Characterization of Fetal Brain Development with Diffusion Tensor Magnetic Resonance Imaging

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Abstract

Human brain anatomy is characterized by dramatic structural changes during fetal development. It is extraordinarily complex and yet its origin is a simple tubular structure. Revealing detailed anatomy at different stages of human fetal brain development not only aids in understanding this highly ordered process, but also provides clues to detect abnormalities caused by genetic or environmental factors. For example, the characterization of white matter axon growth could provide important clues to understanding the inhomegeneity of white matter injuries in cerebral palsy. However, anatomical studies of human brain development during this period are surprisingly scarce, and histology-based atlases have only recently become available. Diffusion tensor imaging (DTI), a novel method of magnetic resonance imaging (MRI), is capable of delineating anatomical components with high contrast and revealing structures at the microscopic level. The volumetric measurement from 3D DTI data can quantify structural growth. As discussed in this article, the fetal brain DTI database will be a valuable resource for human brain developmental study and will provide reference standards for diagnostic radiology of premature newborns.

Keywords

Brain development, cerebral palsy, diffusion tensor imaging (DTI), fetal, newborn, atlas, tractography

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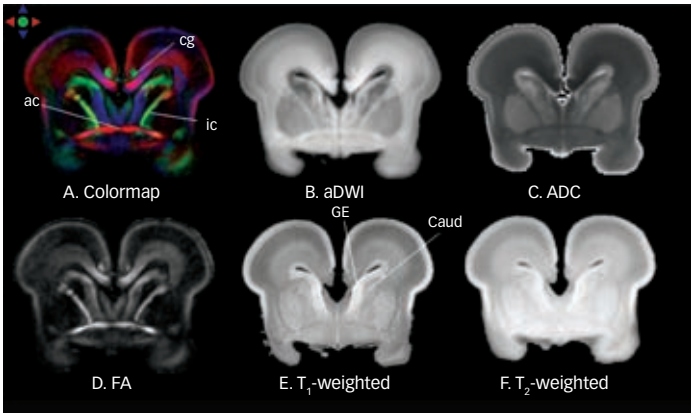
Diffusion tensor imaging (DTI) is a new type of magnetic resonance imaging (MRI) that allows non-invasive mapping of the diffusion properties of brain water and reveals unique tissue property 'diffusion anisotropy'.[1–5] MRI can measure the extent of water diffusion along an arbitrary axis. From this measurement, it is often found that the water tends to diffuse along a preferential axis, which has been shown to coincide with the orientation of the ordered structures. Based on the diffusion orientation of water molecules, the DTI technique can provide several imaging contrasts such as anisotropy maps and orientation maps or a combination of the two, called a color-coded orientation map or simply colormap hereafter. In the colormap, the brightness shows the extent of the anisotropy and the color represents fiber orientation. It is known that the tensor-based data processing is only an approximation of the underlying tissue properties and more sophisticated and time-consuming data acquisition and processing schemes have been postulated.[6–8] However, for developmental brains we believe that the tensor approximation is an available and accepted method to characterize the gross white matter architectures and microstructures. Scanning time is best used to enhance the image resolution rather than to perform the complicated data acquisition.

The contrast from diffusion tensor MRI has been used to provide unique information about axonal tracts of human brain white matter.[1,9–13] It is especially useful for delineating the anatomy of premature brain that is not myelinated, and for which relaxation-based contrast is inadequate.[14–22] The technique can detect injuries in specific white matter tracts as well as demonstrate the rearrangement of tracts.[23–27] As DTI becomes widely available in clinical scanners, it is likely that DTI will be an important diagnostic tool for premature infants in the future.

Diffusion Tensor Imaging Contrasts and Primary Eigenvector Provide Unique Information About Brain Anatomy

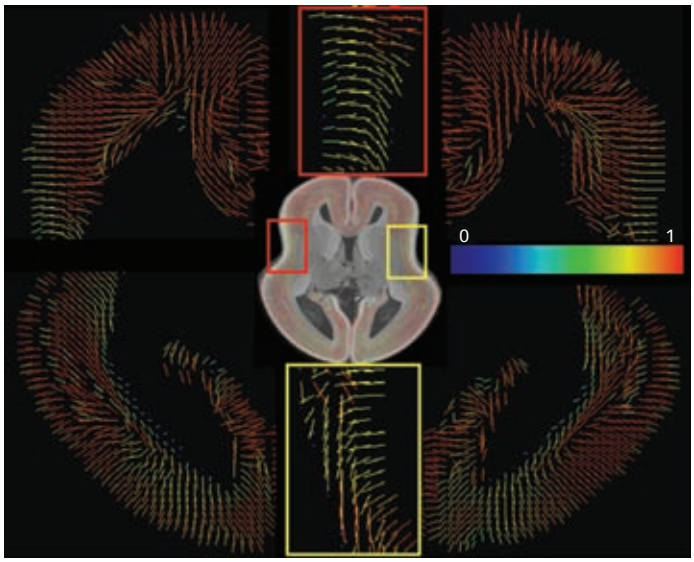
In this section, different contrasts derived from DTI are described. For fetal brains, the primary eigenvector from diffusion tensor can be further used to reveal the microstructures in the cerebral wall. *Figure 1* shows a comparison of different MRI contrasts from a *post mortem* fetal sample at 20 gestational weeks of age. Coronal images at the anterior commissure (ac) level are shown. Four of them (averaged diffusion-weighted image [aDWI], fractional anisotropy map [FA], and apparent diffusion constant map [ADC]) are derived from DTI. *Figures 1E* and *1F* show a conventional T_1-weighted and T_2-weighted image, respectively. The relaxation-based images (see *Figures 1E* and *1F*) excel in delineating overall brain shape, several cortical layers, and the ganglionic eminence (GE), a transient structure for basal ganglion. However, because of lack of myelination, differentiation between gray matter and white matter is not clear. For example, the boundary

Figure 1: High Diffusion Tensor Imaging Contrast (A–D) Reveals More Anatomical Structures in 20-week Fetal Brain than T_1- and T_2-weighted Images (E–F)



aDWI = averaged diffusion-weighted image; ADC = apparent diffusion coefficient; FA = fractional anisotropy. For colormap, R(ed)/G(reen)/B(lue) indicates the structural left–right, anterior–posterior, and superior–inferior orientations, respectively.

Figure 2: Primary Eigenvectors of the 20-week Fetal Brain



The orientations of the primary eigenvectors are magnified in the surrounding areas of the axial 20-week fetal brain image. The color of the line segment indicates the magnitude of eigenvectors projected to the image plane.

between the internal capsule (ic) and the caudate nucleus (Caud) is not well appreciated.

DTI-based contrasts provide very different information from T_1/T_2-weighted images. White matter tracts and the fiber-rich intermediate zone in the cerebral wall have high intensity in the FA and color-coded maps. For example, the location of the cingulum bundle (cg) can be appreciated only in the FA and colormaps. An advantage of conventional T_1/T_2-weighted images is that they achieve higher image resolution than DTI. However, for other regions where T_1/T_2-weighted images lack contrasts, the higher resolution does not necessarily provide more anatomical information. Relaxation-based contrasts and DTI thus seem to provide complementary information.

Besides the high contrasts from DTI shown in *Figure 1*, primary eigenvectors of diffusion tensor can be used to reveal the orientations of the microstructures. *Figure 2* shows the directions of primary eigenvectors in the cerebral wall of a 20-week fetal brain. They are highly regular and perpendicular to the cerebral wall. The radial orientation of primary eigenvectors reveals microstructures that are formed by radially arranged scaffolding of the glial cells and are paths for neuron migration during development. It can be appreciated from *Figure 2* that DTI offers a unique insight into these microstructures and helps us to understand that development takes place in the cerebral wall in a well-ordered manner. This radially arranged pattern has been found in *ex vivo* mouse brains and *in vivo* pre-term fetal brains.[16,17,19]

Fetal Brain Atlas with Diffusion Tensor Imaging

To study structural changes during fetal brain development, *post mortem* fetal brains of 13–22 gestational weeks were scanned in Bruker 11.7T (13–16 weeks) and 4.7T (17–22 weeks) scanners. *Figure 3* shows the DTI color map, aDWI, and apparent diffusion coefficient map of 13–22-week fetal brains at ac level. Image resolution ranges from 200 to 500µm, depending on the brain sizes. Younger brains have higher resolution. The *ex vivo* DTI scanning time for each brain is about 20 hours. From *Figure 3*, it is clear that the ventricles of the fetal brain are getting smaller with increasing gestational age. The cerebral wall is getting thicker during development. This database covers the second trimester of fetal brain development, when dramatic changes of neural structures take place. The oldest age (22 gestational weeks) is about the earliest possible survival time-point of the infant. With the DTI database of the second trimester, structural changes in this period can be systematically and quantitatively studied.

Dramatic Anatomical Changes During Brain Development

Multiple neural structures can be identified and segmented with the high contrasts provided by DTI. By segmenting neural structures with our developmental brain DTI database, we can quantitatively depict the volumetric changes of these structures shown in *Figure 4*. From *Figure 4*, the volumes of basal ganglia and ganglionic eminence increase accordingly, except that the volume of the ventricle is decreasing later in the second trimester. Note that ganglionic eminence is a transient structure that is replaced by the caudate nucleus, the putamen, the globus pallidus, and basal ganglia later in development.[28] The ganglionic eminence has the most volumetric increase, followed by thalamus, putamen and globus pallidus, and caudate nucleus. The volumes of these structures increase almost linearly.

One of the important features of DTI is that it can non-invasively trace the major white matter axons. We explored the potential of DTI to trace the time courses of development of different white matter tracts. Four groups of white matter tracts—callosal tracts, association tracts, limbic tracts, and projection tracts—were traced with DTI-based tractography.[29] The overall pattern of white matter development is that limbic fibers develop first and association fibers last, and commissural and projection fibers form from the anterior to posterior part of the brain. DTI data at three time-points—20 gestational weeks, 0 days of age, and five to six years of age—were used. Fetal brain data at 20 gestational weeks come from our *post mortem* fetal brain DTI

Figure 3: Coronal Views at Anterior Commissure Level of Diffusion Tensor Imaging Color Map (A), Averaged Diffusion-weighted Image (B), and Apparent Diffusion Coefficient Map (C) of 13–22-week Fetal Brains

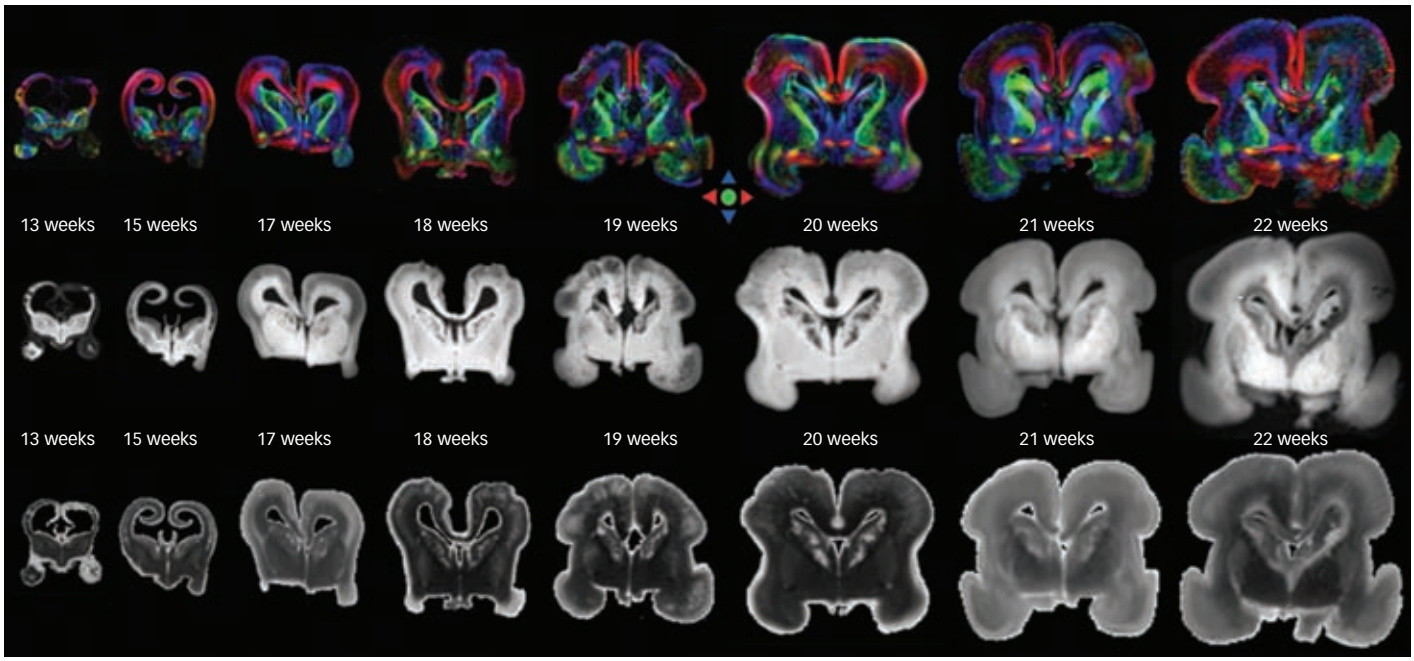
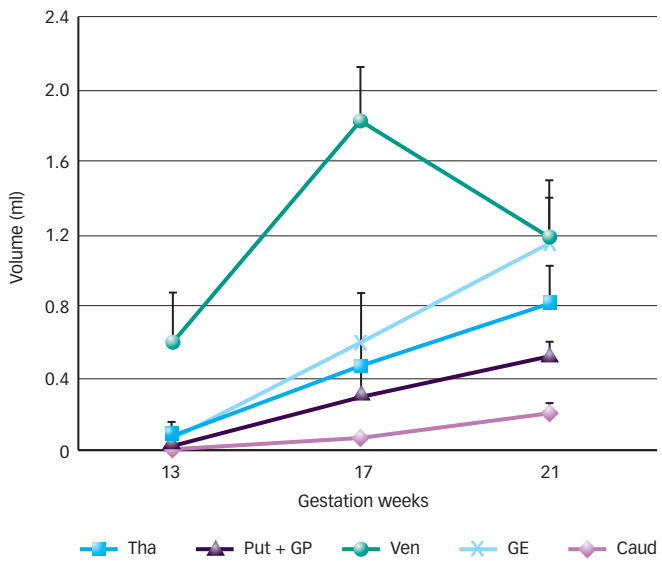
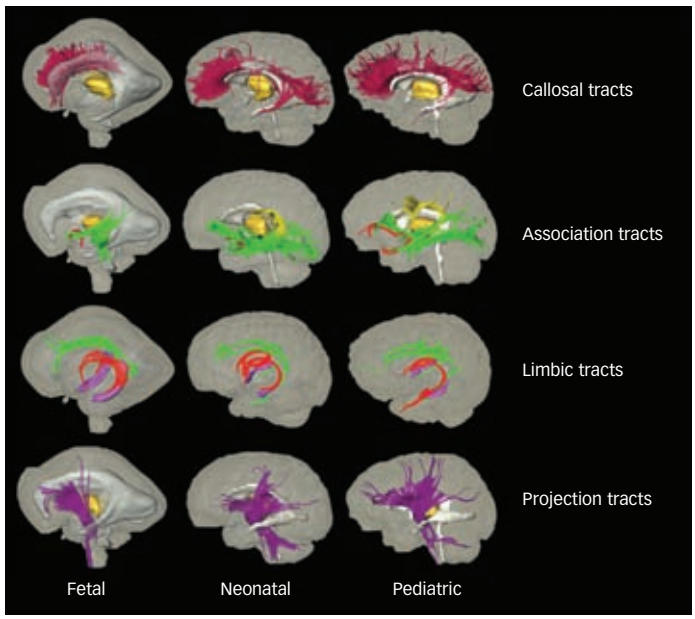


Figure 4: Measurement of Volumes of Brain Structures from 13–22 Gestational Weeks Fetal Brains



Caud = caudate nucleus; GE = ganglionic eminence; Put + GP = putamen and globus pallidus; Tha = thalamus; Ven = ventricle.

Figure 5: Three-dimensionally Reconstructed Callosal, Association, Limbic, and Projection Fibers of 20-week Fetal, Neonatal, and Pediatric Brains



database. For 0-day-old infants and five- to six-year-old children, *in vivo* DTI data were acquired. The 0-day-old infants were full-term, and we imaged healthy volunteers while asleep. These images can be considered a normal reference for the full-term infant. The children were five years old. Around this age, pediatric brains seem to mature to the point where MR images appear very similar to those of an adult brain. Three-dimensionally reconstructed tracts from data at three time-points are shown in *Figure 5*. From *Figure 5*, morphology of the limbic tracts, including cingulum (green fibers) and stria terminalis (red fibers) connecting to the purple hippocampus, are quite similar across the three developmental stages. The projection and callosal tracts display the anterior-to-posterior developmental pattern. In association tracts, red, green, and yellow fibers represent uncinate fasciclus, inferior longitudinal fasciclus/inferior fronto-occiptial fasciclus, and superior longitudinal fasciclus, respectively. The lack of a superior longitudinal fasciculus is most striking in the fetal brain. The superior longitudinal fasciculus is not prominent enough, even at birth, to be reliably reconstructed by tractography. The temporal projection of the

superior longitudinal fasciculus is clearly identifiable in the five-year-old volunteer but completely missing in the fetal brain.

Clinical Correlation

Among pediatric cases, imaging of pre- or full-term infants for clinical indications is of great interest. Routinely used diagnostic methods, such as electronic monitoring and ultrasound, often have poor sensitivity to significant abnormalities in neonate brains. A new imaging modality that can precisely delineate anatomical and physiological abnormalities is urgently needed. Furthermore, it has been demonstrated that various injuries, due to perinatal risks, often lead to damage in selective white matter. Precise delineation of the status of specific white matter tracts may provide more accurate diagnosis. Due to the advances in the critical care of pre-term infants, the survival rate of premature infants has increased dramatically in recent years. Identification of abnormalities in the early phase of injuries and perinatal risk factors, and understanding of injury development, are becoming more important than ever. We expect that our DTI database will help in the understanding of the contrasts on DTI images from premature infants and in the detection of anatomical abnormalities. ■

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