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A spatio-temporal latent atlas for semi-supervised learning of fetal brain segmentations and morphological age estimation

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ABSTRACT

Prenatal neuroimaging requires reference models that reflect the normal spectrum of fetal brain development, and summarize observations from a representative sample of individuals. Collecting a sufficiently large data set of manually annotated data to construct a comprehensive *in vivo* atlas of rapidly developing structures is challenging but necessary for large population studies and clinical application. We propose a method for the semi-supervised learning of a spatio-temporal latent atlas of fetal brain development, and corresponding segmentations of emerging cerebral structures, such as the ventricles or cortex. The atlas is based on the annotation of a few examples, and a large number of imaging data without annotation. It models the morphological and developmental variability across the population. Furthermore, it serves as basis for the estimation of a structures' morphological age, and its deviation from the nominal gestational age during the assessment of pathologies. Experimental results covering the gestational period of 20–30 gestational weeks demonstrate segmentation accuracy achievable with minimal annotation, and precision of morphological age estimation. Age estimation results on fetuses suffering from lissencephaly demonstrate that they detect significant differences in the age offset compared to a control group.

1. Introduction

The analysis of the early development of a fetus in utero offers rich insights into the genesis of human anatomy. In particular, the emerging cerebral morphology is of both clinical and academic interest. The advance of novel imaging methods, such as ultra-fast Magnetic Resonance Imaging (MRI), allows for high-resolution image acquisition in utero (Garel, 2004) and the observation of the rapid fetal cerebral development. Fig. 1 shows an example of the developing brain from 20th to 30th gestational weeks (GW).

Even though fetal MRI provides a wealth of information, clinical assessment is typically performed qualitatively (Ghai et al., 2006). Both, clinicians and researchers need models capturing the developmental characteristics and variability in a large population. They can serve as basis for the study of developmental paths in healthy and patient groups, and as reference during quantitative assessment of individual cases in a clinical setting. One possible solution are spatio-temporal models and corresponding segmentations of brain structures learned from large numbers of in vivo data. A main limitation of this approach is the difficulty of acquiring complete annotation for a sufficiently large number of cases. We propose to learn a model or *atlas* of the development of a fetal anatomical structure as a latent spatio-temporal prior that connects the segmentations across subjects at different gestational ages. Starting from a small set of annotated cases, we learn segmentations for a large population together with spatio-temporal priors that link segmentation and gestational age.

The need to perform quantitative group-wise studies in neuroimaging has motivated intense research aiming at establishing accurate correspondences across individuals and labeling anatomical regions in the brain. In studies investigating the adult brain, this is typically achieved by an annotated atlas that serves as reference template (Fischl et al., 2002, 2004; Smith et al., 2004; Woolrich et al., 2009; Ashburner, 2007). Each individual is

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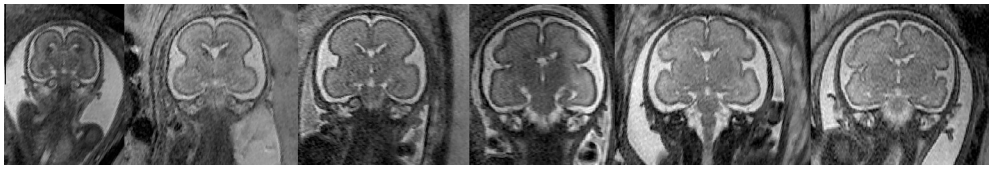

Fig. 1. A consistently positioned coronal slice of different individuals illustrating the cerebral development at GW 20, 22, 24, 26, 28, 30 (from left to right).

registered to the template, and coordinates and region labels such as Brodmann areas (Brodmann, 1909) are transferred accordingly. Templates and reference spaces range from the single subject Talairach template (Talairach and Tournoux, 1988), to the Montreal Neurological Institute (MNI) space with a template based on larger control cohorts (Evans et al., 1993; Mazziotta et al., 1995). Aside from transferring labels to new subjects, an atlas can also reveal characteristics of the population it is build from. Examples are population studies based on voxel-based morphometry or shape analysis to detect differences between adult subject groups (Ashburner and Friston, 2000; Karas et al., 2003), or fetal cohorts (Gholipour et al., 2012). Davis et al. (2007) performed kernel regression to capture spatio-temporal characteristics of the aging human adult brain from MR scans. A similar method using an adaptive kernel was published by Serag et al. (2012) for the developing brain. Spatio-temporal atlases detected developmental speed differences in two chimpanzee species (Durrleman et al., 2009, 2010). Aljabar et al. (2011) reported results on manifold learning as representation of a neonatal dataset, and Kuklisova-Murgasova et al. (2010) introduced an atlas for the developing brain from pre-term infants between the 29th and 44th GW. Encouraging results for fetal data covering a period from GW 20 to 24 were reported in Habas et al. (2010), where the authors presented a spatio-temporal atlas for a dataset of 20 fetal brains imaged in utero by T2-weighted MRI. Spatio-temporal tensor-based volume morphometry was proposed to study the sulcal formation of fetal brains (Rajagopalan et al., 2011). In a recent paper by Gholipour et al. (2012), a spatio-temporal atlas facilitated fetal brain MRI segmentation of patients and normal controls for the detection of ventricle atrophies due to pathologies. Fishbaugh et al. (2012) introduce an interesting approach that learns an atlas of the population via shape regression. In addition, subject-specific growth trajectories are estimated. To measure shape variability, the generic model is warped to individual subjects using diffeomorphic mapping. In their experiments, they analyzed the growth scenario of two different population groups. Results were reported on both a synthetic and a clinical dataset. Latent atlases have been proposed to connect segmentations in multi-modal imaging data of pathologies, such as brain-tumors (Riklin-Raviv et al., 2009). The latent atlas is learned from partially annotated imaging data to capture the varying representation of tissue properties across modalities. It learns potentially different segmentations in all modalities and a latent prior that represents the tumor presence across the registered imaging data. While Riklin-Raviv et al. (2009) accounts for variability across the data, it does not incorporate parameters such as time, or age, that might have a systematic effect on the shape, or distribution of anatomical structures. Time is crucial when observing developmental processes or disease progression. Its effect can be substantial, and the integration of parameters that have a characteristic effect is conceptually different from random variability in a population.

In this paper, we propose a method to build a spatio-temporal latent atlas capturing the development characteristics of cerebral structures during early human brain development. Instead of exhaustive annotation of anatomical structures, it simultaneously learns a spatio-temporal latent atlas and segmentations of individual structures based on a small number of annotated examples, and a large number of examples without annotation. We refer to this as a semi-supervised approach as opposed to fully-supervised approaches that use annotations on all examples, such as the leave-one-out experiments in Habas et al. (2010) or Gholipour et al. (2012). To connect the atlas with individual imaging data, we use a statistically-driven level-set segmentation framework. It translates the prior or uncertainty shared across the data as the logistic function of the corresponding level-set values, similar to Pohl et al. (2007). The spatio-temporal latent atlas is a probabilistic prior or map of the presence of an anatomical structure as a function of location and gestational age (GA). We use kernel regression for a continuous representation of the temporal domain, allowing the interpolation for GA that are not represented in the training dataset. Initial results were reported in Dittrich et al. (2011). The resulting four-dimensional atlas links the segmentations, and represents the cross-sectional component of variability in the population for a specific age, and the developmental gradient of the structure along the age axis. This is visualized in Fig. 2 for the period between GW 20 and 30. The gradient of the spatio-temporal atlas can be regarded as measure of uncertainty in two ways. In Fig. 2(a), the variability among cases of the same age is depicted as the local spatial gradient of the atlas at the surface boundary. Red areas are regions of high variability among the subjects, the gradient is low in these areas since segmentations are dissimilar across subjects. Yellow corresponds to relatively stable areas with a high local gradient of the prior. Fig. 2(b) shows the gradient of the atlas along its longitudinal axis at the structure surface. Red areas are expanding, blue areas are shrinking.

The atlas has several uses: it can serve as reference to represent characteristic development and its variability in a population, it can be used to identify deviations from a healthy population quantitatively, and it is a prerequisite for group-studies of the fetal development such as (Schöpf et al., 2012a,b), since it provides the means to establish correspondences across subjects, and age. Finally, it allows for estimating a morphological age, by matching individuals to the atlas along the age axis.

The remainder of this paper is structured as follows. In Section 2, we introduce the dataset and preprocessing methods followed by an in-depth explanation of the methodology. We define the problem, and detail methods for the learning of the latent atlas, and its use for morphological age estimation. In Sections 3 and 4 we present and discuss our experimental results in detail, and Section 5 closes with a conclusion and outlook.

2. Material and methods

2.1. Study data collection

This work is part of an ongoing collaboration with neuroradiologists and anatomists specialized on fetal MRI assessment. We took advantage of two distinct datasets. The first includes 32 fetal MR images of singleton pregnancies depicting the brain between GW 20 and 30 were retrospectively investigated. Cases suspicious for cardiac abnormalities, complex syndromes or chromosomal abnormalities were excluded from this study. The second dataset