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Longitudinal Chinese Population Structural Fetal Brain Atlases Construction: toward precise fetal brain segmentation

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Abstract— **In magnetic resonance imaging (MRI) studies of fetal brain development, structural brain atlases usually serve as essential references for the fetal population. Individual images are spatially normalized into a common or standard atlas space to extract regional information on volumetric or morphological brain variations. However, the existing fetal brain atlases are mostly based on MR images obtained from Caucasian populations and thus are not ideal for the characterization of the brains of the Chinese population due to neuroanatomical differences related to genetic factors. In this paper, we use an unbiased template construction algorithm to create a set of age-specific Chinese fetal atlases between 21-35 weeks of gestation from 115 normally developing fetal brains. Based on the 4D spatiotemporal atlas, the morphologically developmental patterns, e.g., cortical thickness, sulcal and gyral patterns, were quantified from in utero MRI. Additionally, after applying the Chinese fetal atlases and Caucasian fetal atlases to an independent Chinese pediatric dataset, we find that the Chinese fetal atlases result in significantly higher accuracy than the Caucasian fetal atlases in guiding brain tissue segmentation. These results suggest that the Chinese fetal brain atlases are necessary for quantitative analysis of the typical and atypical development of the Chinese fetal population in the future.**

I. INTRODUCTION

Fetal brain development is a highly dynamic and complex process. Early stages of human brain development are particularly important as any abnormality in development may result in long-term neuro-developmental impairment and may even affect survival in the perinatal period and later in childhood [1][2]. Thus, it is essential to characterize early brain growth patterns in-utero. Especially during the second and third trimesters of gestation, the brain dramatically changes in terms of shape, with the gyrification or folding of the cerebral cortex. Moreover, adequate characterization of these developmental processes may provide insight into the pathophysiology underlying neurological disorders such as autism and developmental delay, which are thought to begin in the very early stages of life. However, human brains are highly variable between different individuals within a group and between phenotypic groups (e.g., age, gender, race). To date, little is known about the ethnicity-based structural differences in fetal brains. Thus, a population-specific fetal brain atlas may be more appropriate for studies involving Chinese populations.

The atlas of fetal brain MRI is an excellent tool that fills the gap in coverage on normal brain development. The need to perform quantitative group-wise studies in neuroimaging also motivates research aiming at establishing accurate correspondence across individuals and labeling anatomical regions in the brain.

However, construction of fetal brains from MRI is more challenging than that of the adult brain due to the rapid morphological changes and it requires additional processing techniques [1]. Recently, Habas, P. et al.[3] proposed the first spatiotemporal probabilistic MRI atlas of the fetal brain by using the 20 healthy fetuses data in the GA range of 20.57 to 24.71 weeks. More Recently, Serag, A. et al.[4] using the FFD-based atlas construction method to construct a spatiotemporal atlas of the fetal brain in the GA range of 22 to 38 weeks from MRI of 80 fetuses. Xia et al.[5] used two complementary similarity matrices to construct an age-specific fetal cortical surface atlas and used the growth patterns of cortical properties to define distinct regions' parcellation. The authors focus on motor, premotor, and parietal regions (the dorsal cluster) from the prefrontal, temporal, occipital, and precuneus regions (the ventral cluster) using the 25 normal from 26 to 29 gestational weeks. There are a few other fetal brain atlases, such as a spatiotemporal latent atlas of the fetal brain in 20 to 30 weeks GA [6] , a spatiotemporal cortical surface atlas of the fetal brain through sulcal matching from MRI of 80 healthy fetuses [7]. All of the aforementioned atlases were created based on Caucasian populations.

Yet, the use of brain atlases in spatial normalization is typically limited to studies involving subject cohorts of similar phenotype, e.g., race. Genetic factors make the Oriental and Occidental populations dissimilar, and how the genetic factors lead to brain development difference is still unknown. Thus, using existing Caucasian fetal brain atlases for Chinese populations may cause inaccurate measurements, comparison and interpretations of clinical imaging results. Additionally, differences in developmental brain patterns between races may underly different fetal brain functions in-utero. Surprisingly, Chinese fetal brain atlases have not been well developed to the best of our knowledge.

In the present study, we aimed to build spatio-temporal

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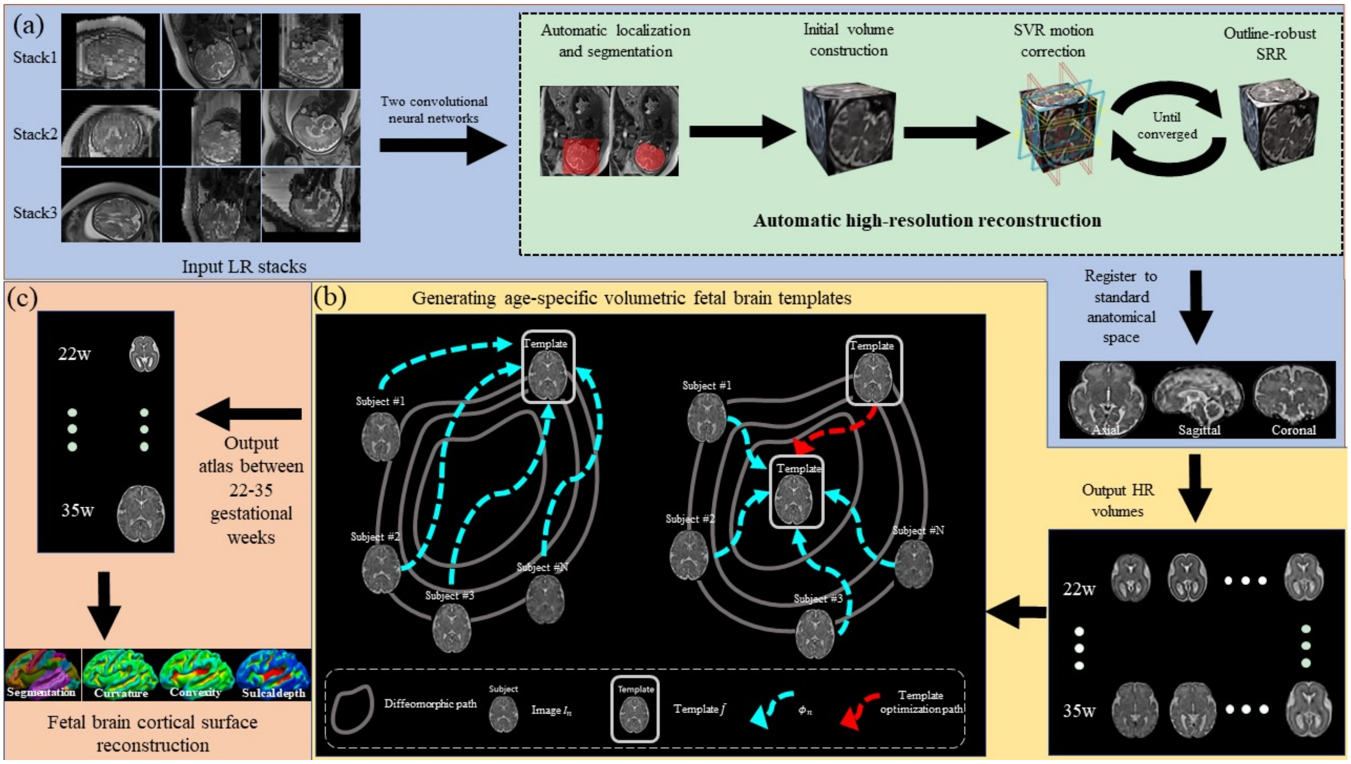

Fig. 1. (a) The framework for 3D individual fetal brain MR image reconstruction including brain extraction, high-resolution (HR) volume reconstruction in standard anatomical space, and cortical surface reconstruction; (b) The overview of the two-step optimization atlas construction strategy. Firstly, referring to the current template space $\bar{J}$, the diffeomorphic transforms ϕ_n between the subject volumes I_n and the template $\bar{J}$ are estimated. Then the template $\bar{J}$ is updated by optimizing the distance in a diffeomorphic path with ϕ_n; (c) cortical surface reconstruction.

altas to capture the development characteristics of the Chinese population's fetal brain structures. To this end, we first collected 735 fetal brains in the gestational age range of 21 to 39 weeks on a 1.5 T MRI scanner. Brain images of 115 normal fetuses in the gestational age of 22 to 35 weeks were included for further analysis. Then, we employed an unbiased template construction pipeline to generate a set of normal fetal brain atlases that provide a normative brain template for anatomical reference with a one-week interval (dynamic or 4D). The morphological growth properties, e.g., sulcal and gyral patterns, was labeled and characterized. We also compared the power of the Chinese fetus atlases and Caucasian fetal atlases in guiding brain region segmentation.

II. MATERIALS AND METHODS

A. Subjects and Data Acquisition

The present study was approved by the Ethics Committee of International Peace Maternity And Child Health Hospital (IPMCH) and was performed in accordance with the Declaration of Helsinki.

The Fetal brain structural MR images were acquired on a 1.5 T scanner (Siemens Magnetom Aera Syngo MR E11) with an eight-channel body coil. Three orthogonal planes (axial, coronal, and sagittal) of the fetal brain were scanned separately using a T2-weighted half-Fourier acquisition Single-shot turbo spin-echo (T2w SSFSE) sequence. The parameters are: field of view (FOV) = 300 × 300 mm2, imaging matrix = 256 × 256, repetition time (TR) = 1400 ms, echo time (TE) = 92 ms, slice thickness = 4.0 mm without slice gap, scan time 24 seconds per view.

Fetal brain MRI data of 735 healthy singleton pregnancy fetuses at a gestational age (GA) between 20 and 39 weeks were collected. After excluding 620 normal fetal brain data with noticeable motion artifacts, 115 normally developing fetal brains between 22-35 weeks (mean=30.5, stand deviation=4.7) were included for the gestational-age-specific atlas construction.

B. Image processing and atlas construction

The procedures of the volumetric fetal brain reconstruction and four-dimensional (4D) gestational-age-specific (3D volumetric atlas + age) atlas construction were shown in Fig. 1. Firstly, we performed a fully automatic framework to reconstruct high-resolution (HR) isotropic volumetric images from the low-resolution (LR) 2D fetal brain stacks as proposed previously[8] . Briefly, a Convolutional Neural Network (CNN) was firstly used to automatically localize the fetal brain in each input LR stack to obtain an initial segmentation of the fetal brain. Secondly, a second CNN was further applied to the localized segmentation to extract brain regions. Thirdly, all stacks passed through N4 intensity correction [9] and were rigidly aligned to an automatically selected target stack to generate an initial volumetric brain. An HR volume was then reconstructed by the super-resolution reconstruction (SRR) method with a two-step motion-correction/volumetric reconstruction cycle until it converged. Lastly, the reconstructed HR volume was rigidly registered to a standard anatomical space. Then, we used ANTs unbiased group-wise registration algorithm to generate age-specific volumetric fetal brain templates [10][11].

C. Cortical surface reconstruction and quantification

In human brain, the folding process takes place during gestational weeks 16–40, spanning the second and third trimesters of pregnancy [12][13]. Freesurfer software (http://surfer.nmr.mgh.harvard.edu/) was used to construct the fetal brain cortical surface properties as detailed in the literature[2][14][15][16][17][18][19]. Briefly, cortical surface reconstruction process includes white matter filling, right/left hemispheres smoothing, right/left hemispheres surface inflating. For the quantification of fetus cortical folding, the cortical measurements such as surface area, convexity, curvature, regional volume, sulcal depth and cortical thickness, were calculated for each subject. Especially, the sulcal depth measurement was calculated as described in [5].

D. Evaluation of the atlas representativeness (Chinese vs. Caucasian) for Chinese population brain region segmentation

To evaluate the proposed fetus's representativeness in guiding brain spatial normalization for the Chinese population, we performed the atlas-based segmentation method as illustrated in Fig. 2. Intuitively, the atlas space is a more precise representation of the Chinese fetal anatomical structure. It was built based on the Chinese population, which would lead to more accurate special normalization for Chinese fetal brains. We firstly manually segment the bilateral putamen of the lenticular nucleus region on six independent subjects at GA 32-week. Then these subject images were registered to the proposed atlas and the CRL atlas at GA 32-week, respectively. Using the deformation fields yield from the registration process, each bilateral putamen label is projected into the two atlas spaces. We assume that with more accurate spatial normalization, the individual brain regions would be better aligned to the label in the atlas space. Thus, the DICE coefficients of the transformed putamen labels were calculated and compared between different atlas spaces. A higher DICE value indicates a higher accuracy of the atlas for guiding brain anatomical normalization.

III. EXPERIMENTAL RESULTS

A. The age-specific structural atlases for Chinese fetal brains

All fetal MRI images were pre-processed by the methods as described in section 2.2.1. The fetal brain of each subject was located and extracted separately. Then the segmented fetal brains were reconstructed with a spatial resolution of 0.8 mm isotropic using the 3D voxel-wise super-resolution reconstruction as describe in Fig. 1. The weekly gestation-age-specific anatomical fetal brain atlases are generated from 22w to 35w using ANTs. Fig. 3 shows seven representative atlases in sagittal, coronal, and axial views.

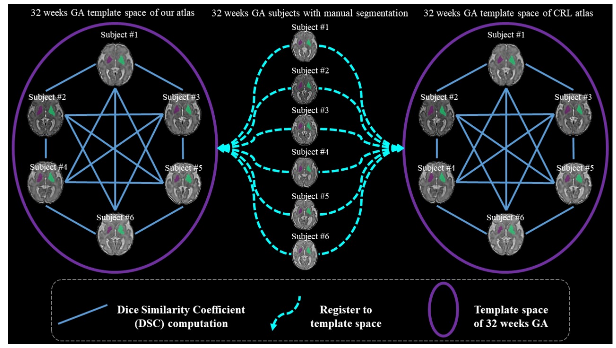

Fig. 2. The pipeline of the atlas representativeness evaluation. Firstly, six subjects at GA of 32-week with the manual label were registered to the proposed template (left) and CRL template (right) at the same GA. DICE coefficients between different subjects are calculated and compared.

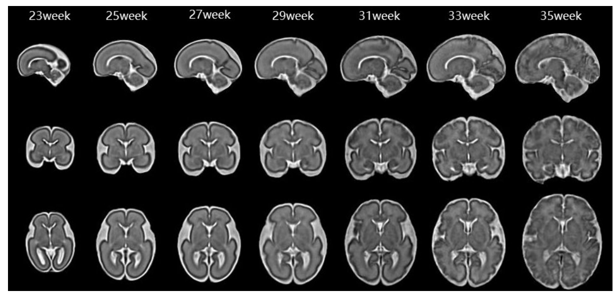

Fig. 3. The gestation-age-specific anatomical fetal brain atlases for the Chinese population at 7 representative gestational ages (GAs) in 23, 25, 27, 29, 31, 33, and 35 weeks.

B. Brain tissue segmentation and quantification

Cortical GM, WM and CSF were segmented based on proposed fetal brain atlases. Fig. 4 shows cortical gray matter segmentation (red color) on the second row and 3D cortical surface color-coded by cortical thickness on the bottom row. The cortical gray matter has a thickness of 1.5-2.5 mm as color-coded by green. The thickness of the cortical gray matter of temporal lobe has a thickness of less than 1.5 mm. The frontal cortical regions show a rapid development from 33 week with a thickness more than 3 mm. Interestingly, the superior temporal sulcus appeared in 27w GA and formed in 31w GA while the visual cortex appeared thicker at 31w GA.

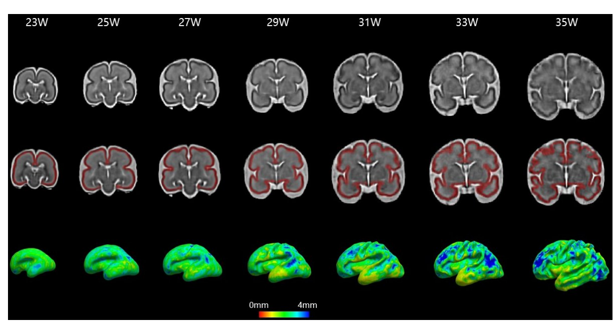

Fig. 4. Segmentation of fetal brain cortical gray matter (with red overlay on the second row) and 3D reconstruction of cortical thickness (bottom row). Note that blue color represents a thicker thickness of cortical gray matters.

C. Cortical morphometric analysis

Three geometric properties (i.e., curvature, convexity, and sulcal depth) were used to quantify the fetal brain cortical development. Figure 5 illustrates cortical geometric properties of age-specific fetal brain atlases both in atlas space and spherical space. The dynamic cortical folding pattern of Chinese fetuses was well observed. For example, the lateral sulcus has formed in 23w GA. In 25w GA, a subtle concavity was observed on the parietal lobe, indicating the appearance of the central sulcus. In 27w GA, the precentral sulcus and the superior temporal sulcus formed, followed by the appearance of the postcentral sulcus, inferior frontal sulcus, and superior frontal sulcus between 27w and 29w GA. The dramatic folding of these sulci was observed after 29w GA. The majority of the sulci have well developed at 35 weeks. Those observations are consistent with previous studies that primary sulci are already formed at 33 weeks [20][21].

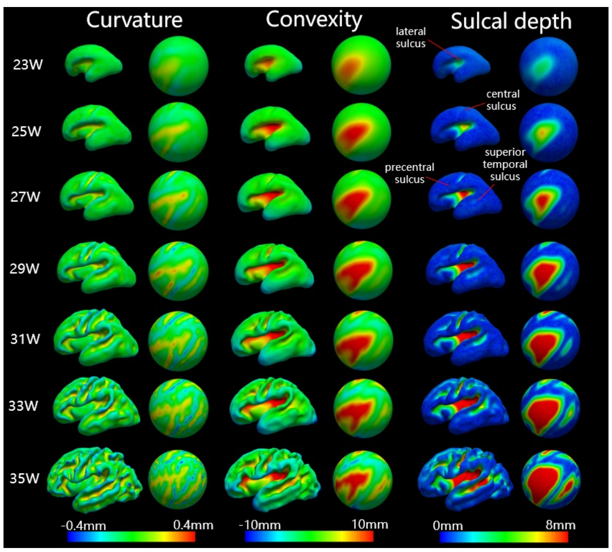

Fig. 5. Dynamic development of cortical surface properties (curvature, convexity, and sulcal depth) of the proposed fetal brain atlases

D. Spatiotemporal atlases of Chinese fetal brain and parcellation

Fig.6 shows the whole brain parcellation at each week. The GM and DGM of fetal atlases were anatomically labeled as 121 different brain regions, similar to the AAL parcellation used in the adult brain template. Additionally, the WM and CSF were also labeled according to CRL fetal brain tissue segmentation [22]. The division of brain regions presents symmetrical distribution between the left and right hemispheres. The size of brain atlas shows a dramatic change with weeks.

E. Assessment of atlases for ROI segmentation for the Chinese population

Table 1 and Table 2 show the DICE values between different subjects based on the segmentation of two templates. Generally, the DICE coefficients in Table 1 are higher than those in Table 2. For example, the DICE is 0.8223 between subject#2 and subject#3 in Table 1, which is higher than that as shown in Table 2. The segmentation results indicate that our atlas is more proper when guiding brain region segmentation for the Chinese fetal population.

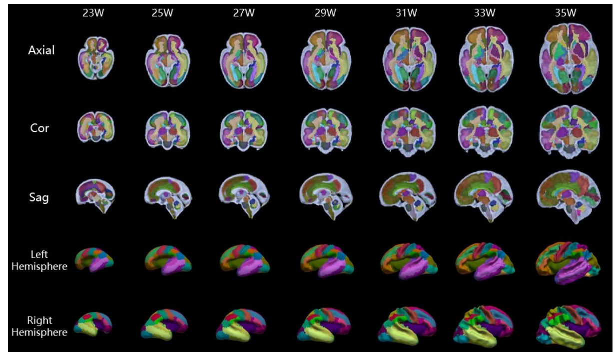

Fig. 6. Tissue segmentation of spatiotemporal Chinese fetal brain atlases was shown in three views (axial, coronal, and sagittal) and in 3D with left and right hemispheres, respectively.

TABLE I
DICE COEFFICIENT IN THE PUTAMEN BETWEEN DIFFERENT SUBJECTS AT 32 WEEKS IN OUR ATLAS SPACE.

	Subject#1	Subject#2	Subject#3	Subject#4	Subject#5	Subject#6
Subject#1		0.746	0.795	0.737	0.796	0.786
Subject#2			0.822	0.800	0.846	0.803
Subject#3				0.765	0.826	0.812
Subject#4					0.754	0.745
Subject#5						0.833
Subject#6						

TABLE II
DICE COEFFICIENT MATRIX OF THE PUTAMEN BETWEEN DIFFERENT SUBJECTS AT 32 WEEKS IN THE CRL ATLAS SPACE.

	Subject#1	Subject#2	Subject#3	Subject#4	Subject#5	Subject#6
Subject#1		0.716	0.728	0.721	0.825	0.780
Subject#2			0.775	0.723	0.816	0.783
Subject#3				0.765	0.806	0.790
Subject#4					0.743	0.705
Subject#5						0.811
Subject#6						

IV. CONCLUSIONS

In this study, 115 reconstructed 3D fetal brains were included to generate age-specific 4D structural fetal brain atlases based on the Chinese population. The proposed fetal brain atlases could be a reference for early brain development for Chinese fetus. The spatio-temporal patterns of cortical thickness, curvature, convexity, and sulcal depth were measured. Finally, we employed an independent dataset to evaluate the Chinese fetus atlas in guiding brain region segmentation.

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