of Health (NIH) MRI Study of Normal Brain Development (Evans, 2006). This multi-site longitudinal study provided anatomical MRI to map typical pediatric brain development. There were two age cohorts in this NIH repository, and we used the first cohort that included children and adolescents aged from 4.88 to 18.35 years. We used anatomical MRI images of 303 subjects at their first visit, and a subsample of 115 subjects that had MRI scans available for a follow-up visit after 2 years (Table 1). The first visit scans were used to develop the brain maturation index to predict the individual age, and the predictions were further validated with the second visit scans that were acquired longitudinally.

Image acquisition

T1-weighted images were acquired at six imaging centers (Children's Hospital, Boston; Children's Hospital of Philadelphia; Cincinnati Children's Hospital Medical Center; University of California, Los Angeles; University of Texas, Houston Health Sciences Center; Washington University in St. Louis, School of Medicine) with 1.5 Tesla systems by General Electric (GE) and Siemens Medical Systems. For the GE scanners, the following parameters were used: sequence type: 3D spoiled gradient recalled (SPGR); TR = 22 ms; TE = 10–11 ms; flip angle = 30°; orientation: sagittal; field of view: 250 mm × 250 mm; slice numbers: 124; slice thickness, 1.5 mm. For the Siemens scanners, the following parameters were used: sequence type: 3D spoiled gradient recalled (SPGR); TR = 25 ms; TE = 11 ms; flip angle = 30°; orientation: sagittal; field of view: 256 mm x 256 mm; slice numbers: 160 or 180; slice thickness, 1 mm.

Table 1
Subject demographics.

	Number of subjects (female percentage)	Age range in years (mean ± standard deviation)
Visit 1	303 (53%)	4.88–18.35 (11.19 ± 3.76)
Visit 2	115 (53%)	6.95–17.82 (12.10 ± 3.08)

Image pre-processing

All T1-weighted images were visually inspected to exclude images with apparent motion artifacts and abnormal distortions in space or in contrast (see supplementary materials for details). Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suites (http://surfer.nmr.mgh.harvard.edu). The technical details of the procedures are described in detail elsewhere (Dale, Fischl, and Sereno, 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl, Sereno, and Dale, 1999; Fischl, Sereno, Tootell, and Dale, 1999; Fischl et al., 2002; Fischl, Liu, and Dale, 2001; Fischl, Salat, et al., 2004; Fischl, Van Der Kouwe, et al., 2004; Han et al., 2006; Jovicich et al., 2006; Ségonne et al., 2004). Briefly, the procedure involved motion correction, intensity normalization, automated topology corrections and automatic segmentations of cortical and subcortical regions. The volumes of the resulted 105 cortical (Desikan et al., 2006) and subcortical (Fischl et al., 2002) regions after segmentation were scaled by the intracranial volume for each subject and then used as input features to the prediction model.

Brain maturation index

The brain maturation index is a composite index of brain volume changes during maturation. This index was generated using a regularized linear regression algorithm, called the Least Absolute Shrinkage and Selection Operator (LASSO) (Tibshirani, 1996). The LASSO is a multivariate linear regression that can make predictions. It minimizes the sum of squared errors in the linear regression, with a bound on the sum of the absolute values of the coefficients. For a linear regression problem with m predictors (brain region volumes, or brain features) and n observations of the age y_i ($i = 1, 2, \ldots, n$) and these brain features, x_{ij} ($i = 1, 2, \ldots, n; j = 1, 2, \ldots, m$), the estimated age, $y_i^{\sim}$ can be expressed as follows:

$$\tilde{y_i} = b_0 + \sum_{j=1}^{m} (b_j x_{ij}); \tag{1}$$

in addition to minimizing only the commonly used sum of squared residuals, $\sum_{i=1}^{n} (y_i - \tilde{y}_i)^2$, the LASSO adds an additional bound to the sum of absolute values of regression coefficients (Tibshirani, 1996):

$$\sum_{j=1}^{m} |b_j| \leq s. \tag{2}$$

The bound s, selected by an internal 10-fold cross-validation for each prediction, limited coefficient values and made the coefficients sparse during the minimization. It prevented over-fitting and made it possible to generate predictions on new data. This allowed the algorithm to select only a small set of brain region volumes that were the most informative to predict individual brain maturity and 'prune' brain regions that were not contributing to the predictions. As a result, the brain maturation index generated with a regression based on the LASSO algorithm accounted for about 80% of the age-related variance with only a small number of brain features, and was also able to predict the brain maturity of individuals that the model have never been exposed to. The minimization subject to bound was performed using the cyclical coordinate descent algorithm (Friedman, Hastie, and Tibshirani, 2010; Rosset and Zhu, 2007).The LASSO was implemented in Matlab (version R2013a, The Mathworks Inc., Natick, Massachusetts) with Glmnet (Qian, Hastie, Friedman, Tibshirani, and Simon, 2013).

Cross-validation and longitudinal validation procedure

For the first visit, the brain maturation index was cross-validated with the leave-one-out procedure: each individual's brain maturation

index was predicted based on the rest of 302 subjects of the first visit. Within each iteration, the coefficient bound was selected based on an internal 10-fold cross-validation with the 302 subjects after one subject was left out. Since each leave-one-out cross-validation generated a set of coefficients, we had 303 models with 303 sets of linear regression coefficients. For the longitudinal validation, we needed one model with one set of coefficients derived from the first visit data. Thus, a new regression using LASSO algorithm was trained based on the first visit data. Only the brain features that appeared all the time for the individual predictions during the leave-one-out cross-validation were used as predictors in the new LASSO regression for all the first visit subjects. Then the coefficients of new LASSO regression were directly used to predict the brain maturity of the subjects scanned approximately 2 years later. The LASSO 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 brain maturation index generated by LASSO based on cross-sectional data (the first visit) with longitudinal data (the second visit). The purpose of longitudinal validation is to elucidate whether the brain maturation index can correctly predict that individual subjects' brain maturation 2 years after the first visit.

Results

In this section, we will show the validation results of the individual predictions of longitudinal brain maturation using the brain maturation index we developed based on cross-sectional neuroanatomical scans. We will also show the volume changes of brain regions that were most informative for maturation prediction between the two visits and compare them with volume changes over the whole brain across the 13.5 years measured in the first visit.

Validation of cross-sectional brain maturation index with longitudinal data

The brain maturation index of the first visit significantly correlated with the chronological age, with Pearson correlation $r = 0.82$ and a mean absolute error (MAE) = 1.69 years. Only 37 brain regions were objectively selected every time for each individual prediction during the leave-one-out cross-validation of the first visit, and these regions were used in a regression based on LASSO that was further used to validate the brain maturation index with longitudinal data. The regressed biological age based on these 37 brain regions of all the 303 subjects of the first visit is shown in Fig. 2a (light gray dots). A single global scaling factor was applied to the regression coefficients due to regression attenuation (see supplemental materials). The thick black line shows the linear fitting of the brain maturation index with the chronological age, and the thin black lines indicate the 95% confidence interval.

The brain maturation index of each 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 brain maturation indices for the second visit correlated with the chronological age significantly, with $r = 0.83$ and MAE = 1.71 (Fig. 2a blue dots). The linear fit of the brain maturation index with chronological age for the second visit overlapped closely with the linear regression for the first visit with slopes 1.03 versus 1. 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, as indicated by the correlations between the chronological age and predicted age ($r = 0.83$ vs. $r = 0.82$; $p \geq 0.74$ derived using Olkin & Finn, 1995 method; see supplementary materials). Specifically, for the subjects who had the second scans, the accuracy of their second scan predictions ($r = 0.83$) was comparable to that of their first scan predictions ($r = 0.80$; $p \geq 0.46$), and was also comparable to the accuracy of the other subject who did not have the second scans ($r = 0.83$; $p \geq 0.94$). The accuracy of longitudinal predictions on males ($r = 0.84$) and females ($r = 0.82$) was not significantly different ($p \geq 0.66$). Moreover, the brain maturation index captured the brain maturation between the first and second visits over the 2-year period with an error of only 0.27 years as shown in Fig. 2b.

Longitudinal volume changes of brain regions predictive for brain maturation

The 37 brain structures apparently had high predictive power of individual brain maturation index when they were used together, both on cross-sectional and longitudinal scans. However, it was still important to confirm that these brain regions used to predict individual brain maturation index reliably change in volume over the 2 years between the first and second visits.

We investigated this question by showing the volume changes of the 37 brain regions used to predict brain maturation index. Fig. 3 shows the average volume changes of these brain regions of the 115 subjects between the first and second visits, normalized by the corresponding standard deviations of the volume changes. The normalized average volume changes show how reliable the changes are greater or smaller than zero across subjects, similar to a simple t test, where the null hypothesis is that there is no volume change. In Fig. 3, we show that even with only about 2 year difference, the volumes of the selected 37 brain regions change reliably across subjects that were longitudinally scanned.

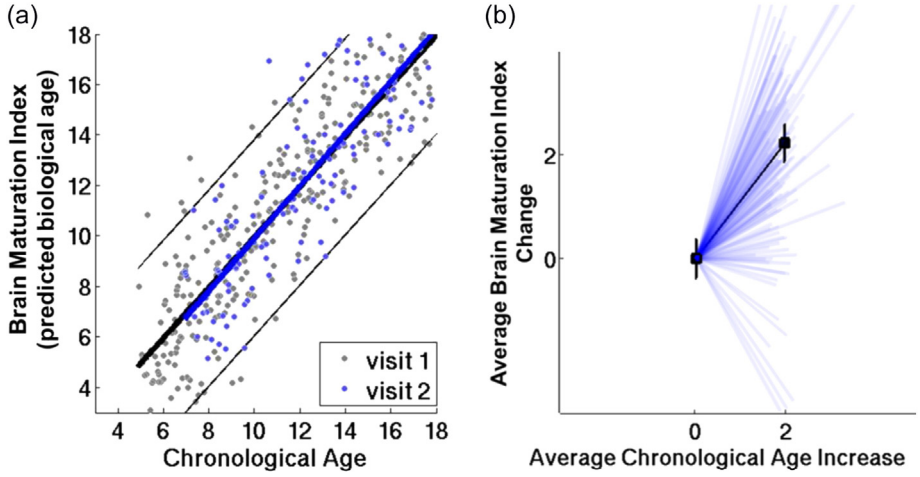

Fig. 2. Brain maturation index of cross-sectional data and longitudinal validation. (a) The brain maturation indices for each individual of visit 1 (gray dots) and visit 2 (blue dots). The corresponding regression lines are black and blue, respectively. Thin gray lines are the boundaries of the 95% confidence interval for the regression of visit 1 data. (b) The average brain maturation index change between visit 1 and visit 2 is 2.23 years compared to the average chronological age change, 1.96 years. Error bars show the standard errors of the brain maturation index changes.

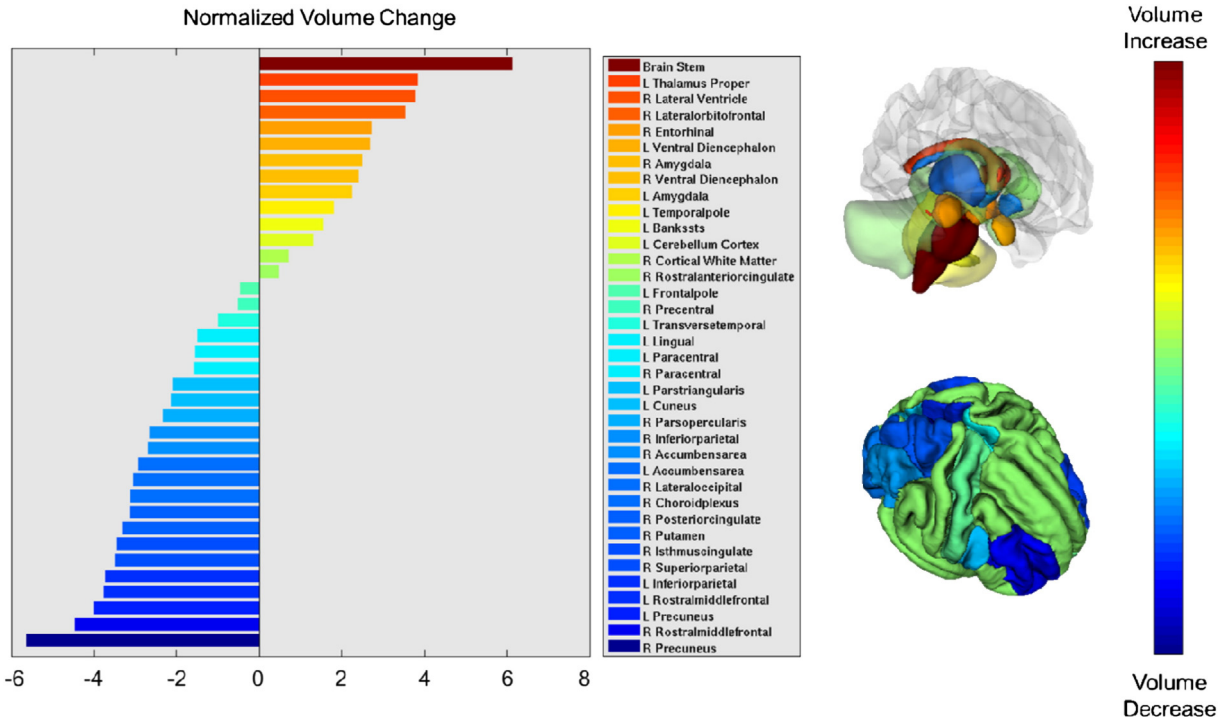

Fig. 3. Normalized volume changes of the brain regions selected by the brain maturation index. The average volume changes are normalized by the standard deviation of volume changes. The regions selected by LASSO reliably change volumes even with only a two-year interval. Bankssts refers to banks of the superior temporal sulcus as in the freesurfer segmentation (Desikan et al., 2006). The images of the brain were reconstructed and rendered in 3D slicer (http://www.slicer.org) (Fedorov et al., 2012).

In order to compare the two-year volume changes of LASSO-selected regions with the volume changes of all the brain regions over a larger time window, we show a summary of the average brain volume changes for the 303 subjects aged from 4.88 to 18.35 at the their first visit (Fig. 4). We observed volume decreases in cortical regions and volume increases in subcortical regions other than caudate, putamen and pallidum—all bilaterally. Cortical gray matter volume decreases in both sides of precuneus, isthmus cingulate, superior parietal and frontal pole areas can be around 18% over these roughly 13 years, while volume increases in brain stem, left ventral diencephalon and right lateral ventricle can be 16%. The pattern of volume changes of the LASSO-selected regions over the 2 years shown in Fig. 3 is quite similar to the maturation pattern of these regions over 13 years shown in Fig. 4.

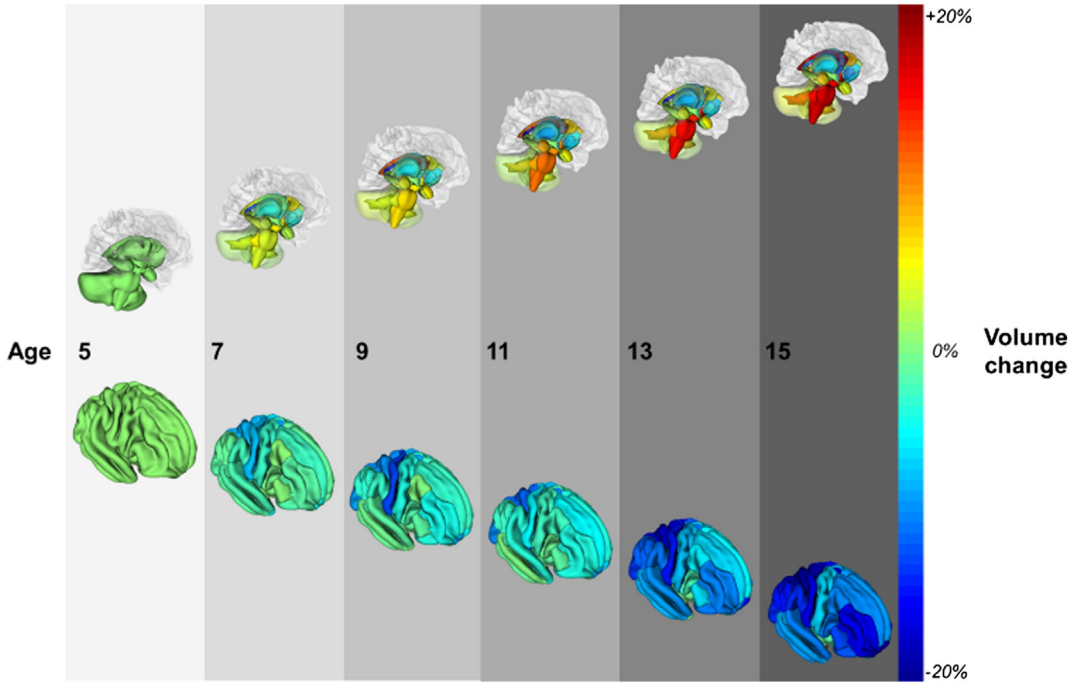

Fig. 4. Cortical and subcortical volume changes of 303 healthy subjects aged 4.88 to 18.35 years. Cortical regions decrease in volume and subcortical regions increase in volume other than caudate, putamen and pallidum.

Discussion

We have shown that the brain maturation index we developed based on cross-sectional neuroanatomical scans can accurately predict individual brain maturation longitudinally. The accuracy of predictions on longitudinal scans is similar to the accuracy of cross-validated predictions on cross-sectional scans. We have also shown that the brain regions that are informative for brain maturation prediction can capture the longitudinal brain maturation between the two visits. To our knowledge, this is the first study that validates the longitudinal change captured by a brain maturation index based on cross-sectional data in children and adolescents.

Comparison with other brain maturation indices

There are different ways to develop a brain maturation index. The focus of the current study was to use a small number of brain features (brain region volumes) that were objectively selected and were easy to interpret in predicting individual brain maturation measured both cross-sectionally and longitudinally.

Brain maturation index developed with voxel-based data, such as voxel-based morphometry (VBM), usually involves more than 100,000 voxel features (Franke et al., 2012). The large number of features requires special methods to spatially register the image to a common template (Ashburner and Friston, 2000), as well as perform data dimensionality reduction using computational tools, such as principle component analysis (PCA), in order to reduce the number of features (Mwangi, Tian, and Soares, 2014). The prediction is made with predictors in a transformed space. Thus, to interpret the result in these studies, we need to transform the predictors back to the original voxel space with high dimensions (Erus et al., 2014; Franke et al., 2012). The brain maturation index we have developed uses atlas-based brain region volumes in each subject native brain space without any further spatial registration and transformation after preprocessing. Thus, our brain maturation index involves no transformation, and every predictor, the region volume, is in its original form. Furthermore, the total number of brain region features is only 37, selected objectively by the same model that is used to make the individual subject maturation prediction. These factors make the model more tractable, though with a slight sacrifice of prediction accuracy, compared with other brain maturation indices (Brown et al., 2012; Franke et al., 2012). It will be also interesting to compare brain maturation index derived from neuroanatomical features with growth charts derived from neurocognitive measurements (Gur et al., 2014).

Potential clinical applications

The brain maturation index as a potential clinical marker

We suggest that the brain maturation index may have potential valuable clinical applications. For example, a given subject with a brain maturation index that is much lower than the index of majority normal subjects could have a delayed maturation and may need to be followed-up closely, which provides the opportunity of early preventive intervention. Erus and colleagues showed that the subjects with lower than normal brain maturation indices have worse cognitive performances than subjects with higher indices (Erus et al., 2014). Gaser and colleagues successfully used a brain aging index to predict patients with mild cognitive impairment, who later converted to Alzheimer's disease (Gaser, Franke, Klöppel, Koutsouleris, and Sauer, 2013).

With longitudinal data available, we can further check the trajectory of an individual's brain maturation index with multiple measurements, and confirm if the trajectory deviates from the normal trajectory (Fig. 1b). For each of different psychiatric disorders, it will be possible to establish a longitudinal brain maturation index trajectory. The disorder specific trajectory will help to consolidate and clarify the existing diagnosis derived from symptoms alone, especially when the symptoms are similar between several morbidities. The trajectory could possibly help to verify treatment effect, as an individual positive responder to a treatment may show a trajectory different to an individual who does not respond to a treatment (Chen et al., 2007).

The brain maturation index components as clinical markers

Our brain maturation index can be decomposed into different components, such as cortical and subcortical components. The component index can give us an overall picture of a subset of brain features used by the brain maturation index. This will be useful, when we know that for a population at risk for psychiatric disorders, certain brain regions are more possible to be altered during brain maturation.

Data integration beyond brain imaging with the same method

The implementation of the current brain maturation index is a general method, and can be extended to other brain imaging methods, such as functional imaging, as well as genetic expressions and clinical assessments. The best way to put together data that are acquired from distinguishingly different modalities, such as brain imaging data, genetic data and behavioral/neuropsychological data, is still not clear. However, similar methods that regulate a group of features based on how they are measured are available, such as group LASSO (Wang and Leng, 2008; Yuan and Lin, 2006).

Limitations

The brain maturation index generated by LASSO could only capture the linear relationship between the multiple brain region volumes and brain maturity and it does not directly take the non-linear component into account. However, the current brain maturation index can still be applied to a linear combination of brain regions that follow non-linear trajectories during maturation, as long as explicit non-linear functions are given. A more thorough brain maturation index that takes into account the non-linearity may have a better accuracy than the current one, with a possible sacrifice of simplicity, tractability and ease of explanation.

A possible dilemma we may face when using the brain maturation index as a clinical marker is that a high accuracy of predictions of normal brain maturation does not guarantee a high sensitivity of detecting abnormal maturation. The reason is that, as the brain maturation index takes into account individual differences, some abnormal differences of brain features are absorbed into the index and are considered as normal. One way to prevent this situation is limiting the numbers of predictors used in the brain maturation index and making each predictor tractable and explainable in the original brain image, such as the brain maturation index we have developed in this study. The optimal way is to use disorder-specific brain features that are also predictive for normal individual.

Conclusion

In this study, we developed a brain maturation index based on cross-sectional atlas-based brain images. The cross-sectional brain maturation index was validated with longitudinal brain images. The brain maturation index could accurately summarize and predict neuroanatomical changes in the brain during maturation at individual level. From a neuropsychiatric perspective, this brain maturation index can be applied to identify individuals following abnormal neurodevelopment, which may help identifying people at risk for psychiatric disorders, consolidating diagnosis based on symptoms and verifying treatment effect.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.05.071.

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