Medical Image Analysis 21 (2015) 72–86

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

Learning-based prediction of gestational age from ultrasound images of the fetal brain

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form 29 October 2014
Accepted 18 December 2014
Available online 3 January 2015

Keywords:
Fetal brain ultrasound
Gestational age
Regression forest
Surface parametrization
Brain development

ABSTRACT

We propose an automated framework for predicting gestational age (GA) and neurodevelopmental maturation of a fetus based on 3D ultrasound (US) brain image appearance. Our method capitalizes on age-related sonographic image patterns in conjunction with clinical measurements to develop, for the first time, a predictive age model which improves on the GA-prediction potential of US images. The framework benefits from a manifold surface representation of the fetal head which delineates the inner skull boundary and serves as a common coordinate system based on cranial position. This allows for fast and efficient sampling of anatomically-corresponding brain regions to achieve like-for-like structural comparison of different developmental stages. We develop bespoke features which capture neurosonographic patterns in 3D images, and using a regression forest classifier, we characterize structural brain development both spatially and temporally to capture the natural variation existing in a healthy population ($N = 447$) over an age range of active brain maturation (18–34 weeks).

On a routine clinical dataset ($N = 187$) our age prediction results strongly correlate with true GA ($r = 0.98$, accurate within ± 6.10 days), confirming the link between maturational progression and neurosonographic activity observable across gestation. Our model also outperforms current clinical methods by ±4.57 days in the third trimester—a period complicated by biological variations in the fetal population. Through feature selection, the model successfully identified the most age-discriminating anatomies over this age range as being the Sylvian fissure, cingulate, and callosal sulci.

1. Introduction

Accurate gestational age (GA) estimation forms an integral part of obstetric prenatal care. It defines the estimated date of delivery (EDD), and can influence the success or safety of a clinical intervention. Moreover, it is essential for the screening of fetal abnormalities. The anomaly scan, which is routinely offered in the early second trimester, forms the legal basis for time-critical care decisions as it enables expectant parents to make informed reproductive decisions about their unborn child (e.g. termination of pregnancy, intrauterine therapy or intervention) (National Collaborating Centre for Women's and Children's Health, 2008).

Traditional approaches to GA estimation include (a) menstrual dating, which makes use of the first day of the last menstrual period (LMP) as a reference point for the EDD and (b) extraction of diameter and circumference measurements from 2D ultrasound (US) images of the fetal cranium, abdomen, and femur (ISUOG, 2007). These measurements are regressed to population-based dating charts to estimate age and assess normality of fetal growth (Loughna et al., 2009). However, beyond 24 post-menstrual weeks, measurement accuracy is dependent on operator expertise and compromised by increasing biological variation, inconsistencies in skull size approximation, and subjectivity in 2D diagnostic plane finding, all contributing to age approximation errors (Bottomley and Bourne, 2009). As pregnancy advances and biological variation amongst normal fetuses increases, the range of values of each biometric measurement associated with a specific GA also increases and so equations based upon size become less accurate. In practice, this means that whilst the predictive error at 22 weeks' GA (±10 days, Altman and Chitty (1997)) is considered acceptable in the majority of clinical settings, the predictive error at 28–42 weeks (±18 days) is considered to offer little clinical value (Hadlock et al., 1983).

Pregnancy dating becomes particularly important in low-income settings where pregnant women typically attend for

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http://dx.doi.org/10.1016/j.media.2014.12.006
1361-8415/

obstetric care late in pregnancy, when menstrual history is unavailable or unreliable. In the absence of clinically-useful LMP information, US measurements provide the most accurate estimation of GA (Geirsson, 1991). However, in the third trimester of pregnancy, even US-based dating may produce estimation errors up to ±3 weeks (Hadlock et al., 1984; Altman and Chitty, 1997). Thus, in a setting where screening occurs in the second and third trimesters, the error margins yielded by current methods render them as not clinically useful, potentiating the need for alternative techniques for estimating GA.

Post-mortem neuroanatomical studies have observed that during early development the fetal brain undergoes dramatic structural changes and have established a spatiotemporal timetable which characterises normal brain development (Chi et al., 1977; Dorovini-Zis and Dolman, 1977). Specifically, the fetal brain surface, or *cortex*, rapidly transitions from a relatively smooth agyric surface in the early second trimester to progressively bearing more indentations or folds (*gyrification*) over the course of pregnancy until it resembles the adult brain at birth. Deviations from this pattern have been indicative of cortical malformations as a result of defective neuronal migration, as is the case of lissencephaly which occurs when gyrification is reduced or stunted. Depending on severity, cortical malformation may result in adverse outcomes ranging from developmental delays and retardation to infant mortality (Ghai et al., 2006). This, in turn, is suggestive of a direct link between healthy gyrification and chronological age. These findings raise the question whether changes in brain morphology could be used as a robust indicator of GA and developmental normality in clinical practice.

1.1. Related work

To date, several methods have been developed to automatically map neuroanatomical structure from MR image data to neonatal or adult age. Using voxel-based morphometry or shape analysis to capture tissue growth (Good et al., 2001; Gholipour et al., 2012), tensor analysis to characterize regional growth patterns (Thompson et al., 2000), or discriminative classifiers to capture characteristics of the developing or ageing brain (Franke et al., 2012; Sabuncu and Van Leemput, 2012; Toews et al., 2012), a clear link between anatomical changes and cerebral progression (or regression) has been demonstrated. With the advent of image preprocessing methods such as slice-to-volume reconstruction and image mosaicing (Jiang et al., 2007; Rousseau et al., 2006), and super-resolution techniques (Gholipour et al., 2010; Kim et al., 2010; Rousseau et al., 2010), 3D MR images with high signal-to-noise ratio and improved spatial resolution are now available and have stimulated studies of fetal (Caldairou et al., 2011; Gholipour et al., 2012; Habas et al., 2010; Habas et al., 2012; Jacob et al., 2011; Rajagopalan et al., 2011; Scott et al., 2011; Scott et al., 2013; Serag et al., 2012; Dittrich et al., 2014; Wright et al., 2014) and neonatal (Kuklisova-Murgasova et al., 2011; Serag et al., 2012) brain development from MR images. However, these techniques are tailored for the challenges affecting MR images and may not be appropriate for application in neurosonography, which continues to be the modality of choice in routine clinical care.

In the clinical literature, the age-related changes in echogeneity of fetal brain structures have been well-described. The timing of emergence of cortical sulci has been observed in US images and described as following a predefined spatiotemporal timetable (Bernard et al., 1988; Monteagudo and Timor-Tritsch, 1997; Toi et al., 2004; Cohen-Sacher et al., 2006; Pistorius et al., 2010), in agreement with MR and post-mortem neuroanatomical findings. In particular, the process of cortical maturation observable in US images of the fetal brain has been detailed by means of simple subjective scoring techniques to define the appearance of sulci and gyri beyond 20 gestational weeks (GW) (Quarello et al., 2008; Pistorius et al., 2010).

Unlike MR images, US images are complicated by intensity artefacts such as signal attenuation, acoustic shadows, and occlusion due to cranial calcification. US probe placement also generates reverberation caused by multiple reflections of the US beam on the fetal skull and other maternal tissues. These factors can affect the visibility of key anatomical landmarks necessary for image registration—the primordial step in image-based brain analysis. However, given that cranial calcification and fusion progress with GA (Malas and Sulak, 2000), the complex image patterns generated by these artefacts may be used along with structural image features to inform on developmental maturation.

Our work is the first to exploit age-related sonographic activity to predict GA and hence neurodevelopmental maturation from US images. We present bespoke appearance-based features designed to capture these age-specific sonographic patterns and use them to develop a model which automatically maps them to GA and hence neurodevelopmental maturation. Learning-based approaches are well-suited for this task due to their ability to take high-dimensional data (i.e. longitudinal images producing 5000+ features representing image appearance at different ages) and establish a compact representation of fetal brain development. In the literature, relevance vector machines (RVM) (Franke et al., 2010) and relevance voxel machines (RVoxM) (Sabuncu and Van Leemput, 2012) have demonstrated the feasibility of learning a mapping between image-based biomarkers and pathologies in adult brains. More recently, Konukoglu et al. (2013) applied neighbourhood approximation forests (NAF) to estimate adult age. While the work of Konukoglu et al. (2013) also presents a forest-based method for predicting age from brain images, their approach relies on accurate alignment and registration of anatomical landmarks, which remains a challenge in US images of the brain. Unlike MR images, the appearance of anatomies in an US image varies with the relative position of the brain with respect to the probe, which results in acoustic shadows, occluded anatomical features, and reverberation artifacts (Kuklisova-Murgasova et al., 2013). Consequently, approaches requiring images of similar intensity appearance and one-to-one inter-subject anatomical correspondence are not, at present, directly applicable to a study of US images of the brain; a local feature-based approach is more appropriate (e.g. Toews et al., 2010).

The advantages of employing decision forests for such tasks are their built-in automatic feature selection, which allows for identification of salient and age-discriminating image features, and their generalizability to images from different age groups and acquisitions. Thus, decision forests are appropriate for our work in which we seek to identify the structures which are informative for GA decision-making, and aim to apply the model to images from patients at different developmental stages.

1.2. The proposed method

We propose a feature-based model for characterizing neuroanatomical appearance both spatially and temporally, capturing the natural variation existing in a healthy fetal population over a period of active brain maturation: 18^{+0} to 33^{+6} GW (weeks$^{+\text{days}}$). Specifically, we present an automated machine learning-based predictive model to learn the pattern of fetal brain changes through dynamic features observable in multiple subject images and apply it to demonstrate successful age estimation from a single unseen scan. Our proposed model comprises of two steps: (i) 3D parametrization of the fetal skull and (ii) feature extraction for learning age-related sonographic patterns from 3D volumes, resulting in the development of an age-predictive model. The model can then be