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A Bayesian approach to the creation of a study-customized neonatal brain atlas

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ABSTRACT

Atlas-based image analysis (ABA), in which an anatomical "parcellation map" is used for parcel-by-parcel image quantification, is widely used to analyze anatomical and functional changes related to brain development, aging, and various diseases. The parcellation maps are often created based on common MRI templates, which allow users to transform the template to target images, or vice versa, to perform parcel-by-parcel statistics, and report the scientific findings based on common anatomical parcels. The use of a study-specific template, which represents the anatomical features of the study population better than common templates, is preferable for accurate anatomical labeling; however, the creation of a parcellation map for a study-specific template is extremely labor intensive, and the definitions of anatomical boundaries are not necessarily compatible with those of the common template. In this study, we employed a volume-based template estimation (VTE) method to create a neonatal brain template customized to a study population, while keeping the anatomical parcellation identical to that of a common MRI atlas. The VTE was used to morph the standardized parcellation map of the JHU-neonate-SS atlas to capture the anatomical features of a study population. The resultant "study-customized" T1-weighted and diffusion tensor imaging (DTI) template, with three-dimensional anatomical parcellation that defined 122 brain regions, was compared with the JHU-neonate-SS atlas, in terms of the registration accuracy. A pronounced increase in the accuracy of cortical parcellation and superior tensor alignment were observed when the customized template was used. With the customized atlas-based analysis, the fractional anisotropy (FA) detected closely approximated the manual measurements. This tool provides a solution for achieving normalization-based measurements with increased accuracy, while reporting scientific findings in a consistent framework.

Introduction

Advances in magnetic resonance imaging (MRI) have enabled significant progress in the characterization of neonatal brain development (Chan et al., 2012; Courchesne et al., 2000; Hasan et al., 2010; Huppi et al., 1998; Knickmeyer et al., 2008; Knickmeyer et al., 2011; Lodygensky et al., 2010; Oishi et al., 2011; and Qiu et al., 2013), and in the early detection of neurological abnormalities (Bartzokis, 2002; Bava et al., 2007; Brown et al., 2002; Courchesne et al., 2001; Hazlett et al., 2012; Hermann et al., 2010; Kalpakidou et al., 2012; Murakami et al., 1999; Worley et al., 1996). These studies commonly applied whole-brain analysis as a hypothesis-free method to quantify neuroanatomical development, or to explore the effects of various brain injuries. Whole-brain analysis could be performed on a template space or on original image space. For example, voxel-based analysis uses a template space to which all raw images are mathematically transformed. This template space provides a basis for common anatomical locations on multiple images to allow voxel-by-voxel statistical analysis. On the other hand, atlas-based analysis (ABA) can be performed on an original image space. Namely, a pre-segmented set of anatomical structures for the entire brain (parcellation map) in a template space can be transformed to the original image to quantify the volume of each anatomical structure, as well as to measure the intensities of the images (Aljabar et al., 2009; Collins et al., 1995; Heckemann et al., 2006; Heckemann et al., 2010; Jia et al., 2012; Joshi et al., 2004; Klein and Hirsch, 2005; Maldjian et al., 2003; Mori et al., 2008; Oishi et al., 2009; Oishi et al., 2008; Tzourio-Mazoyer et al., 2002; Warfield et al., 2004). This ABA is suitable for creating a "growth percentile chart" of each anatomical

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structure, which is necessary to interpret individual images based on population statistics (Oishi et al., 2013).

To perform the whole-brain analysis of the neonatal brain, a common atlas has become a pressing demand for both VBA and ABA. The brain tissue composition of the neonatal brain is substantially different from that of the adult brain; for instance, the gray/white matter contrast is reversed compared to the adult brain. Furthermore, rapidly increasing myelination during early brain development alters the gray/white matter contrast, but at different rates depending on the brain regions (Barkovich et al., 1988; Huppi et al., 1998; van der Knaap and Valk, 1990). These unique features of the neonatal brain have motivated the development of dedicated neonatal brain MRI templates (Kazemi et al., 2007; Oishi et al., 2011; Prastawa et al., 2005; Sanchez et al., 2012; Shi et al., 2010; Shi et al., 2011; Song et al., 2007; Weisenfeld et al., 2006; Weisenfeld and Warfield, 2009; Xue et al., 2007). Among these, the Johns Hopkins University (JHU)-neonate atlas (Oishi et al., 2011) was specifically developed for multimodal (T1- and T2-weighted structural MRI and DTI) analysis and ABA. The JHU-neonate atlas consists of group-averaged templates based on linear and nonlinear image transformations, as well as a single-subject template (JHU-neonate-SS). A single-subject template, with an image contrast similar to that of an original subject image, is suitable for high-order nonlinear registration (Wu et al., 2011; Zhang et al., 2014), in which the image intensity provides a cost function for optimizing mapping. The sharp image contrast also enables the definition of clear boundaries of various anatomical structures, which results in a detailed parcellation map (PM) of 122 anatomical structures. The main advantage of using this parcellation map is that it provides a common reference for consistent anatomical labeling. Indeed, the definition of the anatomical boundary of each brain structure is often ambiguous; for example, the reported normal hippocampal volumes differ by up to 2.5-fold, depending on the definition of the boundary that is manually drawn to measure the volume (Boccardi et al., 2011). The use of a standardized PM is important to avoid inter-institutional, inter-reader, and intra-reader variability of anatomical boundary definitions, and thus, enables researchers to report their findings in a consistent manner (Bai et al., 2012; Qiu et al., 2013; Ratnarajah et al., 2013).

It is well recognized that a study-specific template that is created based on the average anatomical features of a study group, rather than on a generic template, is important for achieving higher registration accuracy (Fonov et al., 2011; Hamm et al., 2009; Jia et al., 2011; Klein et al., 2010; Tang et al., 2009). However, little attempt has been made to create a study-specific neonate template for ABA due to several challenges. The creation of a parcellation map is extremely labor intensive because it must cover the entire brain three-dimensionally, and manual drawing requires professional anatomical knowledge. More importantly, even if such a study-specific template with a parcellation map could be created, the anatomical boundary of the study-specific parcellation map would not exactly match that of the standardized parcellation map; therefore, results may not be directly comparable to those obtained with a standardized parcellation map.

The purpose of this study was to create a neonatal brain template with a parcellation map (PM) specifically customized for a study group, while keeping the PM boundary definitions consistent with that of the JHU-neonate-SS atlas. The volume-based template estimation (VTE) technique (Ma et al., 2008; Zhang et al., 2011, 2014) was employed to customize the JHU-neonate-SS atlas to represent the average anatomical features of the study group. In a deformable template model of computational anatomy, the images are regarded as the orbit under the diffeomorphic transformations acting on templates. The VTE technique is based on this model; namely, the brain anatomical shapes are treated as a random orbit under the action of the group of diffeomorphisms (Grenander and Miller, 1998), and the variability of anatomical shapes is balanced based on a geodesic metric measure. That means that, when the created atlas remains in the orbit of the initial JHU-neonate-SS template in shape space, the topology of the atlas image remains unchanged. The group 'center' is obtained by a metric-based averaging, which is different from relying on cross-subject intensity averaging (Joshi et al., 2004). In addition, a Bayesian framework is combined with the metric averaging for atlas estimation by iteratively deforming an initial atlas (chosen as the JHU-neonate-SS atlas) to the 'center' of the group (Allassonniere et al., 2007; Ma et al., 2008, 2010; Zhang et al., 2011, 2014). The neonatal atlas thus created is expected to remain in the orbit of the initial JHU-neonate-SS in shape space. We further examined the registration performance of our customized neonatal atlas with respect to the original JHU-neonate-SS atlas, and applied our new atlas to the atlas-based analysis of FA measurements.

Materials and methods

Neonatal brain MRI data

Subjects

The subject scans used for this study were obtained from neonates who were recruited and scanned at the MR Research Center at the University of Hawai'i and the Queen's Medical Center in Honolulu, HI. The research was reviewed and approved by the institutional review boards from both institutions, and each parent provided a written consent for the neonates to be studied and for data sharing. The brain MRI data for these infants were de-identified to create our database. The database contains nine full-term, healthy neonates from two to 13-days old (38.4 to 41.1 weeks post-menstrual age (PMA) at birth; 39 to 42.8 weeks PMA at scan), and includes two boys and seven girls.

Data acquisition

The MR scans were performed without sedation while the infants were asleep. The infants were fed by their mothers and allowed to fall asleep naturally. Each baby was wrapped in a vacuum immobilization mat (Noras MRI Products, Hoechberg, Germany) and the ears were covered with earmuffs. The subjects were then placed on cushions that occupied the space between the subject and the RF coil.

T1- and diffusion-weighted images were acquired using a 3 Tesla Siemens scanner (TIM Trio, Siemens Medical Systems, Erlangen, Germany). MPRAGE images were acquired using an echo time of 4.15 ms and a repetition time of 3.2 s, a flip angle of 7°, with an imaging matrix of $176 \times 256 \times 160$, and a 1 mm isotropic in-plane resolution. The slice orientation was sagittal and the slice thickness was 1 mm. For DTI data, diffusion-weighted images were acquired with an imaging matrix of 80×80 and a field of view of 160×160 mm, which gave a nominal 2 mm isotropic in-plane resolution. The matrix was zero-filled to 256×256 mm. The slice orientation was axial with a 2.5 mm thickness parallel to the anterior–posterior commissure (AC–PC) line. Forty to fifty slices covered the entire hemisphere and the brainstem. The echo time was 90 ms and the repetition time was 9.5 s. Diffusion weighting was applied along 12 independent axes (Jones et al., 1999), with $b = 1000$ s/mm^2. The scanning time for one complete DTI dataset was approximately three minutes.

Data processing

The quality of the raw images was reviewed to remove scans without whole-brain coverage. The T1-w images were manually skull-stripped and rigidly aligned to the JHU-neonate-SS atlas (Oishi et al., 2011) according to the AC–PC line, and re-sampled to match the dimension of the JHU-neonate-SS (matrix: $180 \times 220 \times 180$, with 0.6 mm isotropic resolution). Pre-processing of the diffusion-weighted images was performed using the DTIStudio software (Jiang et al., 2006). The fractional anisotropy (FA) and TRACE contrasts were calculated, and these images were skull-stripped with manual touch-up, and rigidly aligned to the JHU-neonate-SS atlas according to the AC–PC line.