Development of laminar organization of the fetal cerebrum at 3.0T and 7.0T: a postmortem MRI study

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Abstract

Introduction The purpose of this study is to show the condition of laminar organization on 3.0T and 7.0T postmortem magnetic resonance imaging (MRI) and analyze developmental changes.

Methods Heads of 131 fetal specimens of 14–40 weeks gestational age (GA) were scanned by 3.0T MRI. Eleven fetal specimens of 14–27 weeks GA were scanned by 7.0T MRI. Clear images were chosen for analysis.

Results On T_1-weighted 3.0T MRI, layers could be visualized at 14 weeks GA and appeared clearer after 18 weeks GA. On 7.0T MRI, four zones could be recognized at 14 weeks GA. During 15–22 weeks GA, when laminar organization appeared typical, seven layers including the periventricular zone and external capsule fibers could be differentiated, which corresponded to seven zones in histological stained sections. At 23–28 weeks GA, laminar organization appeared less typical, and borderlines among them appeared obscured. After 30 weeks GA, it disappeared and turned into mature-like structures. The developing lamination appeared the most distinguishable at the parieto-occipital part of brain and peripheral regions of the hippocampus. The migrating thalamocortical afferents were probably delineated as a high signal layer located at the lower, middle, and upper part of the subplate zone at 16–28 weeks GA on T_1-weighted 3.0T MRI.

Conclusions T_1-weighted 3.0T MRI and T_2-weighted 7.0T MRI can well demonstrate the laminar organization. Development of the lamination follows a specific spatio-temporal regularity, and postmortem MRI of the parieto-occipital part of brain obtained with 3.0T or 7.0T is an effective way to show developmental changes.

Keywords Fetal brain · Development · Laminar organization · Cerebral cortex · Postmortem MRI

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Introduction

During all the developmental stages of the fetal cerebrum, development of the cerebral cortex is prominent, and changes of laminar organization are the most typical. Although these changes, which can be visualized on histological stained sections [1–3], in vitro or in vivo magnetic resonance imaging (MRI) [2–6], are transient in the developmental process of the cerebrum, laminar organization is important in evaluating the health status of the whole brain, and changes can be recognized as indirect parameters for an assessment of normal histogenetic events involved in the prenatal shaping of the human cerebral cortex [2, 3, 7].

In previous histological research [8, 9], layers in the lamination were divided into seven separate zones from inner to outer. They are the ventricular zone, the periventricular zone, the subventricular zone, the intermediate

zone, the subplate zone, the cortical plate, and the marginal zone. With the development of MRI techniques, especially the application of rapid acquisition with relaxation enhancement sequence, image quality of in vivo fetal MRI has been greatly improved [10, 11] and supplies new possibilities for analysis of structural maturation and for identification of abnormalities of the fetal brain. But, as in vivo fetal MRI is limited by the special sequence and scanning magnetic strength [12], it cannot clearly demonstrate the lamination, and so, it is not effective enough to assess developmental changes. By contrast, postmortem MRI, without being constrained by the limitations of in vivo fetal MRI, can clearly demonstrate developmental changes. Previous research, which was commonly performed under magnetic strength less than 3T, confirmed its value in studying fetal brain development and revealing precise correlations with findings in histological sections [2–4, 13, 14]. Thus, it would be necessary and more valuable to scan fetal specimens with an MRI scanner of high magnetic strength.

In this study, 3.0T and 7.0T postmortem MRI of 131 fetal specimens of 14–40 weeks gestational age (GA) were combined to analyze the condition of the laminar organization and its developmental changes. It is thought that the results of the present study may have positive influences on evaluation of the developmental status or clinical diagnosis of the fetal brain in the uterus.

Materials and methods

Selection of the specimens

From 2005, 131 fetal specimens of 14–40 weeks GA (GA dispositions and numbers of the specimens are listed in Table 1) were collected from medically indicated or spontaneous abortions, fetal deaths caused by maternal diseases, stillbirths during abnormal labor, and premature deaths attributed to diseases outside of the brain (such as respiratory disease) in hospitals of Shandong Province. The specimens were first examined with ultrasonography (US) and 3.0T MR pre-scanning to exclude those with brain diseases or developmental disorders by two pediatric neuroradiologists with clinical experience of more than 10 years. The criteria by which a fetus was deemed to be anatomically normal were based on the size of the cerebrum and developmental status of sulci, lateral ventricle, and corpus callosum. Fetuses with discrepancies between the two radiologists about brain development were excluded, and only those which had a morphologically normal central nervous system were reserved for study. The GA of the fetuses was estimated on the basis of their crown–rump length, head circumference, foot length, and/ or pregnancy

Table 1 GA and numbers of chosen specimens in MRI of different Tesla (n=131)

Tesla	GA	Number
3.0T	14	1
	15	4
	16	3
	17	6
	18	5
	19	7
	20	7
	21	12
	22	12
	23	7
	24	12
	25	6
	26	9
	27	9
	28	5
	29	1
	30	3
	31	3
	32	4
	34	1
	36	3
	37	5
	38	1
	39	3
	40	2
7.0T	14	1
	15	1
	16	2
	17	2
	18	1
	20	2
	21	1
	27	1

records and expressed as weeks from the last menstrual period [15]. The specimens were immersed in 10% formalin for preservation and scanned with 3.0T and 7.0T MRI soon afterwards. The time interval between collection of specimens and scanning was within 2 months. This study was conducted on the basis of approval from the Internal Review Board of the Ethical Committee at the School of Medicine, Shandong University. The parents' consent to donate the fetal cadaver was obtained.

Scanned by 3.0T MRI

The specimens were scanned by a GE 3.0T MR scanner (General Electric, Milwaukee, USA). The eight-channel high-resolution brain array was chosen for scanning the fetuses. The slice thickness was the same for all fetal ages.

Parameters were as follows: scanning thickness, 2 mm; slice interval, 1.5 mm; T_1 FLAIR sequence: repetition time (TR) 2,580.0 ms, echo time (TE) 23.4 ms, matrix size 512*512, and number of excitations (NEX) 1; and T_2-weighted: TR 4600.0 ms, TE 111.6 ms, matrix size 512*512, and NEX 1. The field of view was adjusted according to the head circumference so as to have a signal-to-noise ratio of more than 56%.

Scanned by 7.0T MRI

Eleven specimens of 14–27 weeks GA were chosen and scanned by a 7.0T Micro-MRI 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 chosen to scan the fetuses. One specimen of 27 weeks GA was scanned without the cranial bones because of a too-large head circumference. Four out of the 11 specimens (14, 18, 20, 27 weeks GA) were scanned with parameters as follows: slice thickness 0.8 mm; slice interval 0.8 mm; T_1-weighted: TR 384.4 ms, TE 15.8 ms, matrix size 512*512, and NEX 1; and T_2-weighted: TR 3,500.0 ms, TE 36.0 ms, matrix size 512*512, and NEX 4. The other seven were scanned with parameters as follows: slice thickness 0.5 mm; slice interval 0.5 mm; and T_2-weighted: TR 12,000.0 ms, TE 50.0 ms, matrix size 256*256, and NEX 4.

The Nissl-stained sections

Following the selection of a scanned specimen of 18 weeks GA, the brain was obtained after removing the cranial bones and cerebral pia mater. It was cut into slices of 1-mm thick with a monkey brain tooting. The slices were immersed in 0.1‰ thionine overnight and then, after being gradually dehydrated by alcohol, were placed under operating lights for photos taken with a Canon camera (EOS 20D) with eight million pixels.

Results

The Nissl-stained sections

In Nissl-stained sections of the occipital part of fetal brain, seven typical layers could be observed in the cerebral wall. From inside to outside, they were the ventricular zone, the periventricular zone, the subventricular zone, the intermediate zone, the subplate zone, the cortical plate, and the marginal zone (1–7 in Fig. 1).

Laminar organization on 3.0T and 7.0T postmortem MRI

Before 18 weeks GA, laminar organization appeared blurred on 3.0T MRI (Figs. 2a and 3a), while after 18 weeks GA, it
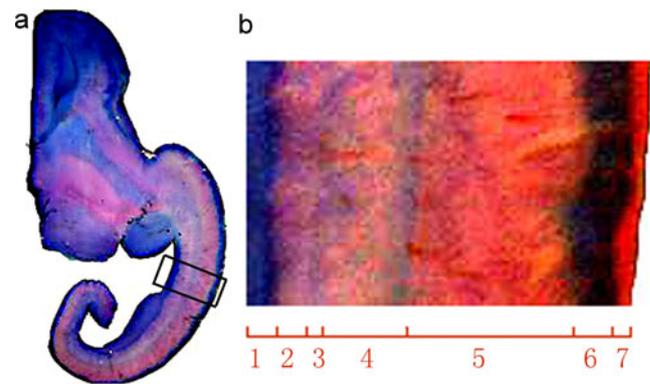
Fig. 1 Semi-horizontal Nissl-stained section of 18 weeks GA reveals the laminar organization of fetal cerebrum. *1* the ventricular zone; *2* the periventricular zone; *3* the subventricular zone; *4* the intermediate zone; *5* the subplate zone; *6* the cortical plate; *7* the marginal zone. The *box* in (**a**) corresponds to the higher power view in (**b**)

gradually appeared clearer (Figs. 4, 5, and 6). In delineating the lamination, on 3.0T MRI, T_1-weighted images had higher image contrast than T_2-weighted images (Fig. 4), while on 7.0T MRI, T_2-weighted images had higher image contrast (Fig. 2b, c). On T_2-weighted 7.0T MRI, the marginal zone (*7* in Fig. 2b) could be observed.

Developmental changes of laminar organization of the fetal cerebrum

On postmortem MRI, the lamination was described as layers with varying signal intensities. Changes related to GA could be revealed by layers' appearance or disappearance, thickness, signal intensities, and borderlines.

The ventricular zone

This zone appeared as a low signal layer on T_2-weighted images, but as a high signal layer on T_1-weighted images. The layer could be visualized at 14 weeks GA (*1* in Fig. 2), and at 16 weeks GA, it appeared as a wide low signal layer (*1* in Fig. 3b) mixed with the periventricular zone (*2* in Fig. 3b) above it. The ventricular zone, whose thickness appeared thinner as GA increased, was delineated as a typical layer linking the germinal matrix and encircling the lateral cerebral ventricle at 18–23 weeks GA (*1* in Figs. 4, 5, and 6a). Borderlines between it and the layer nearby appeared distinct because the signal intensity of the ventricular zone was different from that of the periventricular zone (*2* in Figs. 3, 4, 5, and 6a) above it and that of the cerebrospinal fluid below it. It was still visible until 37 weeks GA (*1* in Fig. 6f).

The periventricular zone

This zone was delineated as a high signal layer on T_2-weighted images, but as a low signal layer on T_1-weighted
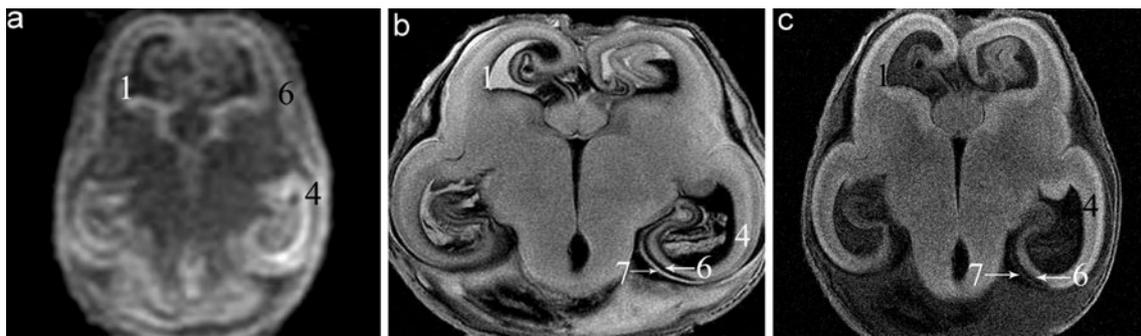
Fig. 2 Transverse T$_1$-weighted (**a**) 3.0T MRI, and transverse T$_2$-weighted (**b**) and T$_1$-weighted (**c**) 7.0T MRI of 14 weeks GA. Three layers can be observed on T$_1$-weighted 3.0T MRI. They are the ventricular zone (*1*), the intermediate zone (*4*), and the cortical plate (*6*). On 7.0T MRI, four layers including the marginal zone (*7*) can be observed, and the T$_2$-weighted image (**b**) has higher image contrast than T$_1$-weighted image (**c**)

images. The zone was visible at 15 weeks GA (*2* in Fig. 3b). During 18–20 weeks GA, it appeared as a continuous layer (*2* in Figs. 4 and 5) encircling the ventricular zone of high signal intensity, with clear border-lines between it and the layers nearby. It appeared discontinuous on 3.0T MRI at 22 weeks GA (*2* in Fig. 6a). At 28 weeks GA, punctiform regions with low signal intensity stood out at the location where the previous periventricular zone had been. They were the periventric-ular fibers crossroads, which appeared apparent as GA increased (white double arrows in Fig. 6d–f).

The subventricular and intermediate zones

The subventricular zone appeared as a low signal layer on T$_2$-weighted images and as a high signal layer on T$_1$-weighted images. It was visible at 16 weeks GA (*3* in Fig. 3b). At 18 weeks GA, mixed with the intermediate zone (*3/4* in Fig. 4), it appeared as a high signal layer above

the periventricular zone. But, most of it disappeared at 22 weeks GA (*3/4* in Fig. 6a) and could not be visualized at 26 weeks GA (*3/4* in Fig. 6c). A borderline between the subventricular and intermediate zones could not be delin-eated on 3.0T postmortem MRI during all developmental stages, but it could be observed in the occipital part of the brain on 7.0T MRI at 16 and 20 weeks GA (*3* and *4* in Figs. 3b and 5b).

The intermediate zone, being visualized at 14 weeks GA (*4* in Fig. 2), appeared as a wide layer with high signal on T$_2$-weighted images (*4* in Fig. 2b). The layers with low signal intensities above and below it were recognized as the pre-cortical plate and ventricular zone, respectively. At 16 weeks GA, the zone appeared apparent (*4* in Fig. 3), with the bilateral sides forwardly linking the bottom part of the external capsule (white single arrow in Figs. 3, 4, 5, and 6d) and upwardly linking the inferior part of the subplate (*5* in Figs. 3, 4, 5, and 6). The intermediate zone appeared wide and typical at 18–22 weeks GA (*3/4* in Figs. 4, 5, and
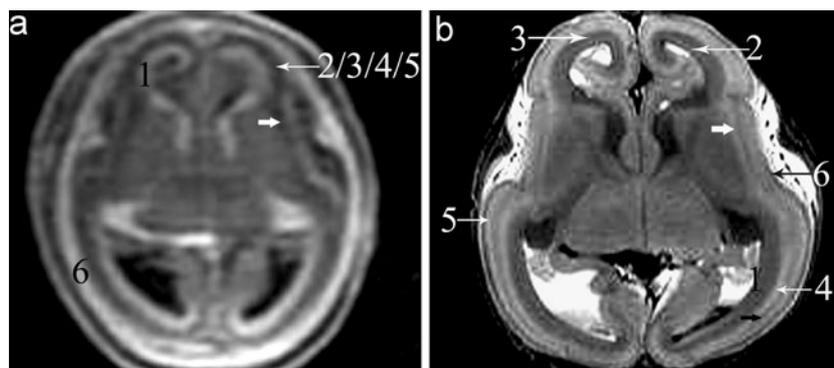
Fig. 3 Transverse T$_1$-weighted (**a**) 3.0T MRI and T$_2$-weighted (**b**) 7.0T MRI of 16 weeks GA. Three layers can be observed on T$_1$-weighted 3.0T MRI, they are the ventricular zone (*1*), the cortical plate (*6*), and the layer with low signal intensity between the two zones above-mentioned, containing the periventricular zone (*2*), the subven-tricular zone (*3*), the intermediate zone (*4*), and the subplate zone (*5*). On T$_2$-weighted 7.0T MRI, six layers can be observed. The marginal zone cannot be visualized because of the high signal emitted by the cerebrospinal fluid. From this GA on, the external capsule (*white single arrow*), which separates the intermediate zone and the subplate zone, can be clearly observed. The *black single arrow* shows that the lower part of the subplate zone is of low signal intensity on T$_2$-weighted image at this GA
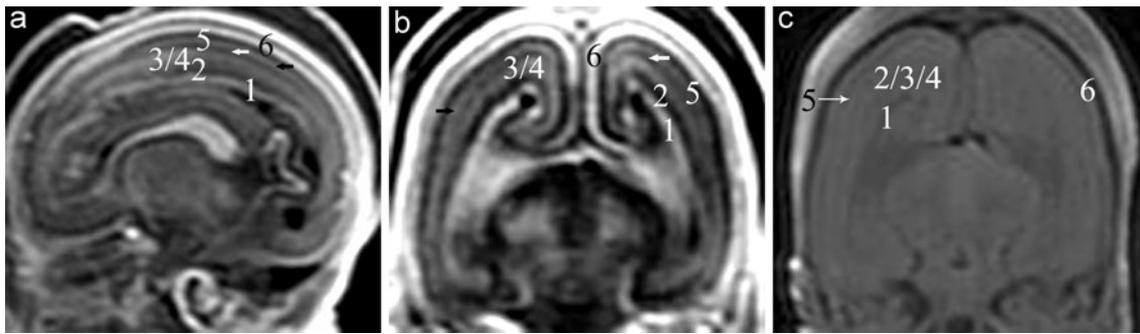
Fig. 4 Sagittal (**a**), coronal (**b**) T$_1$-weighted, and coronal T$_2$-weighted (**c**) 3.0T MRI of 18 weeks GA. The layers appear typical at this GA, six layers including the continuing periventricular zone (*2*) and external capsule fibers (*white single arrow*) can be observed. The image contrast of T$_2$-weighted image is inferior to that of T$_1$-weighted image and only four layers can be distinguished. The borderline between the subventricular (*3*) and intermediate zone (*4*) cannot be delineated. The *black single arrow* shows that the lower part of the subplate zone is of high signal intensity on T$_1$-weighted image at this GA

6a), but after 24 weeks GA, it was hard to discriminate from the subplate zone above it. It eventually differentiated into fetal white matter (*4* in Fig. 6d–f).

At 16–23 weeks GA, the external capsule fibers region (white single arrow in Figs. 3, 4, 5, and 6a), lying parallel to the periventricular zone with similar signal intensity, could be clearly delineated just above the intermediate zone, separating it from the subplate. This zone appeared discontinuous at 22 weeks GA (white single arrow in Fig. 6a) and could not be recognized at the parieto-occipital part of the brain at 24 weeks GA. But, it remained visible at the region near the basal ganglia (white single arrow in Fig. 6b–d).

The subplate zone

The signal intensity of this layer did not appear the same, appearing as a low signal layer on T$_2$-weighted images and a high signal layer on T$_1$-weighted images. The layer was visible at 15 weeks GA, as two adjoining layers of different signal intensities (*5* in Fig. 3b) lying just below the cortical plate (*6* in Figs. 2, 3, 4, 5, and 6). The subplate appeared wide at 18–20 weeks GA, containing two layers with different signal intensities (*5* in Figs. 4 and 5), and it appeared much wider at 22–24 weeks GA (*5* in Fig. 6a, b). The signal intensity of the subplate zone began to increase at 26 weeks GA (*5* in Fig. 6c). At 28 weeks GA, it mixed with the cortical plate, a high signal layer, above it (*5* in Fig. 6d). The subplate zone turned into punctiform regions and began to dissolve at 30 weeks GA (*5* in Fig. 6e). At 37 weeks GA, only narrow layers of low signals, which were the remnants of the subplate zone (white single arrow in Fig. 6e, f), could be visualized in the temporal lobe or the gyral crest of the parieto-occipital part of brain, which constantly remained distinct during the last trimester because of its late disappearance.

Changes of signal intensities in the subplate zone could be visualized. On T$_1$-weighted images at 16–20 weeks GA, the inferior part of the subplate zone had high signal intensity (black single arrow in Figs. 4a, b and 5a) while the superior part had low signal intensity. But, at 22 weeks GA,
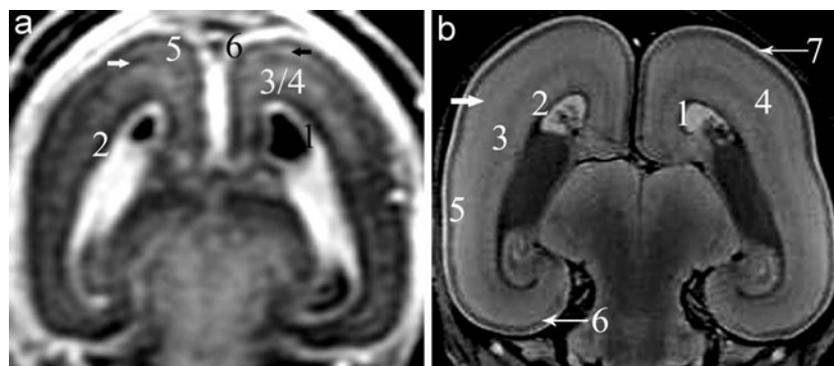
Fig. 5 Coronal T$_1$-weighted (**a**) 3.0T MRI, and coronal T$_2$-weighted 7.0T MRI (**b**) of 20 weeks GA. Layers appear almost the same as that at 18 weeks GA on 3.0T MRI. On 7.0T MRI, seven layers including the marginal zone (*7*) can be observed. The borderline between the subventricular (*3*) and intermediate zone (*4*) can also be distinguished. The external capsule (*white single arrow*) still appears continuous, and the layer of high signal intensity (*black single arrow* in a) still appears at the lower part of the subplate zone on T$_1$-weighted image at this GA
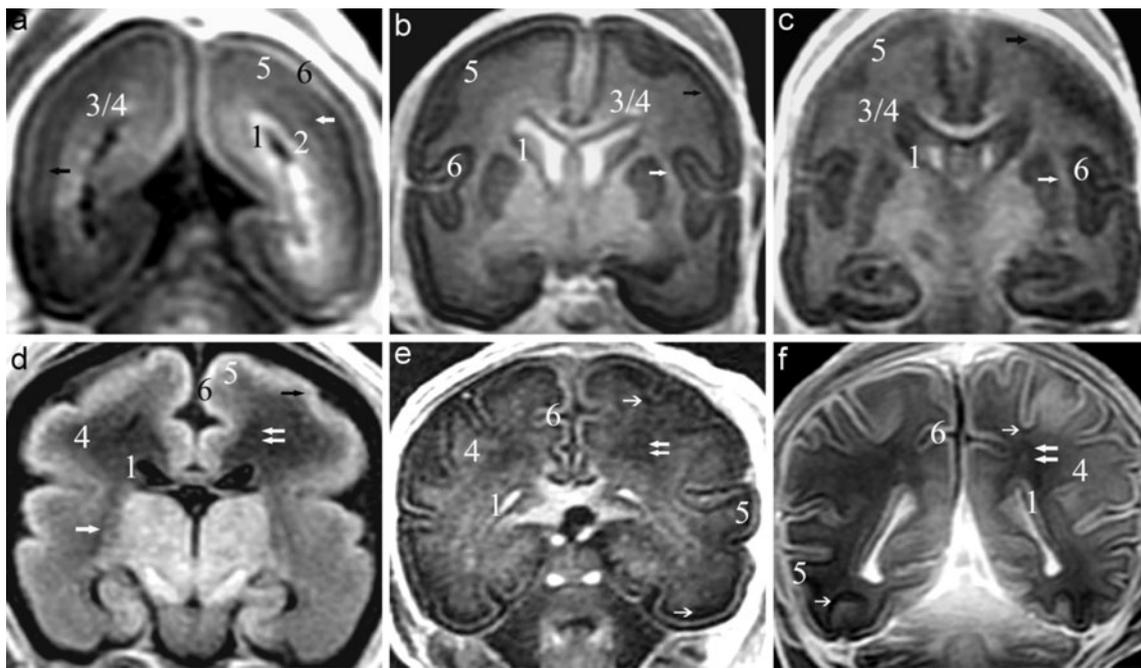
Fig. 6 Coronal T$_1$-weighted 3.0T MRI of 22 (**a**), 24(**b**), 26(**c**), 28(**d**), 30(**e**), 37(**f**) weeks GA. At 22 weeks GA, six layers can be observed but the periventricular zone (*2* in **a**) and external capsule fibers region (*white single arrow* in **a**) appears discontinuous. After this GA, the external capsule (*white single arrow* in **b**–**d**) can only be discriminated at the region near the basal ganglia. The high signal layer (*black single arrow* in **a**), probably the migrating thalamocortical afferents, is now in the middle of the subplate zone (*5* in **a**). Then, it migrates to the upper part of the subplate zone (*5* in **b**–**d**) and mixes together with the cortical plate (*6* in **a**–**f**, *black single arrow* in **b**–**d**). At 24–28 weeks GA, the lamination appears untypical, and the subplate zone appears wide. At 30–37 GA, the lamination almost disappears, and only remnants of the subplate zone (*white single arrow* in **e**, **f**) can be observed in the temporal lobe or the gyral crest. The periventricular fibers crossroads (*white double arrows* in **d**–**f**) can be clearly visualized after 28 weeks GA

there was a high signal layer in the middle part of the subplate zone (black single arrow in Fig. 6a). And during 24–26 weeks GA, the high signal layer gradually migrated to the superior part of the subplate zone and got close to the cortical plate, where it mixed with the cortical plate, a high signal layer, at the parieto-occipital part of brain at 28 weeks GA (black single arrow in Fig. 6b–d). This moving high signal layer probably was the thalamocortical afferents migrating to the cortical plate.

The borderline between the subplate zone and the cortical plate above it could be clearly distinguished because of different signal intensities of the two. But, it appeared obscured at 26–28 weeks GA when the thalamocortical afferents migrated to the superior part of the subplate zone (Fig. 6c, d). At 30–37 weeks GA, the borderline between the cortical plate and remnants of the subplate zone (white single arrow in Fig. 6e, f) remained distinct at the temporal lobe.

The cortical plate

The signal intensity of this layer, different from that of the subplate, remained the same during developmental stages (*6* in Figs. 2, 3, 4, 5, and 6). The cortical plate was located exterior to the subplate zone. After 28 weeks GA, it transformed into most of the gray matter.

The marginal zone

On T$_2$-weighted 7.0T MRI at 14 and 20 weeks GA, the marginal zone could be visualized as a high signal layer exterior to the cortical plate at the frontal, occipital lobe, and regions near the hippocampus (*6* in Figs. 2b and 5b). It could also be vaguely delineated on T$_1$-weighted 7.0T MRI at 14 weeks GA (*7* in Fig. 2c).

Comparing images of different magnetic strength and scanning positions, it was found that the laminar organization was particularly clearer at the peripheral regions of the hippocampus and parieto-occipital part of brain.

Discussion

Laminar organization of the fetal cerebrum and its significances

In this study, it was found that 15–22 weeks GA was the period when laminar organization typically appeared, when

the cerebral wall consisted of seven zones, and most of them could be clearly differentiated during this stage on the 3.0T or 7.0T postmortem MRIs. During 23–28 weeks GA, laminar organization appeared less typical with borderlines among them obscured. After 30 weeks GA, it disappeared and turned into mature-like structures. These results are consistent with previous findings from histological slides and T_1-weighted images [2, 3].

The laminar pattern, which displays age-specific changes, is formed as a result of the development and migration of neurons and fibers [2, 16] and can be recognized as a marker to evaluate whether the brain is developing normally or not [2, 3, 7]. Any malformations of cortical development caused by cellular multiplication, differentiation, or migration disorders may lead to abnormalities of the lamination [17, 18], such as the cobblestone complex, with disruption of the cortical ribbon caused by over-migration of neurons, which may lead to loss of the subventricular zone, intermediate zone, and subplate zone [19].

The ventricular zone contains much germinal matrix which is capable of dividing and proliferating. The periventricular zone, subventricular zone, and intermediate zone form the primary fetal white matter which contains oriented migrating neurons and fibers, whose migration activity is guided by the special cells and molecules in the subplate zone, cortical plate, and marginal zone [20–23].

The subplate zone, which frequently changes in signal intensity, is the most distinct layer revealed by postmortem MRI. This layer plays an important role in the development and relocation of fibers or migration of neurons [2, 3]. In hypoxia or ischemic diseases of premature brains, the subplate zone may be selectively injured so as to disturb the internal neurons and microenvironment, leading to disorders of the synaptogenesis, migration of neurons or fibers, and establishment of nerve systems in later stages [24].

Laminar organization on postmortem MRI

US is the first choice screening method for evaluating fetal anatomy, and in vivo fetal MRI can be an effective complementary mean available when US findings are neither conclusive nor adequate. At present, much research has confirmed the assisting effects of in vivo fetal MRI in diagnosis [11, 25, 26]. But, in vivo fetal MRI cannot clearly show the lamination because of the scanning magnetic strength of 1.5T and rapid acquisition sequences, and it is easily influenced by fetal movement, pulse of the maternal artery, or structures [12]. In this study, it was found that postmortem MRI, which could clearly reveal the developmental changes of laminar organization, allowed a greater understanding of the normal developmental trajectory of the fetal cerebrum. It has become not only an important adjunct/alternative to autopsy, but also an important research tool to aid the interpretation of in vivo MR images and the study of cortical development.

Although it may be noticed that the 7.0T MRI has a higher image resolution than 3.0T MRI, it is thought that the 3T and 7T studies cannot be compared with each other in this study, as the methods used differ widely. For example, the use of the head coil at 3T and 1 NEX, compared with the rat coil at 7T and 4 NEX will definitely have a negative effect on the resolution.

MRI of high magnetic strength can demonstrate some structures that cannot be delineated on MRI of low magnetic strength or in vivo. Histological research has indicated that, as early as 9 weeks GA, thalamocortical afferents assemble in the inferior part of the subplate zone. At 22–24 weeks GA, they gradually migrate to the superior part, and then they penetrate and relocate into the cortical plate at 24–28 weeks GA [2, 27]. Up to now, there have been few reports showing this progress on MRI. In this study, a high signal layer on T_1-weighted images could be observed moving from the inferior to superior part of the subplate zone and finally linking the cortical plate. This was probably the migrating progress of thalamocortical afferents and their relocation into the cortical plate. So, it is thought that migration of the thalamocortical afferents, previously shown in histology, could also be revealed by postmortem MRI of high magnetic strength through the migrating signal layer.

At 15–22 weeks GA, the periventricular zone and external capsule fibers could be clearly visualized on 3.0T or 7.0T postmortem MRIs. But, on previous postmortem MRIs of 2.0T, the two layers could not be continuously delineated [2, 3]. Maas et al. [28] used DTI of 1.5T MRI to demonstrate lamination of the premature cerebrum, but layers interior to the subplate zone could not be clearly described because of low image contrast and a similar apparent diffusion coefficient. Previous research [13, 14, 29] has also demonstrated that 4.7T and 11.7T postmortem MRIs can well delineate the laminar organization, and the findings obtained from postmortem MRIs are consistent with those of histological stained slices.

Before 21 weeks GA, the fetal head was small enough (<60 mm) to be scanned on 7.0T MRI, in which the laminar organization, the hippocampus, and small sulci could be more clearly delineated. In this study, the marginal zone at 16 weeks GA was not observed, perhaps due to the changes of scanning thickness and parameters. A moderate T_2 weighting is capable of providing considerable details with respect to the adjacent layers, while strong T_2 weighting results in images of poor quality, so as not to benefit the detection of the marginal zone with strong intensity of the signal emitted by the cerebrospinal fluid. The present results were coincident with those of previous research on 4.7T MRI [29].

Conclusions

In summary, T_1-weighted 3.0T MRI and T_2-weighted 7.0T MRI can well delineate the lamination. The development of laminar organization of the fetal cerebrum, which is typical at 15–22 weeks GA at the parieto-occipital lobe and peripheral regions of hippocampus on postmortem MRI, follows a specific spatio-temporal regularity. Postmortem MRI, which is free from the limitations of that of in vivo fetal MRI, can more clearly describe the laminar organization, and it can also demonstrate changes of signal intensities in the subplate zone, which are probably the migrating thalamocortical afferents.

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

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