Neuroradiology (2012) 54:1153–1159
DOI 10.1007/s00234-012-1069-x

PAEDIATRIC NEURORADIOLOGY

Development of the subcortical brain structures in the second trimester: assessment with 7.0-T MRI

Haiwei Meng · Zhonghe Zhang · Hequn Geng · Xiangtao Lin · Lei Feng · Gaojun Teng · Fang Fang · Fengchao Zang · Shuwei Liu

Received: 17 April 2012 / Accepted: 4 July 2012 / Published online: 19 July 2012

Abstract
Introduction This study aims to obtain the signal intensity changes and quantitative measurements of the subcortical brain structures of 12–22 weeks gestational age (GA).
Methods Sixty-nine fetal specimens were selected and scanned by 7.0-T MR. The signal intensity changes of the subcortical brain structures were analyzed. The three-dimensional visualization models of the germinal matrix, caudate nucleus, lentiform nucleus, and dorsal thalamus were rebuilt with Amira 4.1, and the developmental trends between the measurements and GA were analyzed.
Results The germinal matrix was delineated on 7.0-T MR images at 12 weeks GA, with high signals on T1-weighted images (WI). While at 16 weeks GA, the caudate nucleus, lentiform nucleus, and internal and external capsules could be distinguished. The caudate nucleus was high signal intensity on T1WI. The signal intensity of the putamen was high on T1WI during 15–17 weeks GA and was delineated as an area with uneven signal intensities. The signal intensity of the peripheral area of the putamen became higher after 18 weeks GA. The signal intensity of the globus pallidus was high on T1WI and low on T2WI after 20 weeks GA. At 18 weeks GA, the claustrum was delineated with low signals on T2WI. Measurements of the germinal matrix, caudate nucleus, lentiform nucleus, and dorsal thalamus linearly increased with the GA.
Conclusion Development of the subcortical brain structures during 12–22 weeks GA could be displayed with 7.0-T MRI. The measurement provides significant reference beneficial to the clinical evaluation of fetal brain development.

Keywords Subcortical brain structures · Magnetic resonance imaging · Fetal brain development · Three-dimensional visualization

H. Meng · H. Geng · X. Lin · L. Feng · S. Liu (✉)
Research Center for Sectional and Imaging Anatomy,
School of Medicine, Shandong University,
44 Wen-hua Xi Road,
Jinan, Shandong Province, People's Republic of China 250012
e-mail: liusw@sdu.edu.cn

Z. Zhang
Department of Medical Imaging,
Provincial Hospital Affiliated to Shandong University,
250021, Jinan, Shandong, China

G. Teng · F. Fang · F. Zang
Department of Radiology, Zhong Da Hospital,
Southeast University School of Clinical Medicine,
210009, Nanjing, Jiangsu, China

Introduction

Development of the human fetal brain is quite complex. It develops from a simple neural tube to a complex structure by continuous neuron differentiation and migration. Traditional histological methods were commonly used to study the fetal brain in previous researches. In recent years, the development of ultrasound (US) and MRI makes it possible to study the fetal brain with two- or three-dimensional images [1–3].

The use of MRI, especially with the application of rapid imaging sequence, has greatly improved the image quality of the fetus in the uterus. It has become the best assistant examination method after US [2–4]. In vivo fetal MRI has its disadvantages on delineating the fetal brain because it is affected by the special acquisition sequence, scanning thickness, fetal movement, maternal structures, and artery pulse. But, postmortem MRI has fewer limitations compared with in vivo fetal MRI, and its imaging quality is improved. Much research has confirmed its value in studying the anatomy and development of the fetal brain [5–10].

During fetal brain development, changes of the subcortical brain structures are obvious, and their developmental regularities have great value in the evaluation of the total brain. Some developmental CNS diseases may begin at the first and second trimesters of fetal brain development. Previous study of human subcortical brain structures mainly focused on histology, and little has been reported by postmortem MRI of high magnetic strength with three-dimensional visualization. Although great details have been reported for the fetal brain by fetal MRI or embryology, we still lack knowledge regarding the three-dimensional visualization model and quantitative measurements of the fetal subcortical brain structures.

In present research, the changes of signal intensities and quantitative measurements of the fetal subcortical brain structures of 12–22 weeks gestational age (GA) were analyzed with 7.0-T MRI, and the three-dimensional visualization model of some subcortical gray matters was rebuilt; then, the volume, surface area, length, width, and height were obtained. It is thought that this research can provide anatomical details for the evaluation of fetal brain development.

Methods

Selection of the specimens

Sixty-nine fetal specimens of 12–22 weeks GA were collected in hospitals of Shandong Province (GA dispositions and numbers of the chosen specimens were listed in Table 1). They were from medically indicated abortions, spontaneous abortions, fetal deaths or stillbirths, and premature deaths. The inclusion criteria were the same as our previous research [5–7], results of US examination for the fetus during pregnancy and results of the US and postmortem MRI examinations for the specimen indicating an anatomically normal and developmentally appropriate fetus. The GA of the fetuses was estimated on the basis of crown–rump length, head circumference, foot length, and/or pregnancy records, and was expressed in weeks from the last menstrual period [11]. The specimens were immersed in 10 % formalin for preservation; then, they were scanned with 7.0-T MR. The time interval between the collection of specimens and the scanning was within 2 months. This study was conducted on the basis of the approval of the Internal Review Board of the Ethical Committee at the School of Medicine, Shandong University. The parents' consent to donating the fetal cadaver was obtained.

Table 1 GA dispositions and numbers of the chosen specimens (n=69)

GA	Number	GA	Number
12	3	18	4
13	3	19	6
14	3	20	16
15	4	21	12
16	5	22	6
17	7		

Scanned by 7.0-T MR

The specimens were scanned by a BRUKER 7.0-T Micro-MR with a maximum gradient of 360 mT (70/16 pharmaScan, Bruker Biospin GmbH, Germany). A rat body coil with an inner diameter of 60 mm was selected to scan all the fetuses. T1-weighted: slice thickness, 0.8 mm; slice interval, 0.8 mm; and the parameters: repetition time, 384.4 ms; echo time, 15.8 ms; matrix size, 512×512; number of excitations, 1; field of view, 6×6 cm. T2-weighted: slice thickness, 0.5 mm; slice interval, 0.5 mm; and the parameters: repetition time, 17,000.0 ms; echo time, 50.0 ms; matrix size, 256×256; number of excitations, 4; field of view, 6×6 cm.

Three-dimensional reconstruction

The T2WI was selected to be segmented and reconstructed by Amira 4.1 software. The germinal matrix, caudate nucleus, lentiform nucleus, and dorsal thalamus were manually traced out on the transverse images and then adjusted on the coronal and sagittal images. Different colors were used to mark the left and right germinal matrix, caudate nucleus, lentiform nucleus, and dorsal thalamus (Fig. 1). To check the reproducibility of the manual segmentation, we manually segmented basal nuclei two times simultaneously by two anatomists to obtain a mean. The time interval of each round of manual segmentation was at least 1 week. After that, the three-dimensional visualization model and quantitative data of the segmented structures, including surface area, volume, length, width, and height, were automatically obtained by Amira 4.1 software.

Statistics

One structure was considered to be present if it was observed in 75 % or more than 75 % of cases. A paired t test was used to detect the asymmetries of the germinal matrix, lentiform nucleus, caudate nucleus, and dorsal thalamus. Differences were considered statistically significant when the probability p was less than 5 % ($p<0.05$). The relationship between each measurement and GA was obtained by a regression analysis. All the statistical work was done on SPSS 17.0.

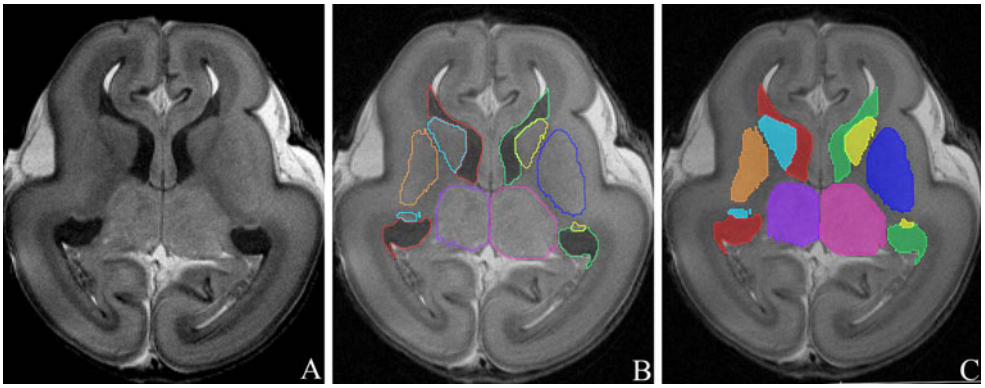

Fig. 1 Methods of image segmentation with Amira 4.1. **a** The original image. **b** Segmentation of the germinal matrix, caudate nucleus, lenticular nucleus, and dorsal thalamus. **c** Different colors filled in the structures after segmentation

Results

The signal intensity changes of the subcortical brain structures on 7.0-T MRI

12–14 weeks GA

The germinal matrix, which was located in the lateral ventricle and lying just above the caudate nucleus with its bilateral sides forwardly connecting the ventricular zone of the cortical lamination, was the most obvious structure in the subcortical gray matters. It could be observed at 12 weeks GA (in all the three cases) and had a high signal intensity on T1WI and low signal intensity on T2WI (Fig. 2a, e). During this period, the putamen and dorsal thalamus could be vaguely discriminated (in two out of the three cases). The putamen had an intermediate signal intensity on T1WI and low signal intensity on T2WI. The signal intensity of the dorsal thalamus was similar both on T1WI and T2WI. The head of the caudate nuclei was not delineated.

15–17 weeks GA

The germinal matrix was the most obvious structure (in all the cases), and its volume quickly increased after 16 weeks GA (in all the cases). The original head, body, and tail of the caudate nuclei were all described and were shown with high signal intensity on T1WI and low signal intensity on T2WI. The borderlines of the subcortical gray matters became clear at 16 weeks GA with the thin internal capsule separating them (in all the cases). The signal intensity of the anterior

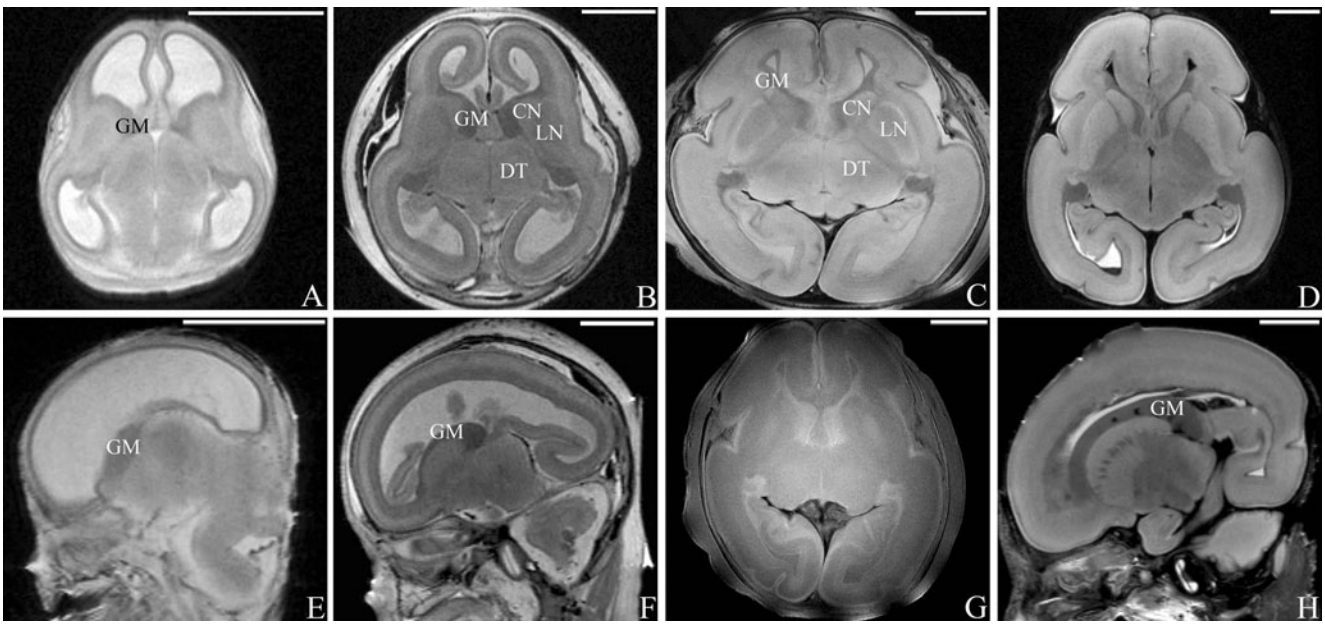

Fig. 2 The transverse and sagittal T2-weighted 7.0-T MRI of 12 (**a**, **e**), 16 (**b**, **f**), 20 (**c**, **g**), and 22 weeks GA (**d**, **h**). The germinal matrix could be observed at 12 weeks GA (**a**, **e**). The borderlines of the subcortical gray matter became clear at 16 weeks GA (**b**, **f**). The claustrum could be described at 18 weeks GA (**c**, **g**). The internal part of the dorsal thalamus could be discriminated at 22 weeks GA (**d**, **h**). *DT* dorsal thalamus, *CN* caudate nucleus, *LN* lenticular nucleus, *GM* germinal matrix

limb was lower than that of the posterior limb on T2WI (Fig. 2b, f).

18–20 weeks GA

On T2WI, the internal part of the putamen had a low signal intensity, but its outer part was delineated as a strap with higher signal intensity. The internal and external globus pallidus were discriminated (in all the cases), which were located below the putamen with low signal intensity on T2WI. The claustrum, which had low signal intensity on T2WI and separated the external capsule and extreme capsule, could not be described until 18 weeks GA (in three out of the four cases). The other structures were similarly delineated as those of the previous GA (Fig. 2c, g).

21–22 weeks GA

The volume of the germinal matrix gradually increased to the largest. The ventral posterior nucleus of the dorsal thalamus could be discriminated (Fig. 2c, h).

The three-dimensional visualization and quantitative measurements of the subcortical gray matters

The three-dimensional visualization model could well demonstrate the morphological changes of the subcortical gray matters (Fig. 3). Quantitative data could be acquired, which coordinately increased with GA (Fig. 4), and we got the regression equation between the volumes, surface area, length, width, height, and GA of these structures. The germinal matrix just lying above the caudate nucleus was delineated on the three-dimensional visualization model, which had a small volume during 12–14 weeks GA (in all the cases) (Fig. 3a, e) but greatly increased and occupied most of the lateral ventricle after 16 weeks GA (in all the cases) (Fig. 3b, f). After 16 weeks GA, the relative position of the subcortical gray matters became typical (in four out of the five cases) (Fig. 3c, d, g, h). Quantitative measurements indicated a significant linear increasing trend between each measurement and GA (Fig. 4). The germinal matrix grew the fastest, followed by the caudate nucleus, while the dorsal thalamus grew the slowest (Fig. 4). For the lentiform nucleus and caudate nucleus, their length increased at a speed faster than their width, height, and volume (Fig. 4). But for the dorsal thalamus, its width grew the fastest (Fig. 4).

No statistically significant hemispheric asymmetry and sexual dimorphism were found in the measurements of the subcortical gray matters.

Discussion

The subcortical brain structures include subcortical white matter, lateral ventricle, and the deep gray matters [12]. In this study, we mainly focused on the germinal matrix, caudate nucleus, lentiform nucleus (putamen and globus pallidus), claustrum, dorsal thalamus, and internal and external capsules, which are important structures deep in the brain. Furthermore, these structures are the common places where

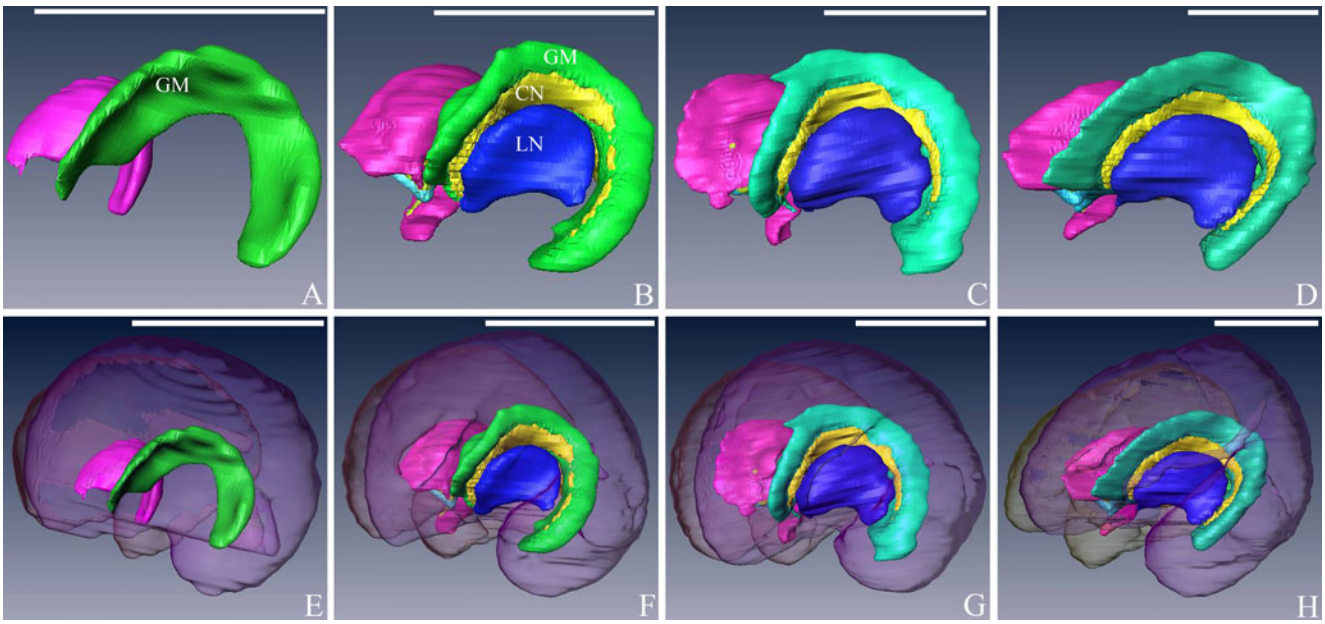

Fig. 3 The three-dimensional visualization model of the caudate nucleus, lenticular nucleus, and germinal matrix and their location in the telencephalon of 12 (**a**, **e**), 16 (**b**, **f**), 20 (**c**, **g**), and 22 weeks (**d**, **h**) GA. They could demonstrate the morphological changes of the subcortical gray matters. *CN* caudate nucleus, *yellow*; *LN* lenticular nucleus, *blue*; *GM* germinal matrix, *green*

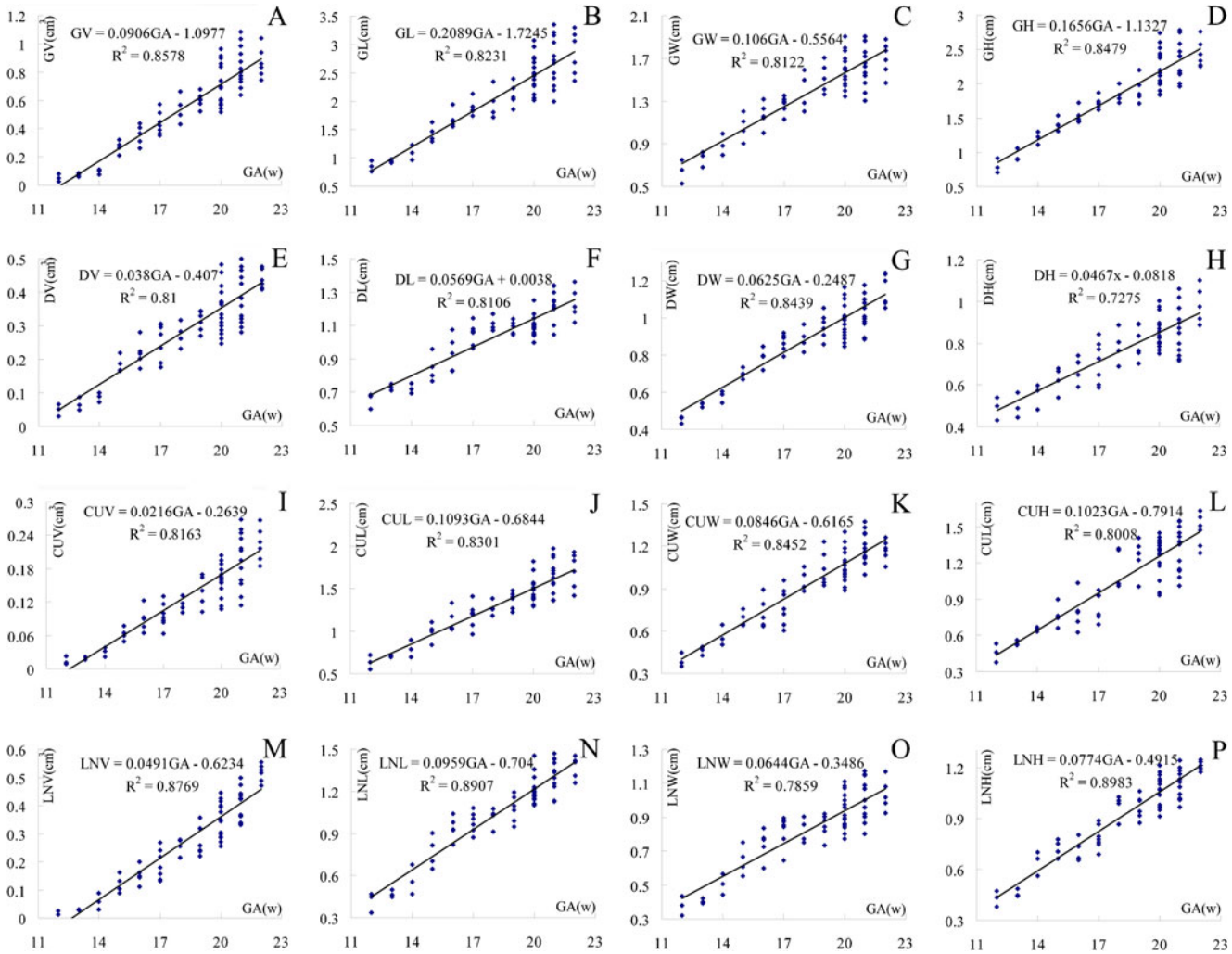

Fig. 4 Quantitative measurements of fetal subcortical gray matter and their relationship with GA. All the measurements linearly increased with GA. *GV*, *GL*, *GA*, *GH*, the volume, length, width, height of the germinal matrix; *DV*, *DL*, *DW*, *DH*, the volume, length, width, height of the dorsal thalamus; *CUV*, *CUL*, *CUW*, *CUH*, the volume, length, width, height of the caudate nucleus; *LNV*, *LNL*, *LNW*, *LNH*, the volume, length, width, height of the lentiform nucleus

cerebrovascular diseases take place in adults and cerebral hemorrhage in fetuses [10]. Exploring their developmental regularities in the second trimester can reveal their characters at an early stage, which may provide valuable suggestions for the control and treatment of these diseases. Development of these structures could be better delineated with high field MRI, three-dimensional visualization, and quantitative measurements. Now, we discuss the structures above respectively.

The germinal matrix

Compared with those of adults, the subcortical brain structures are characterized by the outstanding germinal matrix. The germinal matrix was a temporary structure during fetal brain development, and it can be found as early as 7 weeks GA. The histological research suggested that it was the earliest gathering place for neurons capable of dividing and proliferating. It would differentiate into the caudate nucleus, dorsal thalamus, and lentiform nucleus [10].

Kinoshita [10] studied the germinal matrix with three-dimensional rebuilding by 4.7-T MR. They found that the germinal matrix could be observed at 9 weeks GA. Its size index increasingly enlarged during 9–23 weeks GA and reached its biggest size at 23 weeks GA, then decreased rapidly after 25 weeks GA. In our research, the germinal matrix could be clearly displayed at 12 weeks GA on 7.0-T MRI. Its size linearly enlarged with GA. This result was different with that of Kinoshita's. We further measured the parameters such as length, width, and height. We think that our results were more accurate because we used more fetal specimens and MRI of higher field strength, and images were more legible.

The caudate nucleus, lentiform nucleus, and dorsal thalamus

The rudiment head of the caudate nucleus and lentiform nucleus had formed at 10 weeks GA in histological stained slides. The head, body, and tail had formed at 16 weeks GA. Three-dimensional reconstruction with high field MRI showed the head of the caudate nucleus had already formed, but its tail had not. In the research with 1.5-T MRI [8, 10, 13], the borderlines among the nuclei were undistinguishable. In our study, the head, body, and tail of the caudate nucleus as well as the putamen of the lentiform nucleus were all delineated at 16 weeks GA. The globus pallidus was first to be distinguished at 18 weeks GA, and the internal and external globus pallidus were distinct at 20 weeks GA. All the nuclei at the early period showed low signal intensities on T2WI. The putamen of the lentiform nucleus was demonstrated with low signals inside and high signals in the periphery during 18–22 weeks GA. During fetal brain development, the relaxation time of T1 shortened with the decrease of H_2O and increase of cell density. It was thought that signal changes of the caudate and lentiform nucleus were related to the changes of their component and cell density. Further study was needed to reveal the exact reason.

Some research showed that the medullary sheath began to form at the ventral posterior nucleus of the dorsal thalamus at 22 weeks GA [14–16]. The ventral posterior nucleus of the dorsal thalamus displayed with high signals on T1WI on 4.7-T MRI of neonates [17]. In our study, the dorsal thalamus could be observed at 12 weeks GA on 7.0-T T2WI. The ventral posterior nucleus of the dorsal thalamus could be distinguished at 20 weeks GA.

A three-dimensional research of the caudate nucleus, lentiform nucleus, and dorsal thalamus showed no significant changes on their morphology. Their size linearly increased with GA. In our research, we obtained the same results of size measurement in subcortical brain structures as that of Huang's studies with 11.7- and 4.7-T MRI [12]. We also measured the parameters such as the surface area, length, width, and height. We found that each nucleus had a different growth rate in a different parameter. For the lenticular and caudate nuclei, their length increased fastest. But for the dorsal thalamus, its width increased most rapidly.

The claustrum

The claustrum was located external to the external capsule and displayed clearly in histological dyed slides after 18 weeks GA. But, the claustrum in the fetal brain was undistinguishable on MR images, even in 11.7-T field strength MR imagination [12]. In our study, the claustrum was distinguishable and delineated on 7.0-T T2WI at 18 weeks GA. This was perhaps due to the suitable layer thickness and layer interval.

The internal and external capsules

Histological research shows that the internal and external capsules begin to develop at 10 weeks GA, and the medullary sheath begins to form at the posterior limb of the internal capsule at 32 weeks GA. The external capsule could not be delineated on 1.5-T MRI study, and it was difficult to distinguish the internal and external capsules in premature fetal MRI. The anterior and posterior limbs of the internal capsule were undistinguishable till 21 weeks GA on 1.5-T MRI studies [8, 14–16]. In our study, both internal and external capsules could be distinguished at 16 weeks GA. This is perhaps due to the MRI of high magnetic strength and formation of the medullary sheath at the posterior limb of the internal capsule.

Limitations and innovations

The biggest limitation is that the field strengths used in daily practice are far from 7.0 T, which may limit the clinical application of our results. It is thought that the present results cannot be directly used in the clinical setting. However, they provide certain information that is beneficial for evaluating fetal brain development and interpreting MRI examinations performed at lower field strengths [6, 18].

Compared with the knowledge in pathology textbooks, the core findings are the quantitative data of the subcortical brain structures and the equations that best represented their correlation with GA. In traditional pathology, it is hard to obtain quantitative measurements of the fetal brain due to the deformation caused by gravity and cutting of slices. In this study, the quantitative data obtained of the brain in situ based on the high-quality images may be considered as supplementary data for pathology textbooks.

Conclusions

Seven-tesla MRI can delineate the development of the subcortical brain structures at the mid-trimester of pregnancy and can obtain the normal measurements of these structures. It can provide certain help in evaluating fetal brain development in the uterus. This study provides exact quantitative data and is a supplement to traditional anatomy, embryology, and histology.

Acknowledgments This work was supported by the National Natural Science Foundation of China (no. 31071050), Promotive Research Fund for Excellent Young and Middle-Aged Scientists of Shandong Province (BS2010YY042). The authors thank Bingzhi Liu, Qingcai Zhou, Shuhui Hong, Jianfen Jiao, and Xinting Gai for the postmortem fetus collection.

Conflict of interest We declare that we have no conflict of interest.

References

1. Malinger G, Kidron D, Schreiber L, Ben-Sira L, Hoffmann C, Lev D, Lerman-Sagie T (2007) Prenatal diagnosis of malformations of cortical development by dedicated neurosonography. Ultrasound Obstet Gynecol 29:178–191
2. Guibaud L (2009) Contribution of fetal cerebral MRI for diagnosis of structural anomalies. Prenat Diagn 29(4):420–433
3. Huisman TA, Martin E, Kubik-Huch R, Marincek B (2002) Fetal magnetic resonance imaging of the brain: technical considerations and normal brain development. Eur Radiol 12:1941–1951
4. Ramenghi LA, Fumagalli M, Righini A, Bassi L, Groppo M, Parazzini C, Bianchini E, Triulzi F, Mosca F (2007) Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. Neuroradiology 49:161–167
5. Zhang Z, Liu S, Lin X, Sun B, Yu T, Geng H (2010) Development of fetal cerebral cortex: assessment of the folding conditions with post-mortem magnetic resonance imaging. Int J Dev Neurosci 28:537–543
6. Zhang Z, Liu S, Lin X, Teng G, Yu T, Fang F, Zang F (2011) Development of fetal brain of 20 weeks gestational age: assessment with post-mortem magnetic resonance imaging. Eur J Radiol 80:e432–e439
7. Zhang Z, Liu S, Lin X, Teng G, Yu T, Fang F, Zang F (2011) Development of laminar organization of the fetal cerebrum at 3.0 T and 7.0 T: a postmortem MRI study. Neuroradiology 53:177–184
8. Rados M, Judas M, Kostović I (2006) In vitro MRI of brain development. Eur J Radiol 57:187–198
9. Whitby EH, Paley MN, Cohen M, Griffiths PD (2006) Post-mortem fetal MRI: what do we learn from it? Eur J Radiol 57:250–255
10. Kinoshita Y, Okudera T, Tsuru E, Yokota A (2001) Volumetric analysis of the germinal matrix and lateral ventricles performed using MR images of postmortem fetuses. Am J Neuroradiol 22:382–388
11. Guihard-Costa AM, Ménez F, Delezoide AL (2002) Organ weights in human fetuses after formalin fixation: standards by gestational age and body weight. Pediatr Dev Pathol 5:559–578
12. Huang H, Xue R, Zhang J, Ren T, Richards LJ, Yarowsky P, Miller MI, Mori S (2009) Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. J Neurosci 29:4263–4273
13. Prayer D, Kasprian G, Krampl E, Ulm B, Witzani L, Prayer L, Brugger PC (2006) MRI of normal fetal brain development. Eur J Radiol 57:199–216
14. Jakovcevski I, Zecevic N (2005) Sequence of oligodendrocyte development in the human fetal telencephalon. Glia 49:480–491
15. Taoka T, Aida N, Ochi T, Takahashi Y, Akashi T, Miyasaka T, Iwamura A, Sakamoto M, Kichikawa K (2011) Transient hyperintensity in the subthalamic nucleus and globus pallidus of newborns on T1-weighted images. Am J Neuroradiol 32:1130–1137
16. Counsell SJ, Maalouf EF, Fletcher AM, Duggan P, Battin M, Lewis HJ, Herlihy AH, Edwards AD, Bydder GM, Rutherford MA (2002) MR imaging assessment of myelination in the very preterm brain. Am J Neuroradiol 23:872–881
17. De Vita E, Bainbridge A, Cheong JL, Hagmann C, Lombard R, Chong WK, Wyatt JS, Cady EB, Ordidge RJ, Robertson NJ (2006) Magnetic resonance imaging of neonatal encephalopathy at 4.7 tesla: initial experiences. Pediatrics 118:e1812–e1821
18. Lin X, Zhang Z, Teng G, Meng H, Yu T, Hou Z, Fang F, Zang F, Liu S (2011) Measurements using 7.0 T post-mortem magnetic resonance imaging of the scalar dimensions of the fetal brain between 12 and 20 weeks gestational age. Int J Dev Neurosci 29:885–889