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A new method for structural volume analysis of longitudinal brain MRI data and its application in studying the growth trajectories of anatomical brain structures in childhood

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ABSTRACT

Cross-sectional analysis of longitudinal anatomical magnetic resonance imaging (MRI) data may be suboptimal as each dataset is analyzed independently. In this study, we evaluate how much variability can be reduced by analyzing structural volume changes in longitudinal data using longitudinal analysis. We propose a two-part pipeline that consists of longitudinal registration and longitudinal classification. The longitudinal registration step includes the creation of subject-specific linear and nonlinear templates that are then registered to a population template. The longitudinal classification step comprises a four-dimensional expectation-maximization algorithm, using *a priori* classes computed by averaging the tissue classes of all time points obtained cross-sectionally.

To study the impact of these two steps, we apply the framework completely ("LL method": Longitudinal registration and Longitudinal classification) and partially ("LC method": Longitudinal registration and Cross-sectional classification) and compare these with a standard cross-sectional framework ("CC method": Cross-sectional registration and Cross-sectional classification).

The three methods are applied to (1) a scan–rescan database to analyze reliability and (2) the NIH pediatric population to compare gray matter growth trajectories evaluated with a linear mixed model.

The LL method, and the LC method to a lesser extent, significantly reduced the variability in the measurements in the scan–rescan study and gave the best-fitted gray matter growth model with the NIH pediatric MRI database. The results confirm that both steps of the longitudinal framework reduce variability and improve accuracy in comparison with the cross-sectional framework, with longitudinal classification yielding the greatest impact.

Using the improved method to analyze longitudinal data, we study the growth trajectories of anatomical brain structures in childhood using the NIH pediatric MRI database. We report age- and gender-related growth trajectories of specific regions of the brain during childhood that could be used as a reference in studying the impact of neurological disorders on brain development.

Introduction

Structural age-related change measurements from brain magnetic resonance imaging (MRI) are crucial to the study of normal brain growth and to understanding the biological process underlying brain development. They are also important in assessing the impact of neurological disorders and neurodegenerative diseases on brain growth.

Whereas a cross-sectional study involves only one structural measurement per subject, in a longitudinal study, multiple measurements are taken per subject. Indeed, subjects in cross-sectional MRI studies are scanned only once, while those in longitudinal studies are scanned repeatedly over time. Thus, longitudinal studies allow the observation of individual patterns of change.

To study age-related changes in cerebral structures during childhood, previous studies used either cross-sectional (Lange, 2011) or longitudinal brain MRI scans (Giedd et al., 1999; Lenroot and Giedd, 2006). In studies that used longitudinal pediatric brain MRI scans, each scan of a specific subject was analyzed independently. The

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structural brain measurements were computed without considering the longitudinal consistency between the scans of a single subject.

Recent methods reduce within-subject variability by taking into account longitudinal consistency whether for registration or tissue segmentation (Reuter et al., 2012; Wu et al., 2012).

Longitudinal registration was first proposed by Shen and Davatzikos (2004), who computed deformations between longitudinally acquired subject scans and a four-dimensional (4D) template. Thereafter, methods using consistent diffeomorphic registration of longitudinal images were presented (Durrleman et al., 2009; Lorenzi et al., 2010), and more recently, the creation of a subject-specific linear template was introduced (Reuter et al., 2012).

Regarding longitudinal classification, one proposed method incorporated longitudinal consistency constraints in a 3D fuzzy clustering segmentation (Xue et al., 2006), while another presented 4D image segmentation with a graph cut algorithm (Wolz et al., 2010).

Inspired by this previous work, we introduce a new method to measure structural volume changes in longitudinal MRI scans in which longitudinal information is used for both registration and segmentation. First, we propose the creation of linear and nonlinear subject-specific templates. Each time point is registered to the subject-specific template, which is registered to the population template, thus making the registration of time points to the population template more consistent. Second, we combine this registration with a 4D expectation-maximization (EM) algorithm for tissue classification, using *a priori* classes computed by averaging the tissue classes of all time points obtained cross-sectionally. This step allows us to take advantage of the longitudinal consistency of the classification.

The goal of the present paper is twofold. First, we study how longitudinal registration and longitudinal classification improve the longitudinal measurements. The longitudinal pipeline is compared with both a cross-sectional pipeline and a hybrid pipeline that combines longitudinal registration with cross-sectional tissue classification. These three pipelines are applied to a scan–rescan database to study the variability in the measurements and to the National Institutes of Health (NIH) MRI study of normal brain development (Evans, 2006) to study the impact of the variability in measurements on the gray matter (GM) growth curve models.

Second, we apply the longitudinal pipeline to report the growth trajectories of different anatomical brain structures in childhood using the NIH pediatric MRI database. We compare these growth trajectories with previously reported trajectories obtained from cross-sectional and longitudinal datasets.

Experimental results using the scan–rescan data as well as the longitudinal data from a large ensemble of subjects show that the variability of segmented volumes decreases by half as more consistent priors are used for tissue classification across all time points when using the proposed longitudinal image processing procedures.

Longitudinal method (LL)

The longitudinal pipeline ("LL method": Longitudinal registration and Longitudinal classification) comprises the registration framework and classification framework defined below. Fig. 1 shows a flowchart detailing the steps involved in the LL method and the volume and registration notations used below.

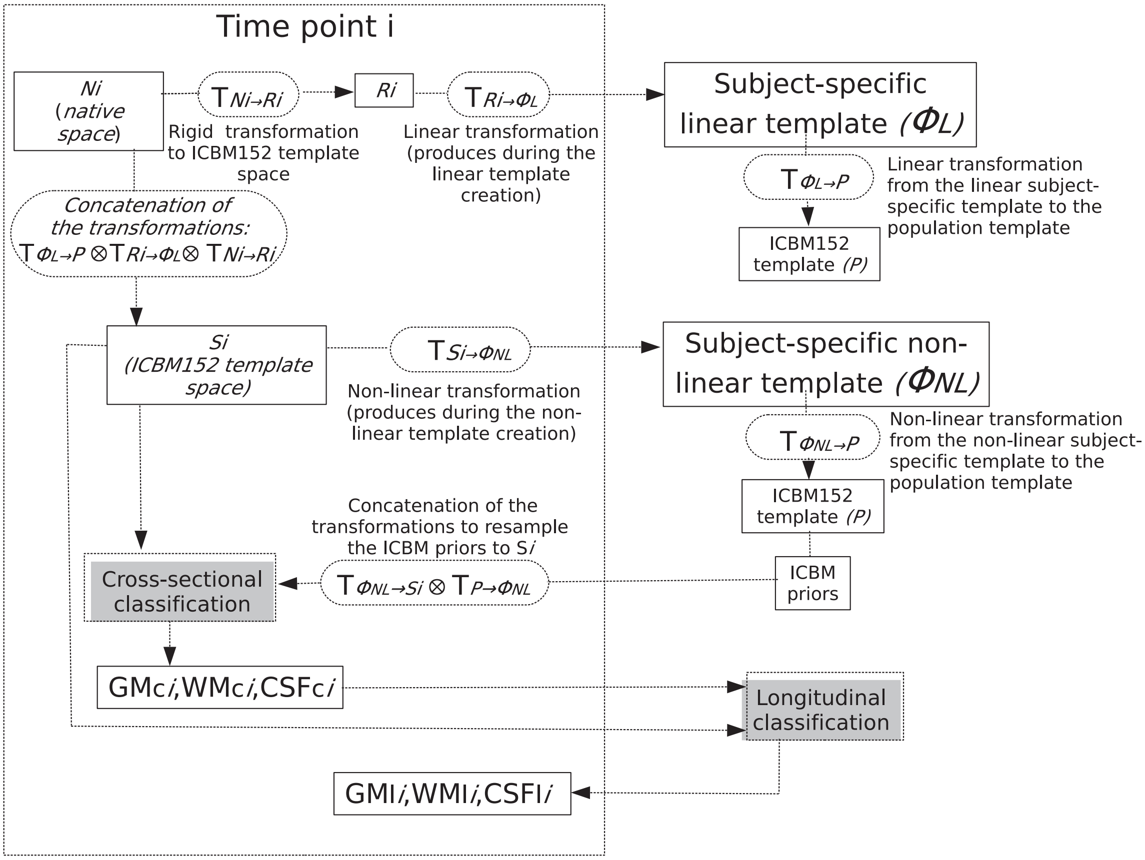

Fig. 1. Flow diagram of the LL method, for time point *i*. (*Ni*: native T1w data from time point i; *Ri*: T1w data from time point i aligned with the other time points in the ICBM152 template space but not scaled; *Si*: T1w data from time point *i* linearly resampled in the ICBM152 template space; GMci/WMci/CSFci: cross-sectional classification results for time point *i*; GMli/WMli/CSFli: longitudinal classification results for time point i; $\mathcal{T}x\rightarrow y$: transformation from volume x to volume y; ⊗: concatenation of transformations using the convention of concatenating paths from right to left.)