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# Diffusion Tensor Imaging for the Development of Neonatal Brain Myelin

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**Abstract**

Magnetic resonance diffusion tensor imaging (DTI) can be used to quantitatively determine fractional anisotropy (FA) values to reflect the white matter microstructure of the brain. In this study, we evaluate the application of DTI for the myelin development of cerebral white matter and compared different FA values in various brain regions for both term and preterm neonates. 100 healthy neonates with perinatal medical records were enrolled in this study. Newborns were divided into term (n = 39) and preterm group (n = 61) regarding to the gestational age (term > 37 weeks). Magnetic Resonance Imaging (MRI) and DTI scan were conducted to all infants to determine FA values in regions of interest (ROI), including bilateral white matter of cerebral hemisphere (WMCH), anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), frontal periventricular zone (FPVZ), occipital periventricular zone (OPVZ), centrum semiovale (CS), subventricular zone (SVZ), corpus callosum genu/splenium (CCG & CCS), external capsule (EC) and middle cerebellar peduncles (MCP). The discrepancy of FA values in white matter regions between term and preterm neonates as well as their interior differences in various regions of newborns were analyzed. FA values in the same ROI between left and right hemisphere had no statistical difference (P> 0.05). The comparison of FA values between CCG and CCS in both preterm and term groups were statistical significant (P< 0.05). The FA values of preterm neonates in white matter regions were lower than that of terms. The comparison of FA values between preterm and term infants in ALIC, PLIC, CCS, CSb, EC and MCP was statistically significant (P< 0.05). The comparison of FA values between the two groups in CCG, FPVZ, OPVZ, CSa, SVZ had no significant difference (P>0.05). The interior FA values of preterm and term neonates in various WMCH were different. Paired comparison found that FA values in PLIC, OPVZ and CCS were higher than that in ALIC, FPVZ and CCG, respectively. All differences were statistically significant (P< 0.05). The comparison between CSa and CSb had no statistical significance (P> 0.05). The FA value was the lowest in FPVZ and highest in CCS and PLIC in all ROIs. The paired comparison of FA values in FPVZ vs. CCS or FPVZ vs. PLIC had a significant difference (P< 0.05). FA values of DTI can be used to quantitatively evaluate the maturity of myelin (brain white matter) development, which solves the problem of the subjective characterization and the absence of objective markers in traditional MRI. FA values also vary in different regions of the brain, reflecting the myelination time, white matter fiber arrangement and myelin self-structure difference.

**Keywords:** neonates, diffusion tensor imaging, fractional anisotropy, myelination

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## 1. Introduction

Advances in perinatal and neonatal medicine have significantly improved the survival rates of premature infants with the increasing rates of neurodevelopmental impairments[1]. It is common to see the neuropathological impairments in intelligence, attention, and behaviors in preterm survivors[2-4]. The relativity of high risk factors during the perinatal period and the above impairments or the abnormality of brain development has not been clearly clarified[5-7]. In addition, the diagnosis of abnormalities using MRI is doubted because those impairments are invisible or the detection is not reliable in conventional MRI sequence diagnosis[8].

Diffusion tensor imaging (DTI) is a non-invasive new technique displaying the direction and integrity of fiber bundle in brain white matter. It can quantitatively evaluate and determine changes in response to brain injury during the early time of diseases[9-11]. DTI can provide quantity measurements such as fractional anisotropy (FA), which is sensitive to microstructure abnormality and can detect injury during early neurodevelopment[12]. The brain maturation in preterm and term neonates over time needs an evaluation method. However, conventional MRI cannot clearly detect changes in myelin development because of the heavy water content in newborns delivered in 4 months[13]. Therefore, this study aimed to explore the application of DTI in brain white matter microstructure and compare the myelination in various regions of the brain by DTI to evaluate the progress of myelin maturation in 39 terms and 61 preterm neonates with normal central nervous systems.

## 2. Materials and Methods

### Ethics statement and patients

This study had been reviewed and approved by the Research Ethics Board of Huai'an First People's Hospital, University of Nanjing Medicine and accepted by the legal guidance of patients involved in this trial. All participating subjects were formally informed for the purpose of using there sample of this study and a letter of consent was signed. We categorized 100 healthy neonates born among January 2015 – April 2017 at Huai'an First People's Hospital, University of Nanjing Medicine. The gestational age of 39 term infants was between 37 – 42 weeks. The gestational age of 61 preterm infants was corrected to 40 weeks to match with the age and gender. There was no abnormal perinatal history of fetal distress during pregnancy and no asphyxia during labor and delivery. Apgar scores of 1 minute and 5 minutes after delivery were all higher than 8 and pH value of umbilical artery blood was above 7. There were no significant neurological syndromes and signs. Craniocerebral conventional MRI and DWI didn't show abnormities.

### Scan method

All tested infants took 10% chloral hydrate solution by mouth or enema at a dose of 0.5 ml/kg. The scan was conducted utilizing Siemens MAGNETOM Avanto 1.5 Magnetic Resonance Machine and Head Matrix Coil when they fell asleep. Conventional MRI and DWI sequence scan were initially conducted. The conventional MR sequence included sagittal T1WI, axial T1WI, T2WI with 4mm layer thickness and 0.32mm layer spacing. Sagittal TIWI had TR：400ms，TE：8.1ms；axial T1WI utilized SE sequence with TR：468ms，TE：11ms；axial T2WI use TSE sequence with TR：4000ms，TE：101ms；and axial DWI use single excitation SE-EPI sequence with TR: 3300ms，TE: 93ms；NEX=1 b value of 0 s/mm2 and 1000s/mm2.

### Image Process

The original data was fed to Syngo MR workstation to automatically produce B0, B1000 and FA image utilizing Neuro 3D software. The 20 regions of interest (ROIs) including ALIC, PLIC, FPVZ, OPVZ, CC, CS, SVZ, EC, and MCP were manually selected in FA image to automatically produce FA value. Measuring ROIs were shown in supplemental files. The size of every ROI (10+_5 mm2) was adjusted and maintained in the center of anatomical position according to anatomical sites to avoid volume effects from the adjacent structure. FA value of every site was an averaged value based on three-time measurements to reduce errors. CCG and CCS were unilateral measurements and the rest were bilateral. There were two layers of CS in neonatal images in which layer a representing the region close to the center and layer b was close to cerebral cortex area. Surveyors were two well-trained image department doctors.

### Statistical analysis

SPSS15.0 software was used for statistical analysis. FA values at the same position of both left and right hemispheres and the difference at CCS and CCG were analyzed by paired t-test. One-way ANOVA was used to analyze the statistical significance of FA values at different regions of preterm and term neonates. $P < 0.05$ was significant.

**3. Result**

Paired *t*-test demonstrated that FA values at the same position in both left and right hemispheres were not significantly different and categorized into one group. The average values were used for analysis. FA values of CCS and CCG had significant difference between preterm and term infants, which were separated into two ROIs for analysis.

The comparison at different regions of preterm and term neonates indicated that FA value of preterm newborns was lower than that of terms. One–way ANOVA demonstrated that differences of FA values at bilateral ALIC and PLIC, CCS, CSb, EC and MCP in preterm and term infants were statistically significant (Fig.1). There were no significant differences of FA values at CCG, FPVZ, OPVZ, CSa and SZ in preterm and term infants (P > 0.05).

Preterm and term neonates had different FA values at various white matter regions (Fig. 1). The pairwise comparison found that PLIC, OPVZ, CCS had significant higher FA values than ALIC, FPVZ and CCG did, respectively. The comparison between CSa and CSb was not significantly different. The FA value was the lowest in FPVZ and highest in CCS and PLIC in all ROIs. The interior comparisons of FPVZ vs. CCS and FPVZ vs. PLIC were both significantly different in preterm and term neonates (Fig. 2 & 3).

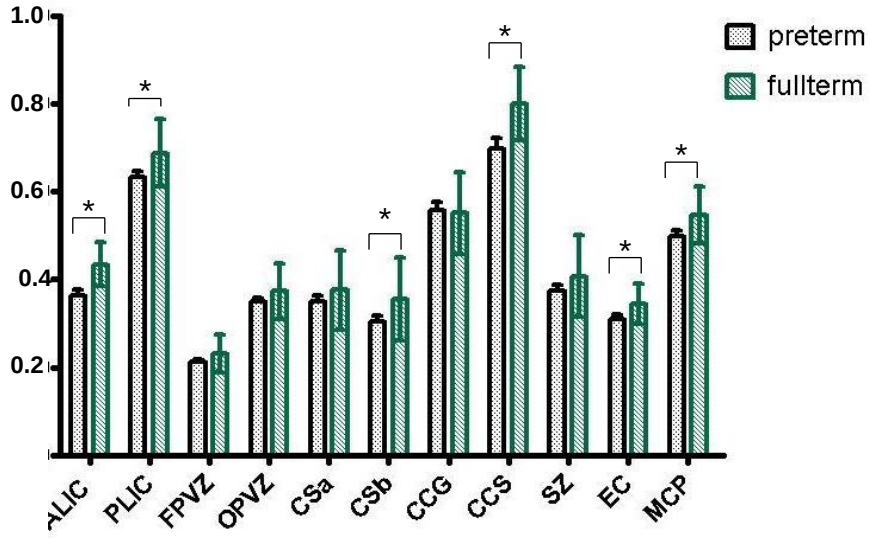


**Figure.1. Comparison of FA values in various ROI white matters for both preterm(n=69) and term neonates(n=31).**The size of every ROI was maintained in the center of anatomical position to avoid volume effects from adjacent structure. FA value of every site was an averaged value based on three time measurements to reduce errors.

* represented *P*< 0.05.

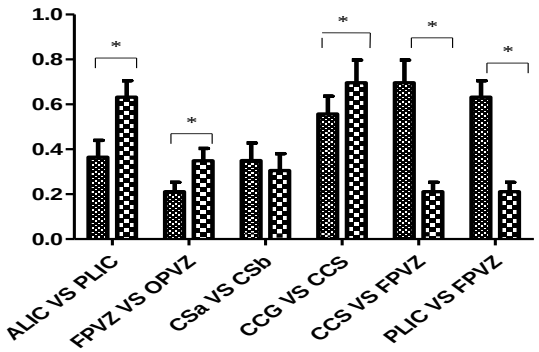


**Figure. 2. Comparison of interior ROIs in preterm neonates group**.The gestational age of preterm infants were corrected to 40 weeks. FA value of every site was an averaged value based on three time measurements to reduce errors.

*represented *P*< 0.05.

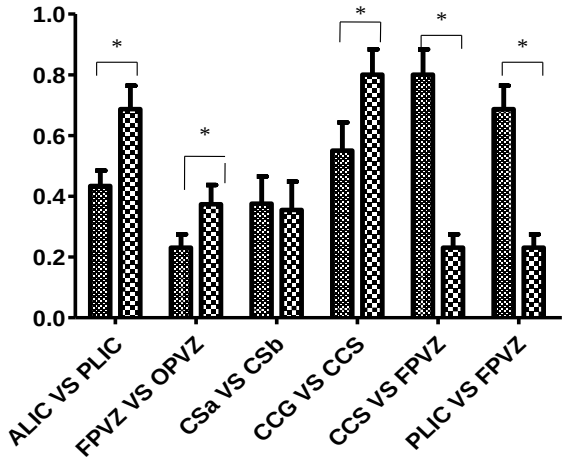


**Figure. 3. Comparison of interior ROIs in term neonates group**.The gestational age of term infants was above 37 weeks. FA value of every site was an averaged value based on three time measurements to reduce errors. * represented $P< 0.05$.

**4. Discussion**

**The development of myelin sheath in normal infants**

The development and maturity of central nervous system is a dynamic and complex process. Myelination initially occurs at gestational 20 weeks from the brain stem and continues after birth. The trend of myelination in the brainstem is from caudal to cephalad, dorsal to ventral, and basal ganglia to cerebral hemispheres. Another trend of myelination is that functional systems utilized in earlier life are prior to those utilized in the later life. This process is faster in the first two years after birth and followed by a slow stage in next 15 years, which can continue throughout life[14].

Myelination of brain refers to the formation of the myelin sheath in white matters, which is an important marker for brain maturation. Selection of axons and initial contact, stable cell connection and formation of a node, regulation of myelin thickness and myelin extension are four key steps for myelination. Myelin sheath is a cell membrane that surrounds an axon with glial cells, which is discontinuous at the nodes of Ranvier. Every glial cell can produce myelin sheath for 50 different axons. Myelin sheath is composed of lipids and proteins - myelin. The myelin membrane is hydrophobic because of the high percentage of lipids to insulate nervous impulse conducting from one axon to another by blocking liquids with ions and avoid the interference of multiple impulses. The presence of myelin enables a rapidly and saltatory impulse conduction. Myelin sheath also plays a crucial role in facilitating the development of axons. Animal studies have shown that loss of myelin sheath in rats lead to the abnormal development of cell cytoskeleton[15].

Changes in water content during myelination are associated with the water structure in myelin sheath and its quantity in axons and extracellular spaces. The brain of infants at postpartum 6 months is occupied by 90% water. Water contained in gray matter is similar with lipid content. With the myelination progress, phospholipids content is increased, following by decreased hydrophobic property.

**The mechanism of DTI and evaluation on the myelination of normal infants.**

Diffusion means the irregular and random movement of molecules, also called Brownian motion. According to the limited degree in water molecules, the diffusion is divided into isotropy (the orbital motion approximates a spheroid) and anisotropy. If the diffusion limit of water in tissues is same in all directions, it is called isotropic diffusion. In some highly organized tissues, such as white matter, the diffusion limit of water is larger in some directions than in other directions and is called anisotropic diffusion. On the basis of DWI, DTI can exert more than 6 gradient fields with non-linear directions to obtain a tensor image to describe the direction of water molecule motion.

FA values are commonly used to reflect the anisotropy. The exact mechanism of anisotropic changes is not yet fully elucidated but is generally believed that it is related to the integrity of axons and myelination maturation, which may be the greatest possibility to reflect the microstructure

change in inspected tissues. Some researchers found that the myelin maturation time in CCG, CCS, and ALIC was postpartum 6, 8, 9 months, respectively.

Most of the myelin has matured to 2 years of age[16][16]. The anisotropic diffusion of white matter during the brain myelination in newborns and infants is gradually increased, which leads to increased FA values. In this case, DTI can be used to objectively assess the brain maturity of children, newborns, and premature infants. To accurately describe the diffusion tensor, it is supposed to have data per voxel from at least 6 different directions, the more directions, the more accurate data. It is even more so for those cross-sections of fiber bundles and other heterogeneous tissue structures. This study used 12 directions to scan involved neonates, which had higher accurate data.

**The application of DTI in neonatal development**

Conventional MRI can qualitatively reflect the process of myelination. T1WI and T2WI are widely used to assess changes in the brain maturation of children, which mainly determine the development of the brain by the change of gray-white signal contrast. Changes in signal contrast are generally thought to be primarily due to myelination progression. The qualitative evaluation of myelination by routine MRI has been shown to be useful for determining if brain development is normal[17], but lacking quantitative indicators, not objective, and sensitive. Brain tissues of normal infants gradually mature with age; following with decreased water content and the average diffusion, while tissue maturation and myelination made the anisotropy gradually increased. The size of diffusion anisotropy is closely related to the directionality and microstructure integrity of white matter fiber bundles. Myelination can be accurately monitored by DTI.

Studies have shown that the enhancement of FA values in hindbrain tissue increased significantly in the first postnatal 3 months. Neil et al. found that FA values of the brain were not significantly associated with gestational age except for the white matter in the semi-oval area, which demonstrates that the decline of water content in hindbrain has limited impact on FA values[18].

The increase of FA value is mainly the result of myelination. With the formation of myelin, the activity of water molecules is restricted, which makes the difference of diffusion velocity in all directions. Faster diffusion speed at parallel than vertical to the axon increases the diffusion anisotropy and FA values[19]. In the experiment, FA values of preterm infants in selected ROIs were lower than those of term infants. The inter-FA values of ALIC, PLIC, CCS, CSb, EC, and MCP were significantly different in both preterm and term infants, suggesting that these areas myelin maturation in preterm infants were late than that in term infants. There were no significant differences in inter-FA values of CCG, FPVZ, OPVZ, CSa, SZ, which needs further verification to confirm if it is because of sample size.

FA values in different regions of the brain are variable. In this study, FA values of neonatal full-term and the preterm infants all have a higher PLIC than ALIC, CCS than CCG, OPVZ than FPVZ, LIC and CC than FPVZ. This is consistent with the basic rule of myelination that the white matter in the central region is higher than surrounding area and the rear area is higher than the front area. This reflects myelination in different brain regions has time difference[18]. Additionally, the arrangement of white matter fibers and structures of myelin sheath, including the degree of myelination, extracellular size and water content, extracellular matrix composition, density and arrangement of white matter axons, nerve basement membrane and other axonal cells maturation of the skeleton and electrical conductivity of the axon membrane are also factors that affect the FA value of brain tissue. Although cells and tissues of the central white matter are not fully developed at birth, axons have started to the orderly arrangement from gestational 20 weeks. While the peripheral white matter is almost unmyelinated, arranged more loosely, more extracellular water, which is the reason that peripheral white matter has low FA value[20]. This also demonstrates that the maturation of peripheral white matter myelin is later than the deep white matter. McGraw et al. found that FA values of white matter fibers in the frontal lobe and loose crown area of radiation crown are lower than the white matter fibers in the closely packed corpus callosum and PLIC[21]. Being closely arranged white matter fibers, those in the internal capsule and the corpus callosum are parallel in a roughly same line direction, in which FA values are higher than the white matter fibers in sector distributed outer capsule. This also explains that the various FA value in different regions although they are same unmyelinated structures[18]. Chepuri et al. pointed out that in addition to the tightness and the direction of the arrangement of white matter fibers,

changes of myelin permeability and axon radius as well as the presence of certain structures within the corpus callosum that limit the diffusion of water molecules may also play an important role when he explained the reason that the degree of anisotropy of the CCS is higher than that of the CCG[22]. Previous two researchers made a similar conclusion during their studies about the myelin development in neonates, even though one of them only focus on term infants and the other one exclusively on preterm neonates[23, 24].

**5**. **Conclusion**

FA values of DTI can be used to quantitatively evaluate the maturity of myelin (brain white matter) development, which solves the problem of the subjective characterization and the absence of objective markers in traditional MRI. The different FA values in ALIC, PLIC, CCS, CSb, EC and MCP of both preterm and term neonates indicated that the late maturity of selected white matter (myelin) in premature infants. Various FA values in different regions of the brain reflected differences of myelination time, white matter fiber arrangement, and myelin self-structure. The myelin of peripheral white matter and front area white matter matured later compared to deep white matter and the rear area. The earliest maturity of myelin occurred in PLIC and CCS and the latest maturity occurred in FPVZ.The comparison of FA values in both preterm and term infants were studied in our experiments, which could provide an advanced reference for the clinical research on diseases relative to neonatal myelin.

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