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Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression

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ABSTRACT

Medical imaging has shown that, during early development, the brain undergoes more changes in size, shape and appearance than at any other time in life. A better understanding of brain development requires a spatio-temporal atlas that characterizes the dynamic changes during this period. In this paper we present an approach for constructing a 4D atlas of the developing brain, between 28 and 44 weeks post-menstrual age at time of scan, using T1 and T2 weighted MR images from 204 premature neonates. The method used for the creation of the average 4D atlas utilizes non-rigid registration between all pairs of images to eliminate bias in the atlas toward any of the original images. In addition, kernel regression is used to produce age-dependent anatomical templates. A novelty in our approach is the use of a time-varying kernel width, to overcome the variations in the distribution of subjects at different ages. This leads to an atlas that retains a consistent level of detail at every time-point. Comparisons between the resulting atlas and atlases constructed using affine and non-rigid registration are presented. The resulting 4D atlas has greater anatomic definition than currently available 4D atlases created using various affine and non-rigid registration approaches, an important factor in improving registrations between the atlas and individual subjects. Also, the resulting 4D atlas can serve as a good representative of the population of interest as it reflects both global and local changes. The atlas is publicly available at www.brain-development.org.

Introduction

In recent years, the ability to perform in-vivo imaging has made it possible to image large and diverse populations with high resolution and high contrast. Furthermore, with recent advances in computational anatomy, we can represent a population as a whole by creating an average model or an atlas to represent the population instead of using a single image of an exemplar subject. Average atlases have received increasing attention in the area of medical image analysis because of their importance in the analysis of population data. For instance, average atlases can be useful in detecting abnormalities by measuring the variations in anatomy between an atlas and an individual subject (Aljabar et al., 2008; Christensen et al., 1994; Essen and David, 2002; Evans and Group, 2006; Evans et al., 1993; Mazziotta et al., 2001a,b; Thompson et al., 2000a,b, 2001).

In early development (before birth and during the first few months), the brain undergoes more changes in size, shape and structure than at any other time in life (Rutherford, 2001). Improved understanding of cerebral development during this critical period is important for mapping normal growth, and for investigating mechanisms of injury associated with risk factors for maldevelopment such as premature birth. Therefore, several studies have reported developmental changes in gray matter (GM) and white matter (WM) volumes, extent of myelination, cortex, and subcortical structures (Aljabar et al., 2008; Ball et al., 2010; Barkovich, 1998; Barkovich et al., 1988; Boardman and Dyet, 2007; Boardman et al., 2003, 2006, 2007; Counsell et al., 2002; Counsell et al., 2003; Ferrie et al., 1999; Gao et al., 2009; Gousias et al., 2008; Huppi et al., 1998; Laule et al., 2007; Ment et al., 2009; Paus et al., 1999, 2001; Prastawa et al., 2005, 2010; Serag et al., 2011; Shi et al., 2010a,b; van der Knaap and Valk, 1990; van der Knaap et al., 1991; Xue et al., 2007). Most of these studies have a limited number of subjects, a narrow age range or focus on a single modality only. The need remains, however, for a multi-modal spatio-temporal atlas to model the dynamic changes during early brain development.

Previous work

Adult brain atlases do not adequately represent the maturational patterns of the developing brain, and the use of an adult model in

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studying early brain growth may introduce substantial bias (Fonov et al., 2011; Kuklisova-Murgasova et al., 2011; Shan et al., 2006; Wilke et al., 2003). Therefore, in the literature, several researchers have proposed to develop a digital atlas of the developing brain. In pediatrics, Joshi et al. (2004) constructed a probabilistic atlas of anatomical structures from 2 year old children, Shan et al. (2006) constructed an atlas of the pediatric human brain from a T1 weighted MR data set of a 9-year old subject, and Jelacic et al. (2006) built a digital atlas facilitates learning about normal changes in the MR appearance of the pediatric brain in subjects younger than 4 years. Also, Wilke et al. (2008) constructed reference templates from 404 healthy children aged 5–18 years. Recently, Fonov et al. (2011) created unbiased, age-appropriate MRI atlas templates for pediatric studies that represent the average anatomy for the age range of 4.5–18.5 years.

In neonates and fetuses, Kazemi et al. (2007) created a neonatal brain template based on high resolution T1 MR images of 7 individuals with gestational ages between 39 and 42 weeks at the dates of examination. Altaye et al. (2008) constructed infant templates and brain tissue probability maps based on the MR brain image data from 76 infants ranging in age from 9 to 15 months. Recently, Habas et al. (2010) constructed a spatio-temporal atlas of the fetal brain that incorporates age-specific MR templates and tissue probability maps from 20 fetuses (20.57 to 24.71 weeks), and Kuklisova-Murgasova et al. (2011) constructed a four-dimensional probabilistic atlas of preterm subjects aged between 29 and 44 weeks.

With regard to methodology, the creation of an atlas requires the mapping of subjects of a population into a common space where they can be compared. Defining such a common space is a major topic of research in medical imaging. In the simplest case, atlases are created from a large number of subjects where a single subject is used to define the common space as in Evans et al. (1993). However, the resulting atlas is biased toward the chosen subject. To reduce or avoid bias in the atlas toward any of the registered subjects, many alternative atlas creation approaches have been proposed. The method presented in Ashburner (2000) and Guimond et al. (2000) endeavors to reduce the bias toward a specific reference by repeating the mapping process of the subjects to a successively updated reference in an iterative manner until the average image converges to a stable atlas. Similar to Joshi et al. (2004) and Avants and Gee (2004), Lorenzen et al. (2005) applied Fréchet mean estimation to develop a statistical framework for constructing unbiased brain atlases. Also, Bhatia et al. (2004) described a groupwise non-rigid registration algorithm to simultaneously register all subjects in a population to a common reference (or natural) coordinate system, which is defined to be the average of the population.

Another method proposed by Seghers et al. (2004) carries out pairwise registration on all pairs of images in the population, and each image is deformed by the average of the deformation fields estimated between the image and all other images. The atlas is thus built by averaging all the deformed images. In the work of Park et al. (2005), an image that is the closest to the geometrical mean of a population is selected as a template by Multi-Dimensional Scaling (MDS) (Cox and Cox, 2000) and subsequently all other images are registered to the selected template in order to achieve the least bias in the atlas construction. However, optimal selection of a single subject does not remove the risk of bias in the final registration. Gerig et al. (2006) described computational anatomy tools for building three-dimensional and four-dimensional atlases of volumetric image data. The method is based on calculating the non-linear average image of a population of images by simultaneous non-linear deformable registration. Rohlfing et al. (2008) created an atlas of normal adult human brain using unbiased non-rigid registration algorithm, which is similar to the one described by Balci et al. (2007). Wilke et al. (2008) proposed a method for constructing reference templates by statistically analyzing a large sample (n = 404) of healthy children. The proposed algorithm was divided into two parts: (a) regression of the reference sample (source population) and (b) template creation for the target population.

Recently, Jia et al. (2010) suggested an atlas construction method using a new group-wise registration framework by constraining each image to deform only locally with respect to its neighbors within the learned image manifold. Avants et al. (2010) proposed an average template generation by finding minimum shape distance in the diffeomorphic space. More recently, Fonov et al. (2011) proposed an atlas generation technique which is based on the work of Guimond et al. (2000). In contrast to Guimond et al. (2000), the work of Fonov et al. (2011) used information from the previous iteration to initialize the non-linear registration at the next iteration, which is particularly important in terms of speed for the convergence of the iterative process.

There are also examples of spatio-temporal atlases in the literature. Davis et al. (2007) proposed a method for constructing a time-varying non-rigid atlas using kernel regression. This kernel regression approach has also been applied to create non-rigid average atlases of the aging brain (Ericsson et al., 2008). Recently, Kuklisova-Murgasova et al. (2011) also used kernel regression to build a 4D probabilistic atlas of preterm subjects, at gestational ages of 29–44 weeks. Habas et al. (2010) used groupwise registration of manual segmentations and voxel-wise non-linear modeling to construct a spatio-temporal atlas of the fetal brain that incorporates age-specific MR templates and tissue probability maps. The main limitations of these atlases lie in their comparatively lower level of anatomic definition and the coverage of a relatively narrow age range.

Contributions

In this paper we present an approach for constructing a 4D atlas of the developing brain using non-rigid registration of MR brain images of preterm infants. We have developed a four-dimensional extension of the approach of Seghers et al. (2004), and have used kernel regression (Nadaraya, 1964) to produce age-dependent anatomical templates. A novelty in our approach is the use of a time-varying kernel width, to overcome the variations in the distribution of subjects at different ages. In order to generate a multi-modal atlas, the registrations are performed on the T2 weighted images and the resulting transformations are used in parallel to deform T1 weighted images. The result is an unbiased spatio-temporal multi-modal atlas with a much clearer level of detail than currently available atlases derived via various affine and non-rigid registration approaches. Moreover, the atlas retains a consistent level of detail at every time-point. We show that the atlas is more suited to specific registration tasks than atlases with lower anatomic definition. Finally, we demonstrate utility of the atlas by constructing growth charts for tissue compartments, which can be used to map brain development in the perinatal period.

Materials and methods

Subjects

This study was carried out using T1 and T2 weighted MR images from 204 premature neonates. The age range at the time of scan was 26.7 to 44.3 weeks post-menstrual age (PMA), with mean and standard deviation of 37.3 ± 4.8 weeks. The histogram of the ages at scan is shown in Fig. 1. All subjects were born prematurely, with mean age at birth 29.2 ± 2.7, range 24.1–35.3 weeks PMA.

MR acquisition

The images were acquired on 3T Philips Intera system with the following parameters: (1) T1-weighted 3D MPRAGE: TR = 17 ms, TE = 4.6 ms, inversion delay = 1500 ms, flip angle = 13°, acquisition