The Value of Diffusion Kurtosis Imaging In Detecting Delayed Brain Development of Premature Infants

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Abstract

Objective Preterm infants are at high risk of adverse neurodevelopmental outcome. Our aim is to explore the value of diffusion kurtosis imaging (DKI) in diagnosing brain developmental disorders in premature infants.

Materials and Methods A total of 52 subjects were included in this study, including 26 premature infants as the preterm group, and 26 full-term infants as the control group. Routine magnetic resonance imaging and DKI examination were performed. Mean kurtosis (MK), radial kurtosis (RK), fractional anisotropy (FA), mean diffusivity (MD) values were measured in the brain regions including posterior limbs of the internal capsule (PLIC); anterior limb of internal capsule (ALIC); parietal white matter (PWM); frontal white matter (FWM); thalamus (TH); caudate nucleus (CN); genu of the corpus callosum (GCC). The X^2, t test, Spearman's correlation analysis and receiver operating characteristic curve (ROC)were used for data analyses.

Results In the premature infant group, the MK and RK values of PLIA, ALIC, and PWM were lower than those in the control group (P<0.05). The FA values of PWM, FWM and TH were also lower than those of the control group (P<0.05). The AUCs of MK in PLIC and ALIC, MD in PWM, and FA in FWM were 0.813, 0.802, 0.842 and 0.867 (P<0.05). In thalamus and caudate nucleus, the correlations between MK, RK values and PMA were higher than those between FA, MD values and PMA.

Conclusions DKI can be used as an effective tool in detecting brain developmental disorders in premature infants.

What Is Known?

- Traditional diffusion tensor imaging (DTI) technique has been used to study the brain development of premature infants.

What is New:

- Diffusion kurtosis imaging (DKI) is an extension of DTI technology.
- Few studies have been done on the application of DKI in brain development studies of premature infants.
- Our aim is to explore the value of DKI in diagnosing brain developmental disorders in premature infants.

Introduction

In recent years, the birth rate of premature babies has increased significantly in many countries[1]. At the same time, with the development of monitoring and treatment technology in the neonatal intensive care unit (NICU), the survival rate of premature babies has also been greatly improved. Compared with full-

term babies, the brain developments of premature babies are impaired due to the young gestational age[2]. To provide objective indicators for clinical evaluation of brain development status, it would be necessary to quantitatively analyze the brain development of preterm and full-term infants.

Traditional diffusion tensor imaging (DTI) technique has been used to study the brain development of premature infants. Although pathological specimens can directly show the degree of brain development, it cannot reflect the level of brain development in a living state. DTI technology can non-invasively provide quantitative parameters to reflect the development of white matter in the living body, with the integrity of tissue evaluated from the microscopic field and the white matter fibers and fiber bundles of the brain tissue being observed [3]. Many studies have shown that the more mature the development of neonatal white matter, the higher the fractional anisotropy (FA) value and the lower the diffusion coefficient (ADC) value[4, 5]. When applying diffusion weighted imaging (DWI) and DTI to assess white matter development, the theoretical premise of these two models is that the diffusion of water molecules is normally distributed[6]. However, the diffusion distribution of human brain water molecules is dominated by non-normal distribution[7, 8]. The current DWI and DTI evaluation methods still have certain limitations.

DKI is an extension of DTI technology, which describes the degree of water diffusion deviating from the normal distribution in tissues. The kurtosis information reflects the non-Gaussian characteristics caused by the complex structure. It can better reflect the changes in the microstructure of brain gray matter and white matter[9], thus be more suitable for grasping the microstructure changes. In recent years, DKI has been used to evaluate brain development. The DKI parameters correlated well with age, and kurtosis parameters showed a potential advantage in detecting the normal brain development of children [10]. In addition, Research has shown that DKI parameters exhibit subtle differences in the parietal WM between the preterm and term control groups, which may help with the understanding of early neurodevelopment[11]. In this study, we aimed to discusses the value and advantages of DKI in evaluating the brain development of preterm infants with multiple parameters.

Materials And Methods

2.1 Subjects

Fifty-two newborns underwent MRI examination from January 2020 to May 2021, including 26 premature infants and 26 full-term infants. Before the examination, the doctor informed the guardian of the purpose and potential risks, and obtained the informed parental consent. This study was approved by the Ethics Committee.

All recruited infants met the following inclusion criteria: no chromosomes or major congenital diseases; no intracranial infection, sepsis and other infectious diseases; no hypoglycemic encephalopathy, bilirubin encephalopathy and other encephalopathy. Imaging criteria: routine MRI showed normal results; no obvious motion artifacts. Groups were divided according to the following criteria. GA > 37 weeks was considered as the term infant group (n = 26); GA < 37 weeks was the premature infant group (n = 26).

2.2 MR Acquisition and Image Analysis

Each newborn was given an intravenous injection of 5 mg/kg of phenobarbital 30 minutes before the MRI scan. After the newborn fell asleep, he was escorted to the MRI room by the attending physician and his family. The nurse put the swaddled baby on the MRI scan bed, then used sponges to properly fix both sides of the head. Finally, anti-noise earplugs were placed in the external auditory canal to reduce the impact of MRI equipment noise.

All MRI scan were carried out on 3.0 T MR scanner (Pioneer, GE Healthcare, Milwaukee, WI) with T1WI, T2WI, DWI and DKI (TR = 2000 ms, TE = 2.32 ms, Directions = 30, b value = 0, 1000, 2000 mm^2/s). Then MK, RK, FA, MD maps were generated from DKI images on vendor-supplied post-processing workstation. Then, two professional physicians outline 7 regions of interest (ROI) including posterior limbs of the internal capsule (PLIC), anterior limb of internal capsule (ALIC), genu of the corpus callosum (GCC), parietal white matter (PWM), frontal white matter (FWM), thalamus (TH), lenticular nucleus (LN) were manually outlined. Took the average after three measurements.

2.3 Statistical Analysis

The statistical analysis was performed on SPSS software (IBM SPSS Statistics 21.0). Student's t test and chi-square test were used to compare the differences in clinical characteristics between groups. Receiver operating characteristic curve (ROC) was used to analyze the differences among different ROIs. Spearman's correlation analysis was used to analyze the correlation between DKI parameters and postmenstrual age (PMA). $P < 0.05$ indicated statistical significance.

Results

3.1 General demographics of infants

There was no difference between preterm group (n = 26) and Term born (n = 26) in gender, delivery method, mean PMA at MRI, mean birth weight, and mean body weight at MRI ($P > 0.05$), as shown in Table 1. The DKI parameters showed good inter-observer agreement, as shown in Table 2.

Table 1
General demographics of infants.

	Preterm infants (n = 26)	Term infants (n = 26)
Male%	11 (42.3)	14 (53.8)
Cesarean delivery%	7 (27)	10 (38.5)
Mean GA (SD;week)	34.22 ± 2.08*	38.67 ± 1.18
Mean PMA at MRI (SD; week)	40.57 ± 3.07	41.53 ± 3.22
Mean birth weight (SD; kg)	2.66 ± 0.74	3.01 ± 0.31
Mean body weight at MRI (SD; kg)	3.55 ± 0.56	3.68 ± 0.63
GA = gestational age; PMA = postmenstrual age. There were no differences between Preterm infants group (n = 26) and Term born (n = 26) in gender, delivery method, mean PMA at MRI, mean birth weight and mean body weight at MRI(P>0.05). Mean GA in the preterm groups was lower than that in the term control group (P < 0.05).		
* indicates P< 0.05		

Table 2
Inter-observer consistency of measurements.

Parameters	Intraclass correlation coefficient, 95% CI
MK	0.894 (0.635–0.993)
RK	0.880 (0.620–0.983)
FA	0.955 (0.716–0.994)
MD	0.903 (0.636–0.993)
95% CI = 95% confidence interval.	

3.2 Comparison of DKI parameters between preterm infants and term infants

Figure 1 displayed T_1WI Flair, T_2WI Flair, DWI, MK and MD images of two newborns. The signal strength on the MK map increased, the contrast of gray matter and white matter on the MD image decreased.

As shown in Fig. 2, significant differences were found between preterm infants and term infants. In the preterm infant group, the MK value (0.605 ± 0.134 vs. 0.734 ± 0.133, P = 0.001) and RK value (0.716 ± 0.148 vs. 0.821 ± 0.150, P = 0.037) of PLIC were significantly different from the term infant group. The MK and RK values of ALIC in the term infant group were significantly higher than those of the preterm infant

group (0.601 ± 0.154 vs. 0.711 ± 0.121, P = 0.006; 0.708 ± 0.144 vs. 0.793 ± 0.142, P = 0.039). MK, RK, FA and MD value were all significantly different from that of the term infant group in PWM (0.268 ± 0.100 vs. 0.355 ± 0.108, P = 0.004;0.366 ± 0.134 vs. 0.489 ± 0.142, P = 0.029; 0.282 ± 0.114 vs. 0.386 ± 0.115, P = 0.002; 1.357 ± 0.083×$10^{-3}$$mm^2$/s vs.1.221 ± 0.106×$10^{-3}$$mm^2$/s, P = 0.002, respectively). The FA values of FWM and TH were significantly lower than those of the term infant group (0.320 ± 0.129 vs. 0.392 ± 0.108, P = 0.035; 0.205 ± 0.043 vs. 0.275 ± 0.090, P = 0.001, respectively).

3.3 Diagnostic performance of DKI parameters

By comparing the DKI parameters between the two groups in different regions, the region and parameter with significant differences were obtained. We performed ROC analyses on these regions and parameters. The AUCs of MK in PLIC and ALIC were 0.813 and 0.802 with the sensitivity of 75.4%, 77.7 % and the specificity of 86.9%, 80.8% (Critical point: 0.703 and 0.649, respectively, P< 0.05). The AUC of MD in PWM was 0.842 with a sensitivity of 72.3% and a specificity of 87.8% (Critical point: 1.419, P< 0.05). Similarly, The AUC of FA in FWM was 0.867 with a sensitivity of 78.5% and a specificity of 92.3% (Critical point: 0.469, P< 0.05). Details are shown in Table 3.

Table 3
Diagnostic performance of DKI parameters in different ROIs.

ROI	Parameters	specificity	sensitivity	Critical point	AUC	P value
PLIC	MK	86.9%	75.4%	0.703	0.813	<0.05*
	RK	80.8%	46.2%	0.882	0.638	>0.05
ALIC	MK	80.8%	77.7%	0.649	0.802	<0.05*
	RK	69.2%	60.4%	0.793	0.614	>0.05
PWM	MK	63.1%	55.4%	0.344	0.542	>0.05
	RK	73.1%	53.8%	0.420	0.571	>0.05
	FA	52.2%	35.7%	0.727	0.522	>0.05
	MD	87.8%	72.3%	1.419	0.842	<0.05*
FWM	FA	92.3%	78.5%	0.469	0.867	<0.05*
TH	FA	82.3%	11.5%	0.479	0.665	>0.05

Diagnostic manifestations of DKI parameters in different ROIs. The AUC of MK in PLIC and ALIC were 0.813 and 0.802 (P< 0.05). The AUC of MD in PWM was 0.842 (P< 0.05). The AUC of FA in FWM was 0.867 (P< 0.05). PLIC = posterior limbs of the internal capsule; ALIC = anterior limb of internal capsule; PWM = parietal white matter; FWM = frontal white matter.

* indicates P< 0.05

3.4 Correlation between DKI parameters and PMA in the gray matter areas

As shown in Fig. 3, in the thalamus the correlation between MK, RK values and PMA (r = 0.643 and 0.594, respectively, $P < 0.05$) was higher than the correlation between FA, MD values and PMA (r = 0.347 and −0.176, respectively, $P > 0.05$). Similarly, the correlation between MK, RK values and PMA (r = 0.519 and 0.605, $P < 0.05$) was greater than the correlation between FA and MD values and PMA (r = 0.450,$P < 0.05$; r=-0.300,$P > 0.05$) in CN.

Discussion

During the brain development of premature infants, DKI can reveal the microstructure changes and maturation processes in different brain regions. Through comparison with term infants, our research shows that DKI can effectively diagnose delayed brain development in premature infants. Compared with the parameter FA, the parameters MK and RK of DKI can better capture microstructure changes. When describing gray matter structure, such as TH and CN, MK is better than FA. These results indicate that MK is superior to FA in diagnosing premature infants with delayed brain development. It is more advantageous in discovering changes in the microstructure of the brain.

Because premature birth may lead to relatively slow brain development in premature infants, there are some brain regions that are less developed than full-term infants. In this study we found that the MK and RK values of PLIC and ALIC were lower than those of the full-term infants. The fibers that made up the internal capsule (IC) came from the descending fibers of the cerebral cortex. The following factors affected the development of the complex structure of IC [12, 13], i.e. the increase of nerve cell axon diameter, change of nerve cell membrane composition, *myelination of axons continued to improve*, increase in the number of microglia, and decreased extracellular space. The parameters of DKI, such as MK, RK can sensitively reflect these microstructure complexity. This is also in line with Paydar's view that MK and RK allow more comprehensive characterization of microstructural changes during children brain development, especially in PLIC and ALIC[14]. Frontal-parietal white matter (FWM, PWM) reflected the degree of brain development in the front and middle brain. In this study, the FA values of PWM and FWM were lower than those in the term infant group. FWM was the language and motor center [15], so it was speculated that preterm infants lag behind full-term infants in language and motor development. Similarly, when PWM of premature babies was underdeveloped, the ability to integrate sensory and language was also lacking. The thalamus was the gray matter nucleus, one of the areas where neonatal metabolism was vigorous. Its myelin development was also very active. At the same time, the thalamus was also the highest sensory center and the most important sensory conduction relay station [16–18].The results showed that the FA value of TH was lower than that in term infants. It was assumed that premature babies were delayed in perception, cognition, and motor development. DKI can be used as an effective tool to assess brain developmental delay in premature infants.

By comparing DKI parameters in different brain regions between the two groups, we selected four ROIs with significant differences, including ALIC, PLIC, PWM and FWM. Our results shown that the area under

curves (AUC) of MK in ALIC and PLIC were statistically significant. Studies have shown that neonatal brain development follows a backward-to-forward pattern. Due to early myelination of ALIC and PLIC, the metabolism is vigorous and the oxygen demand is high. When exposed to risk factors for preterm birth,the metabolically active areas are the first to be damaged[19]. At the same time, MK can reflect the backward development of PLIC and ALIC by capturing the changes in microstructure[20]. When brain development is impaired, the decreased density of cells and axon membranes may also lead to the decreased MK values, which are significantly different from those in the control group[17]. In our study, FA did not show good diagnostic value in ALIC and PLIC. Because the internal capsule acts as a white matter plate connecting the upper and lower fibers of the cerebral cortex to the brainstem, the structure is more complicated[21]. For this complex structure, the diffusion of water molecules actually deviates from the normal distribution, and MK can quantify this deviation.

RK represents the degree to which the molecular diffusion deviates radially from the Gaussian pattern. Compared with the FA value, RK changes more significantly in premature infants brain[22], which is confirmed in our study. The diagnostic value of RK in PWM was statistically significant. We speculated that the RK value may more sensitively reflect the limited radial diffusion of PWM.

With the same view as Vasung, the FA value of FWM has certain diagnostic value in premature infants with brain development disorders[23]. There was a significant difference in the FA value of FWM. It may be because FA is mainly affected by cell changes and fiber bundle density, while MK is mainly affected by the complexity of the microstructure [24, 25]. Therefore, as a major functional area of the brain, we believe that FA value is sensitive in FWM.

This study confirmed that the correlations between MK, RK and PMA was higher than the correlations between FA, MD and PMA in the TH or CN. For homogeneous structures, such as gray matter, MK and RK are more sensitive than FA and MD. MK,RK played an important role in detecting the development of isotropic tissues (such as gray matter)[26]. In the gray matter region, the changes of MK and RK parameters may be related to the increased concentration of mature neuronal macromolecules and the decrease of tissue water content[27, 28], or to other special structures occurring in the development of gray matter. As an advanced and sensitive imaging technique, MK and RK can be used to detect the subtle structural changes of thalamic neurons in premature infants.MK and RK can show hidden manifestations that FA and MD cannot detect in vivo. Therefore, we speculate that the MK and RK parameters have an advantage in reflecting the development of the deep nucleus in premature infants. MK and RK parameters can better reflect the brain maturity of premature infants.

There were several limitations in this study. This study was only a cross-sectional study. The long-period developmental mechanism still need to be further verified by longitudinal data. In addition, the sample size was not large enough. Next we will continue to enlarge sample size. Finally, the PMA range of the research subjects was relatively large. If the same newborn brain template is used, the accuracy of image registration may be improved. The next step will be to establish brain templates for different PMA segments.

Conclusion

In conclusion, our study found that MK of ALIC and PLIC, RK of PWM and FA of FWM have some diagnostic value in detecting brain developmental disorders in premature infants. The MK and RK values of TH and CN can better reflect the brain maturity of the deep gray matter in premature infants. These parameters can be used as reliable imaging markers for the diagnosis of brain developmental disorders in premature infants.

Abbreviations

anterior limb of internal capsule =ALIC; caudate nucleus =CN; diffusion kurtosis imaging =DKI; fractional anisotropy =FA; frontal white matter =FWM; genu of the corpus callosum =GCC; mean diffusivity =MD; mean kurtosis =MK; posterior limbs of the internal capsule =PLIC; parietal white matter =PWM; radial kurtosis =RK; thalamus =TH;

Declarations

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Availability of data and material: The data transparency

Authors' contributions: Xin Zhao: manuscript editing and guarantor of integrity of the entire study; Chunxiang Zhang: manuscript editing; Bohao Zhang: statistical analysis; Jiayue Yan: collect and organize data; Kaiyu Wang: language modification and study design; Zitao Zhu: modify article; Xiaoan Zhang: study concepts and design, funding.

Ethics approval: Research involving human participants was reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University. The patients provided their written informed consent to participate in this study.

Consent to participate: Each author agrees to participate.

Consent for publication: Every participant agrees to publish.

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Figures

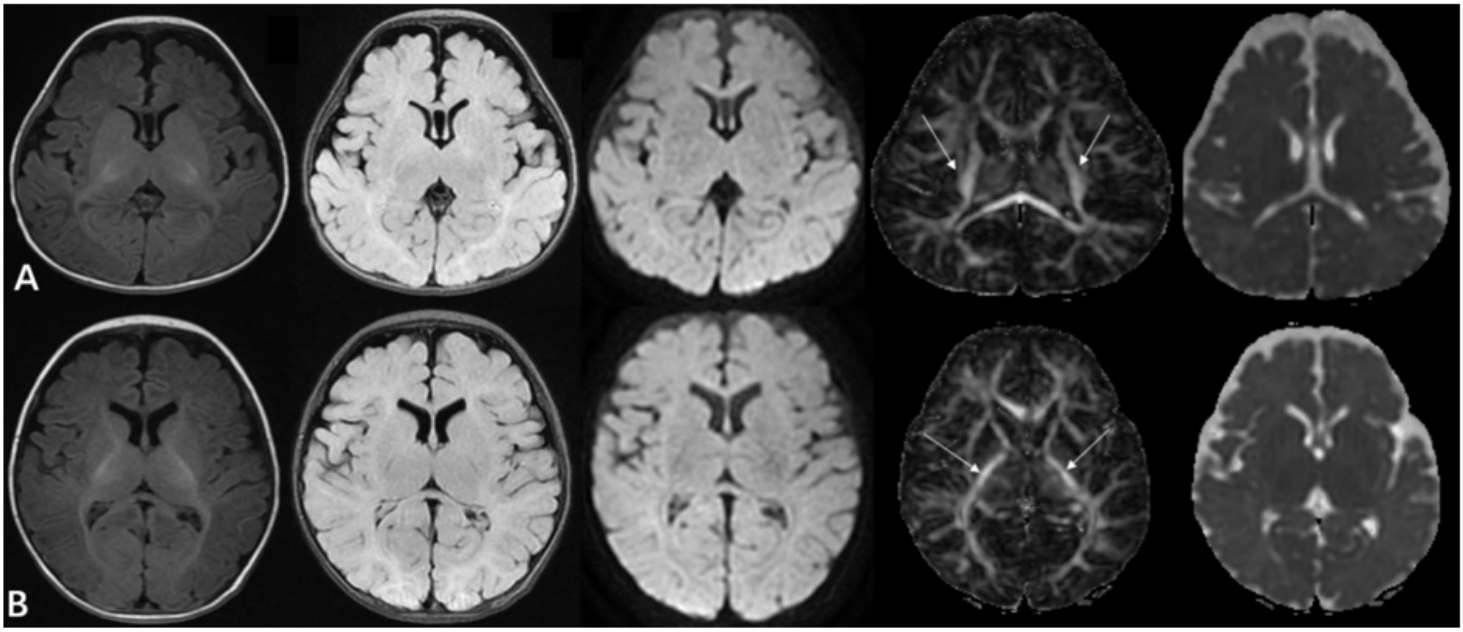

Figure 1

Comparison of multi-parameter images in different PMAs. Row A represented: male, GA 30 weeks, PMA42 weeks. Row B represented: male, GA 37 weeks, PMA44 weeks. From left to right: T1WI Flair, T2WI Flair, DWI, MK and MD maps. The signal strength on the MK map increased, and there was a white arrow on the MK map. As the water content decreases, the contrast of gray matter and white matter on the MD image decreased.

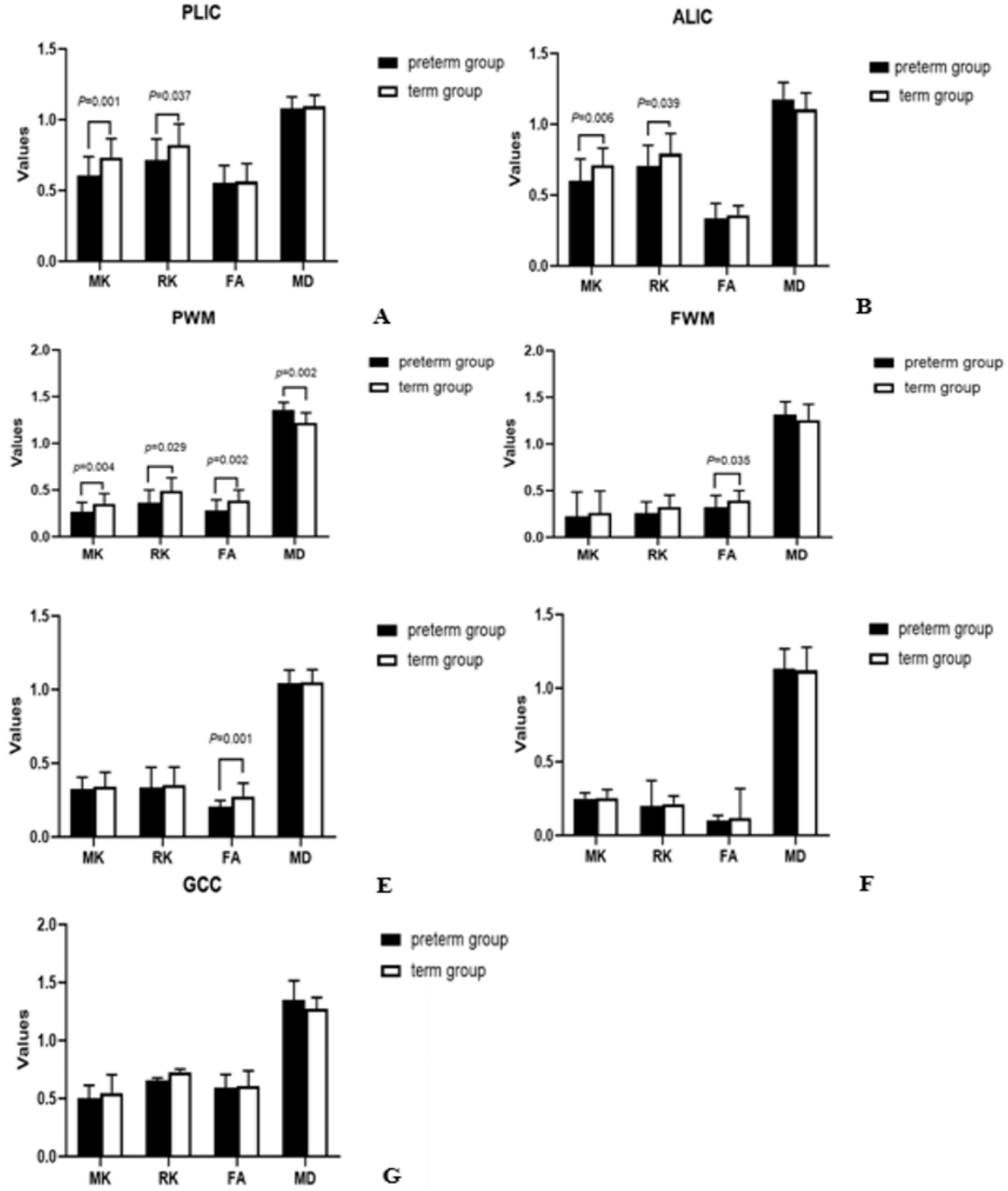

Figure 2

Comparing the difference of parameter values between preterm infants (n=26) and term infants (n=26) in different brain regions. Black represented premature infants,white represented full-term infants. PLIC = posterior limbs of the internal capsule; ALIC=anterior limb of internal capsule; PWM = parietal white matter; FWM = frontal white matter; TH = thalamus; CN=caudate nucleus; GCC = genu of the corpus callosum.

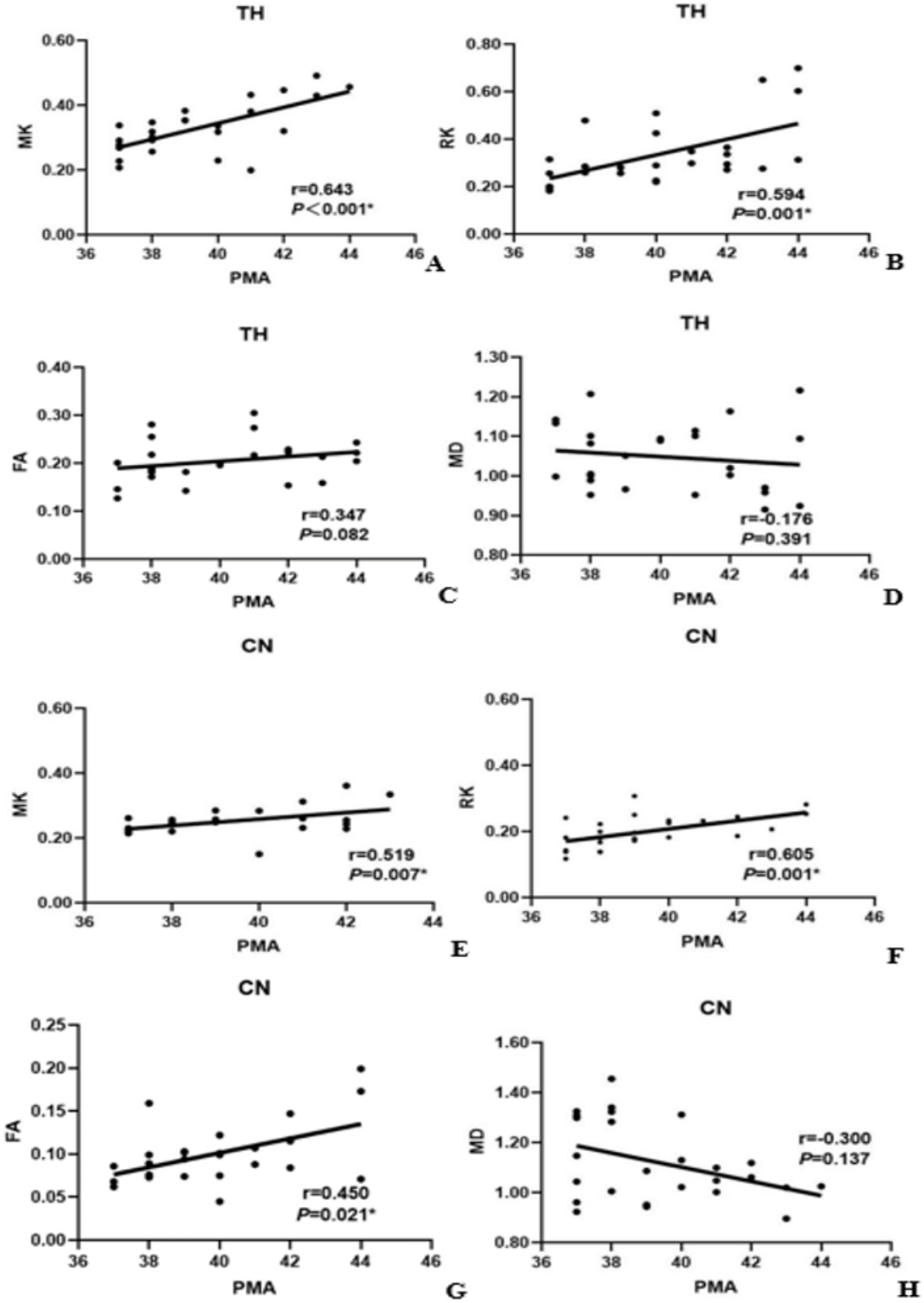

Figure 3

Correlation between MK, RK, FA, MD and PMA in preterm infants (n=26). MK and FA regression lines with correlational coefficient (r). correlation significance (P). A: The selected ROI are the thalamus and the caudate nucleus.