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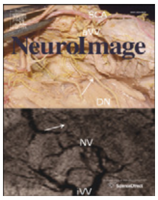

Measuring the dynamic longitudinal cortex development in infants by reconstruction of temporally consistent cortical surfaces

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ABSTRACT

Quantitative measurement of the dynamic longitudinal cortex development during early postnatal stages is of great importance to understand the early cortical structural and functional development. Conventional methods usually reconstruct the cortical surfaces of longitudinal images from the same subject independently, which often generate longitudinally-inconsistent cortical surfaces and thus lead to inaccurate measurement of cortical changes, especially for vertex-wise mapping of cortical development. This paper aims to address this problem by presenting a method to reconstruct temporally-consistent cortical surfaces from longitudinal infant brain MR images, for accurate and consistent measurement of the dynamic cortex development in infants. Specifically, the longitudinal development of the inner cortical surface is first modeled by a deformable growth sheet with elasto-plasticity property to establish longitudinally smooth correspondences of the inner cortical surfaces. Then, the modeled longitudinal inner cortical surfaces are jointly deformed to locate both inner and outer cortical surfaces with a spatial–temporal deformable surface method. The method has been applied to 13 healthy infants, each with 6 serial MR scans acquired at 2 weeks, 3 months, 6 months, 9 months, 12 months and 18 months of age. Experimental results showed that our method with the incorporated longitudinal constraints can reconstruct the longitudinally-dynamic cortical surfaces from serial infant MR images more consistently and accurately than the previously published methods. By using our method, for the first time, we can characterize the vertex-wise longitudinal cortical thickness development trajectory at multiple time points in the first 18 months of life. Specifically, we found the highly age-related and regionally-heterogeneous developmental trajectories of the cortical thickness during this period, with the cortical thickness increased most from 3 to 6 months (16.2%) and least from 9 to 12 months (less than 0.1%). Specifically, the central sulcus only underwent significant increase of cortical thickness from 6 to 9 months and the occipital cortex underwent significant increase from 0 to 9 months, while the frontal, temporal and parietal cortices grew continuously in this first 18 months of life. The adult-like spatial patterns of cortical thickness were generally present at 18 months of age. These results provided detailed insights into the dynamic trajectory of the cortical thickness development in infants.

Introduction

The human cerebral cortex develops from a smooth neural tube into a highly folded and complex structure (Nie et al., 2012), with extensive forming of cortical folding during the third trimester (Chi et al., 1977; Dubois et al., 2008). At term birth, all primary and secondary foldings of the human cerebral cortex have been well established (Chi et al., 1977; Dubois et al., 2008; Hill et al., 2010a), although the cortical surface area is only one-third of that of the adult brain (Hill et al., 2010a). Also, after term birth, the primary and secondary cortical foldings are well preserved during the postnatal cortex development, while the cortex size and some tertiary folding structures are still undergoing dynamic development, especially in the first year of life (Li et al., 2013a; Nie et al., 2012; Shi et al., 2010a, 2011). For example, the cortical surface area expands 1.8 times (Li et al., 2013a) and the cortical gray matter volume doubles (Gilmore et al., 2012) during the first year of life. Quantitative measurement of the dynamic cortex development during this critical stage is of vital importance to understand the normal cortical structural development and its relationship to the high-level functional development (Gilmore et al., 2012; Knickmeyer et al., 2008).

In studying the dynamic cortex development in infants, the reconstruction of cortical surfaces from longitudinal infant brain MR images plays a vital role. In contrast to volume-based analysis, cortical surface-based methods are well-suited for studying the highly convoluted cerebral cortex, as these methods respect the topology of the cortex and facilitate the analysis and visualization of buried

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sulcal regions (Dale et al., 1999; Van Essen, 2005). Therefore, cortical surfaces have been widely used for measuring anatomical attributes of the cortex, such as surface area (Hill et al., 2010b; Li et al., 2013a), cortical thickness (Fischl and Dale, 2000; Xue et al., 2007), sulcal depth (Hill et al., 2010a; Li et al., 2013b), cortical folding (Awate et al., 2010; Dubois et al., 2008; K. Li et al., 2010; Nie et al., 2012; Zhang et al., 2009), and gyrification index (Schaer et al., 2008), as well as for performing surface-based registration/parcellation (Fischl et al., 1999; Li and Shen, 2011; Li et al., 2009; G. Li et al., 2010; Liu et al., 2004; Van Essen, 2004; Yeo et al., 2010) and the functional mapping (Van Essen et al., 1998). Many methods have been developed for reconstruction of cortical surfaces from brain MR images (Dale et al., 1999; Han et al., 2004; Joshi et al., 1999; Kim et al., 2005; Liu et al., 2008; MacDonald et al., 2000; Shattuck and Leahy, 2002; Shi et al., 2013; Van Essen et al., 2001; Xu et al., 1999; Xue et al., 2007), however, these methods were mainly designed for working on a single MR image in the cross-sectional studies.

Recently, longitudinal analysis has become increasingly important in studying normal brain development and neurodevelopmental disorders using serial MR images (Almli et al., 2007; Fan et al., 2011; Geng et al., 2012; Gilmore et al., 2012; Li et al., 2013a; Nie et al., 2012, 2013a, 2013b; Schumann et al., 2010). Compared to cross-sectional studies, longitudinal studies can reduce the confounding effect of between-subject variability and increase statistical power, as well as capture individual temporal trajectories of the underlying biological processes (Bernal-Rusiel et al., 2012). However, applying the cortical surface reconstruction methods developed for cross-sectional studies independently to each time-point image in the longitudinal study will likely generate longitudinally-inconsistent cortical surfaces, and thus lead to inaccurate measurements of cortical changes. This may become more serious in vertex-wise mapping of cortical changes, due to the potential inconsistency of many sub-steps in the sophisticated cortical surface reconstruction pipelines, such as tissue segmentation, topology correction, surface tessellation, and surface evolution (G. Li et al., 2012). To this end, recently several methods have been proposed for the reconstruction of consistent cortical surfaces from the serial adult MR images with subtle longitudinal changes (G. Li et al., 2012; Nakamura et al., 2011; Reuter et al., 2012). For example, in the longitudinal pipeline of FreeSurfer, a within-subject template is first built by rigidly aligning all longitudinal images of the same subject to a mean or median image, and then the cortical surfaces of the within-subject template are reconstructed, which will be rigidly transformed back to the space of each longitudinal image as an initialization and further evolved independently towards the reconstruction of longitudinal cortical surfaces (Reuter et al., 2012). Although this strategy might be suitable for adult brain MR images, it becomes problematic when applied to the longitudinal infant brain MR images with dynamic longitudinal cortex changes. In addition, all longitudinal cortical surfaces of the same infant need to be normalized onto a common space for measuring longitudinal development. This is typically performed by feature-driven surface registration methods, which may lead to temporally inconsistent or even bumpy correspondences especially in the flat cortical surface regions with no distinctive geometric features, and thus eventually affect the accurate and consistent measurement of the dynamic cortical development (Nie et al., 2012).

To deal with these issues, in our previous work (Nie et al., 2012), we have developed a computational cortical growth model for consistent, accurate modeling and measurement of dynamic cortex development using longitudinal MR images in the first year of life. Specifically, in our cortical growth model, the cerebral cortex is represented by its inner cortical surface (white-gray matter interface), and its growth is modeled by a deformable elasto-plasticity sheet with the guidance from the cortical surface at the later developmental stage (Nie et al., 2012). However, one notable limitation in this method is that, since only the inner cortical surface is adopted to represent and model the cerebral cortex development, certain important anatomical attributes of the cortex could not be derived in this model. For example, the cortical thickness, which reflects the underlying microstructure changes of the cortex and is associated with many neurodevelopmental disorders and cognitive functioning, is normally defined relying on both inner and outer cortical surfaces (Fischl and Dale, 2000) and thus cannot be measured (Nie et al., 2012).

In order to accurately and consistently measure the longitudinal development of cortex attributes that are related to the outer cortical surface in infants, in this paper, by taking advantage of the cortical growth model (Nie et al., 2012), we propose a spatial–temporal deformable surface method for consistent reconstruction of both inner and outer cortical surfaces from longitudinal infant brain MR images in the first 18 months. Given the longitudinally-consistent tissue segmentation results of infant brain MR images (Wang et al., 2012), our method consists of the following two major steps as shown in Fig. 1. First, the longitudinal growth model of the inner cortical surface is built by a deformable sheet with the elasto-plasticity property to establish longitudinally-consistent vertex-wise correspondences of the dynamic inner cortical surfaces. Second, the modeled longitudinal inner cortical surfaces are used to initialize all longitudinal inner and outer cortical surfaces and then all longitudinal cortical surfaces are jointly deformed with a spatial–temporal deformable surface method to reconstruct the longitudinally-consistent inner and outer cortical surfaces. The advantage of the proposed method for longitudinal infant cortical surface reconstruction is that all longitudinal inner and outer cortical surfaces of the same infant have the same triangular mesh configurations, and thus both temporal and inner-to-outer surface correspondences are naturally established, importantly for accurate and consistent measurement of dynamic cortex development.

Materials and methods

Subjects

The Institutional Review Board of the University of North Carolina (UNC) School of Medicine approved this study. Pregnant mothers were recruited during the second trimester of pregnancy from the UNC hospitals. Informed consent was obtained from both parents. Exclusion criteria included abnormalities on fetal ultrasound, or major medical or psychotic illness in the mother. Infants in the study cohort were free of congenital anomalies, metabolic disease, and focal lesions. No sedation was employed and all subjects were imaged during natural sleep. A physician or nurse was present during each scan, and a pulse oximeter was used to monitor heart rate and oxygen saturation. A total of 37 healthy infants were recruited to undergo a longitudinal MR imaging study of early brain development, where each infant was planned to be scanned every 3 months from birth till year 1 and again at 18 months. So far, 14 subjects completed all 6 time points, where one subject exhibited severe motion related artifacts and was removed from study. Thus, the proposed method were applied to 13 healthy infants (9 males/4 females), each with 6 serial brain MR scans (acquired at 2 weeks, 3, 6, 9, 12 and 18 months, respectively).

Image acquisition

Longitudinal T1, T2, and diffusion-weighted MR images of infants were acquired using a 3 T Siemens scanner (TIM TRIO, Siemens) with a 32 channel head coil, allowing parallel imaging to shorten acquisition time. T1 images (160 axial slices) were acquired with the following imaging parameters: Time to Repeat [TR] = 1900 ms, Time to Echo [TE] = 4.38 ms, flip angle = 7, acquisition matrix = 256 × 192, voxel resolution = $1 \times 1 \times 1$ mm^3 and field of view (FOV) = 256 × 192 mm^2. T2 images (70 axial slices) were acquired with the imaging parameters: TR/TE = 7380/119 ms, flip angle = 150, acquisition matrix = 256 × 128, voxel resolution = $1.25 \times 1.25 \times 1.95$ mm^3, and FOV = 320 × 160 mm^2. Diffusion-weighted images (60 axial slices) were acquired with the imaging parameters: TR/TE = 7680/82 ms,